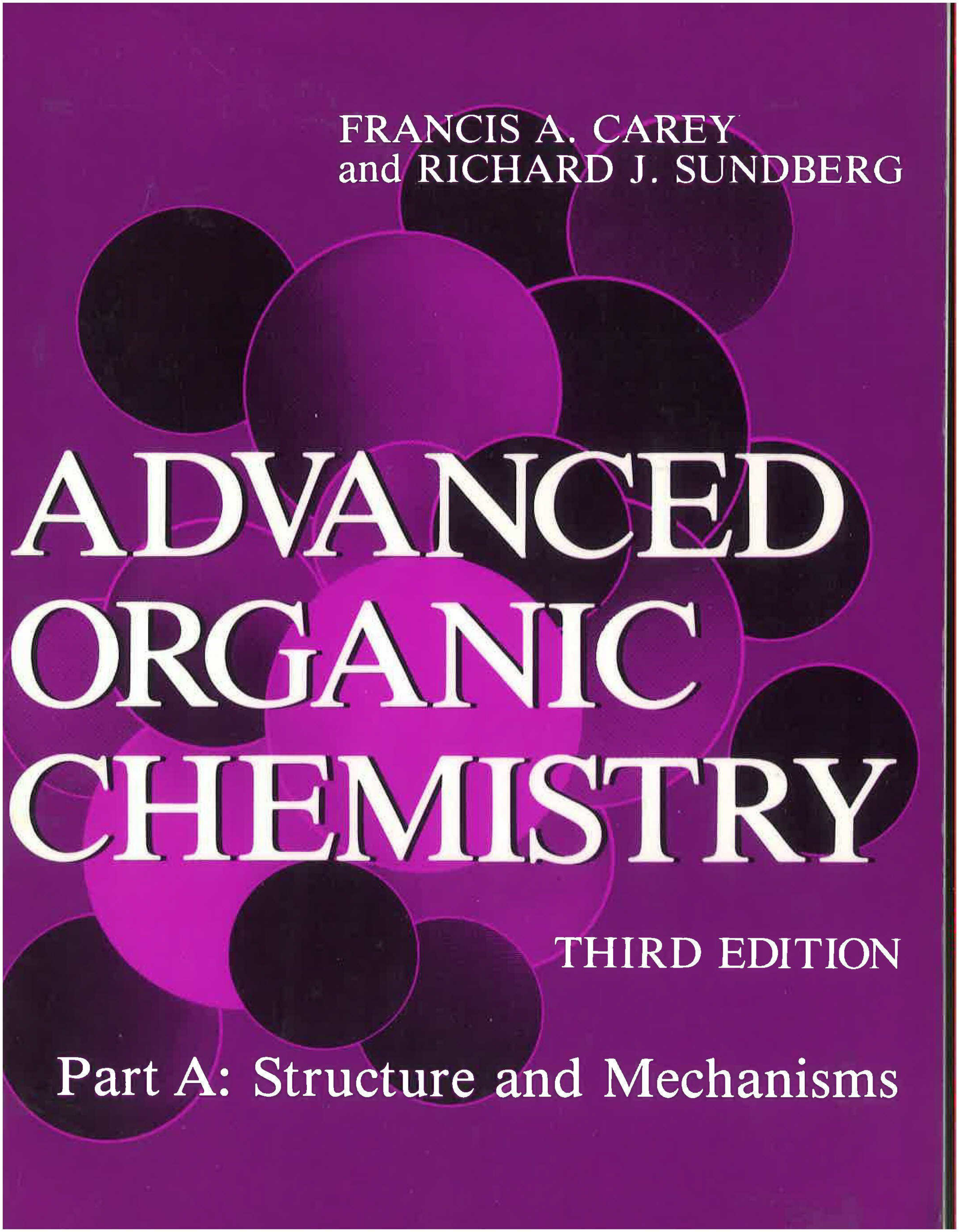

FRANCIS A. CAREY
and RICHARD J. SUNDBERG

ADVANCED ORGANIC CHEMISTRY

THIRD EDITION

Part A: Structure and Mechanisms

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Advanced Organic Chemistry

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Part A: Structure and Mechanisms

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PART A: Structure and Mechanisms
PART B: Reactions and Synthesis

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Part A: Structure and Mechanisms

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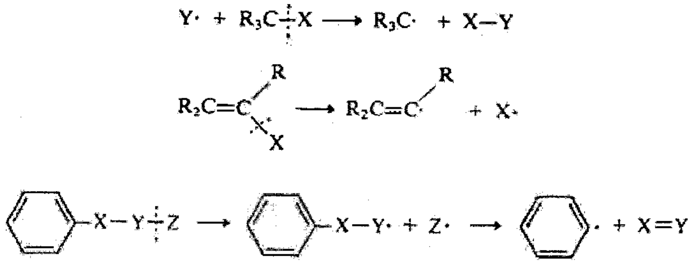
12

Free-Radical Reactions

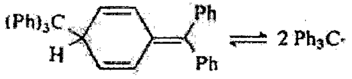
12.1. Generation and Characterization of Free Radicals

12.1.1. Background

A free-radical reaction is a chemical process in which molecules having unpaired electrons are involved. The radical species could be a starting compound or a product, but in organic chemistry the most common cases are reactions that involve radicals as intermediates. Most of the reactions discussed to this point have been heterolytic processes involving polar intermediates and/or transition states in which all electrons remained paired throughout the course of the reaction. In radical reactions, *homolytic* bond cleavages occur. The generalized reactions shown below illustrate the formation of alkyl, vinyl, and aryl free radicals by hypothetical homolytic processes.



The idea that substituted carbon atoms with seven valence electrons could be involved in organic reactions took firm hold in the 1930s. Two experimental studies have special historical significance in the development of the concept of free-radical reactions. The work of Gomberg around 1900 provided evidence that when triphenylmethyl chloride was treated with silver metal, the resulting solution contained $Ph_3C\cdot$ in equilibrium with a less reactive molecule. It was originally thought that the more stable molecule was hexaphenylethane, but eventually this was shown not to be so. The dimeric product is actually a cyclohexadiene derivative.[1]



The dissociation constant is small, only about 2×10^{-4} M at room temperature. The presence of the small amount of the radical at equilibrium was deduced from observation of reactions that could not be reasonably attributed to a normal hydrocarbon.

The second set of experiments was carried out in 1929 by Paneth. The decomposition of tetramethyllead was carried out in such a way that the decomposition products were carried by a flow of inert gas over a film of lead metal. The lead was observed to disappear, with re-formation of tetramethyllead. The conclusion was reached that methyl radicals must exist long enough in the gas phase to be transported from the point of decomposition to the lead film.

$$Pb(CH_3)_{4(g)} \xrightarrow{450°C} Pb_{(s)} + 4\,CH_3\cdot_{(g)}$$

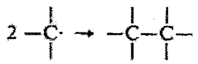
$$4\,CH_3\cdot_{(g)} + Pb_{(s)} \xrightarrow{100°C} Pb(CH_3)_{4(g)}$$

Since these early experiments, a great deal of additional information about the existence and properties of free-radical intermediates has been developed. In this chapter, we will discuss the structure of free radicals and some of the special properties associated with free radicals. We will also discuss some of the key chemical reactions in which free-radical intermediates are involved.

12.1.2. Stable and Persistent Free Radicals

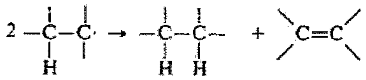
Most organic free radicals have very short lifetimes, but various structural features enhance stability. Radicals without special stabilization rapidly dimerize or disproportionate. The usual disproportionation process involves transfer of a hydrogen from the carbon β to the radical site, leading to formation of an alkane and an alkene.

Dimerization



$$2\,-\overset{|}{\underset{|}{C}}\cdot \rightarrow -\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-$$

Disproportionation

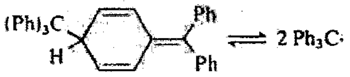


$$2\,-\overset{|}{\underset{H}{C}}-\overset{|}{\underset{|}{C}}\cdot \rightarrow -\overset{|}{\underset{H}{C}}-\overset{|}{\underset{H}{C}}- + \;>C{=}C<$$

---

[1] H. Lankamp, W. Th. Nauta, and C. MacLean, *Tetrahedron Lett.*, 249 (1968); J. M. McBride, *Tetrahedron* **30**, 2009 (1974); K. J. Skinner, H. S. Hochester, and J. M. McBride, *J. Am. Chem. Soc.* **96**, 4301 (1974).

methyl chloride was treated with silver metal, the resulting solution contained $Ph_3C\cdot$ in equilibrium with a less reactive molecule. It was originally thought that the more stable molecule was hexaphenylethane, but eventually this was shown not to be so. The dimeric product is actually a cyclohexadiene derivative.[1]



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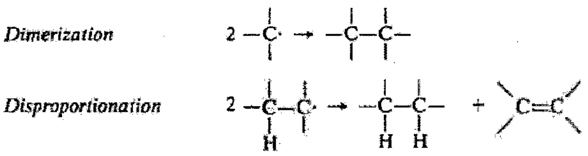

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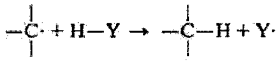
[1] H. Lankamp, W. Th. Nauta, and C. MacLean, *Tetrahedron Lett.*, 249 (1968); J. M. McBride, *Tetrahedron* **30**, 2009 (1974); K. J. Skinner, H. S. Hochester, and J. M. McBride, *J. Am. Chem. Soc.* **96**, 4301 (1974).

Radicals also rapidly abstract hydrogen or other atoms from many types of solvents, and most radicals are highly reactive toward oxygen.

Hydrogen atom abstraction



$$-\overset{|}{\underset{|}{C}}\cdot + H-Y \rightarrow -\overset{|}{\underset{|}{C}}-H + Y\cdot$$

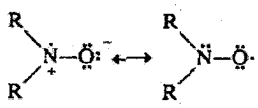
Addition to oxygen

$$-\overset{|}{\underset{|}{C}}\cdot + O_2 \rightarrow -\overset{|}{\underset{|}{C}}-O-O\cdot$$

A few free radicals are indefinitely stable. Entries 1, 4, and 6 in Scheme 12.1 are examples. These molecules are just as stable under ordinary conditions of temperature and atmosphere as typical closed-shell molecules. Entry 2 is somewhat less stable to oxygen, although it can exist indefinitely in the absence of oxygen. The structures shown in entries 1, 2, and 4, all permit extensive delocalization of the unpaired electron into aromatic rings. These highly delocalized radicals show no tendency toward dimerization or disproportionation. Radicals that have long lifetimes and are resistant to dimerization or other routes for bimolecular self-annihilation are called *stable free radicals*. The term *inert free radical* has been suggested for species such as entry 4, which is unreactive under ordinary conditions and is thermally stable even at 300°C.[2]

Entry 3 in Scheme 12.1 has only alkyl substituents and yet has a significant lifetimes in the absence of oxygen. The tris(*t*-butyl)methyl radical has an even longer lifetime, with a half-life of about 20 min at 25°C.[3] The steric hindrance provided by the *t*-butyl substituents greatly retards the rates of dimerization and disproportionation of these radicals. They remain highly reactive toward oxygen, however. The term *persistent radicals* is used to describe these species, since their extended lifetimes have more to do with kinetic factors than with inherent stability.[4] Entry 5 is a sterically hindered perfluorinated radical, which is even more stable than similar alkyl radicals.

There are only a few functional groups that contain an unpaired electron and yet are stable in a wide variety of structural environments. The best example is the nitroxide group, and there are numerous specific nitroxide radicals which have been prepared and characterized.



Many of these compounds are very stable under normal conditions, and heterolytic reactions can be carried out on other functional groups in the molecule without destroying the nitroxide group.[5]

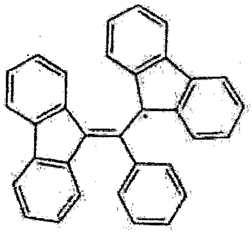
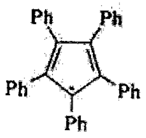
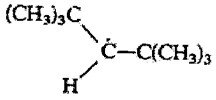
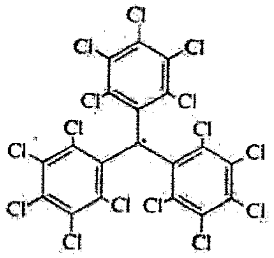
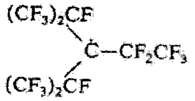
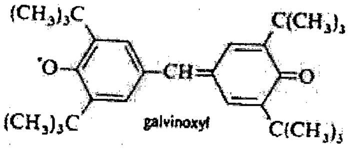
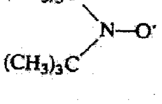
[2] M. Ballester, *Acc. Chem. Res.* **18**, 380 (1985).

[3] G. D. Mendenhall, D. Griller, D. Lindsay, T. T. Tidwell, and K. U. Ingold, *J. Am. Chem. Soc.* **96**, 2441 (1974).

[4] For a review of various types of persistent radicals, see D. Griller and K. U. Ingold, *Acc. Chem. Res.* **9**, 13 (1976).

[5] For reviews of the preparation, reactions, and uses of nitroxide radicals, see J. F. W. Keana, *Chem. Rev.* **78**, 37 (1978); L. J. Berliner (ed.), *Spin-Labelling*, Vol. 2, Academic Press, New York, 1979.

Scheme 12.1. Stability of Some Free Radicals

Structure	Conditions for stability
1[a] 	Indefinitely stable as a solid, even in the presence of air.
2[b] 	Crystalline substance is not rapidly attacked by oxygen, although solutions are air sensitive; the compound is stable to high temperature in the absence of oxygen.
3[c] 	Stable in dilute solution ($<10^{-5}\,M$) below −30°C in the absence of oxygen, $t_{1/2}$ of 50 sec at 25°C.
4[d] 	Stable in solution for days, even in the presence of air. Indefinitely stable in solid state. Thermally stable up to 300°C.
5[e] 	Stable to oxygen; thermally stable to 70°C.
5[e] 	Stable to oxygen; stable to extended storage as a solid. Slowly decomposes in solution.
6[f] 	Stable to oxygen even above 100°C.

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a. C. F. Koelsch, *J. Am. Chem. Soc.* 79, 4439 (1957).
b. K. Ziegler and B. Schnell, *Justus Liebigs Ann. Chem.* 445, 266 (1925).
c. G. D. Mendenhall, D. Griller, D. Lindsay, T. T. Tidwell, and K. U. Ingold, *J. Am. Chem. Soc.* 96, 2441 (1974).
d. M. Ballester, J. Riera, J. Castañer, C. Badia, and J. M. Monsó, *J. Am. Chem. Soc.* 93, 2215 (1971).
e. K. V. Scherer, Jr., T. Ono, K. Yamanouchi, R. Fernandez, and P. Henderson, *J. Am. Chem. Soc.* 107, 718 (1985).
f. G. M. Coppinger, *J. Am. Chem. Soc.* 79, 501 (1957); P. D. Bartlett and T. Funahashi, *J. Am. Chem. Soc.* 84, 2596 (1962).
g. A. K. Hoffmann and A. T. Henderson, *J. Am. Chem. Soc.* 83, 4671 (1961).

Although the existence of the stable and persistent free radicals we have discussed is of significance in establishing that free radicals can have extended lifetimes, most free-radical reactions involve highly reactive intermediates that have relatively fleeting lifetimes and can only be studied at very low concentrations. The techniques for study of radicals under these conditions are the subject of the next section.

12.1.3. Direct Detection of Radical Intermediates

The distinguishing characteristic of free radicals is the presence of an unpaired electron. Species with an unpaired electron are said to be *paramagnetic*. The most useful method for detecting and characterizing unstable radical intermediates is *electron paramagnetic resonance* (EPR) spectroscopy. *Electron spin resonance* (ESR) spectroscopy is synonymous. This method of spectroscopy detects the transition of an electron between the energy levels associated with the two possible orientations of electron spin in a magnetic field. An EPR spectrometer records the absorption of energy when an electron is excited from the lower to the higher state. The energy separation is very small on an absolute scale and corresponds to the energy of microwaves. EPR spectroscopy is a highly specific tool for detecting radical species since only molecules with unpaired electrons give rise to EPR spectra. As with other spectroscopic methods, detailed analysis of the absorption spectrum can give rise to structural information. One feature that is determined is the g value, which specifies the separation of the two spin states as a function of the magnetic field strength of the spectrometer.

$$h\nu = E = g\mu_B H$$

where μ_B is a constant, the Bohr magneton ($=9.274 \times 10^{-21}$ erg/G), and H is the magnetic field in gauss. The measured value of g is a characteristic of the particular type of radical, just as the line positions in IR and NMR spectra are characteristic of the absorbing species.

A second type of structural information can be deduced from the *hyperfine splitting* in EPR spectra. The origin of this line splitting is closely related to the factors that cause spin–spin splitting in proton NMR spectra. Certain nuclei have a magnetic moment. Those which are of particular interest in organic chemistry include ^{1}H, ^{13}C, ^{14}N, ^{19}F, and ^{31}P. Interaction of the unpaired electron with one or more of these nuclei splits the signal arising from the electron. The number of lines is given by the equation

$$\text{number of lines} = 2nI + 1$$

where I is the nuclear spin quantum number, and n is the number of equivalent interacting nuclei. For ^{1}H, ^{13}C, ^{19}F and ^{31}P, $I = \frac{1}{2}$. Thus, a single hydrogen splits a signal into a doublet. Interaction with three equivalent hydrogens, as in a methyl group, gives rise to splitting that produces four lines. This splitting is illustrated in Fig. 12.1. Nitrogen (^{14}N), with $I = 1$, splits each energy level into three lines. Neither

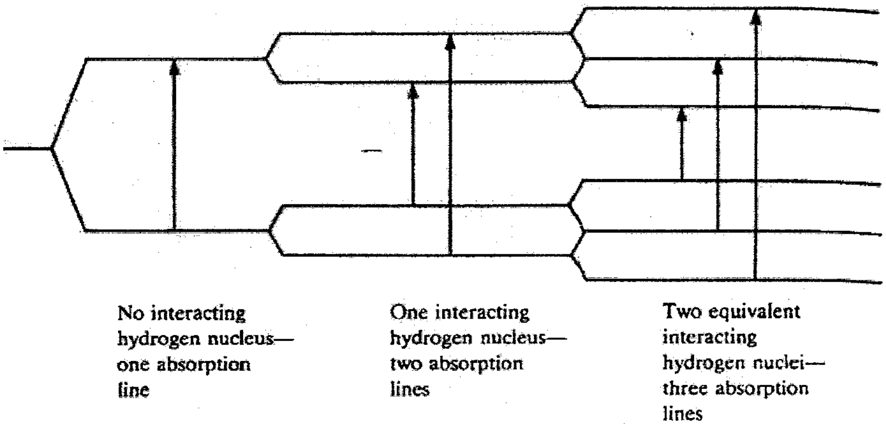

Fig. 12.1. Hyperfine splitting in EPR spectra.

^{12}C nor ^{16}O has a nuclear magnetic moment, and just as they cause no splitting in NMR spectra, they have no effect on the multiplicity in EPR spectra.

A great deal of structural information can be obtained by analysis of the hyperfine splitting pattern of a free radical. If we limit our discussion for the moment to radicals without heteroatoms, the number of lines indicates the number of interacting hydrogens, and the magnitude of the splitting, given by the hyperfine splitting constant a, is a measure of the unpaired electron density in the hydrogen 1s orbital. For planar systems in which the unpaired electron resides in a π-orbital system, the relationship between electron spin density and the splitting constant is given by the McConnell equation[6]:

$$a = \rho Q$$

where a is the hyperfine coupling constant for a proton, Q is a proportionality constant (about 23 G), and ρ is the spin density on the carbon to which the hydrogen is attached. For example, taking $Q = 23.0$ G, the hyperfine splitting in the benzene radical anion may be readily calculated by taking $\rho = \frac{1}{6}$, since the one unpaired electron must be distributed equally among the six carbon atoms. The calculated value of $a = 3.83$ is in good agreement with the observed value. The spectrum (Fig. 12.2*a*) consists of seven lines separated by a coupling constant of 3.75 G.

The EPR spectrum of the ethyl radical presented in Fig. 12.2b is readily interpreted, and the results are of interest with respect to the distribution of unpaired electron density in the molecule. The 12-line spectrum is a triplet of quartets resulting from unequal coupling of the electron spin to the α and β protons. The two coupling constants are $a_\alpha = 22.38$ G and $a_\beta = 26.87$ G and imply extensive delocalization of spin density through the σ bonds.

EPR spectra have been widely used in the study of reactions to detect free-radical intermediates. An interesting example involves the cyclopropylmethyl radical. Much

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[6] H. M. McConnell, *J. Chem. Phys.* 24, 764 (1956).

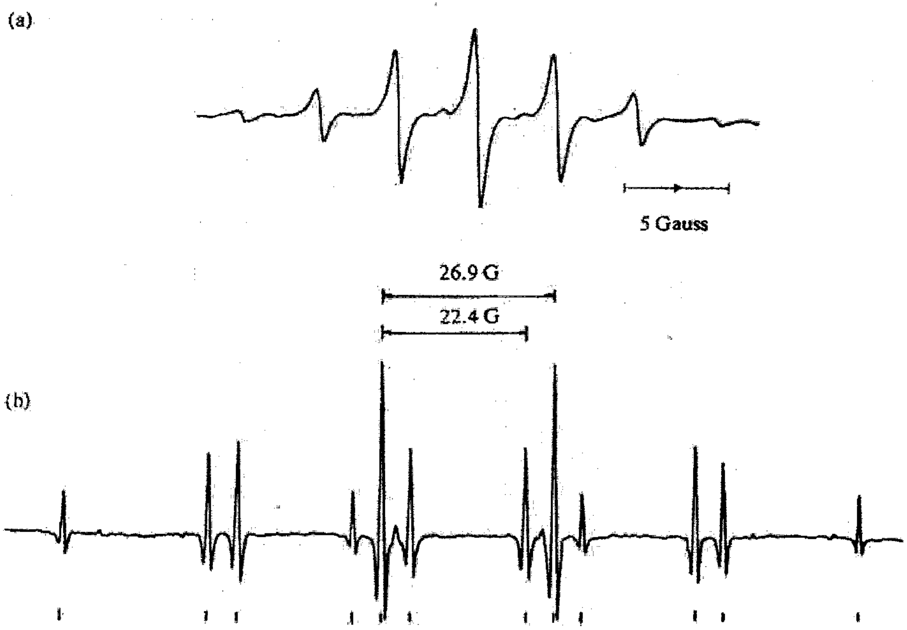
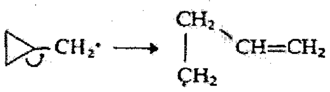


Fig. 12.2. Some EPR spectra of small organic free radicals: (a) Spectrum of the benzene radical anion. [From J. R. Bolton, *Mol. Phys.* 6, 219 (1963). Reproduced by permission of Taylor and Francis, Ltd.] (b) Spectrum of the ethyl radical. [From R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.* 33, 935 (1960); 39, 2147 (1963); Reproduced by permission of the American Institute of Physics.]

chemical experience has indicated that this radical is unstable, giving rise to 3-butenyl radical rapidly after being generated.



The radical was generated by photolytic decomposition of di-*t*-butyl peroxide in methylcyclopropane, a process that leads to selective abstraction of a methyl hydrogen from methylcyclopropane.

$$(CH_3)_3COOC(CH_3)_3 \xrightarrow{h\nu} 2\,(CH_3)_3C{-}O\cdot$$

Below −140°C, the EPR spectrum observed was that of the cyclopropylmethyl radical. If the photolysis was done above −140°C, however, the spectrum of a second species was seen, and above −100°C, this was the only spectrum observed. This spectrum could be shown to be that of the 3-butenyl radical.[7] This study also established that the 3-butenyl radical did not revert to the cyclopropylmethyl radical on being cooled back to −140°C. The conclusion is that the ring opening of the

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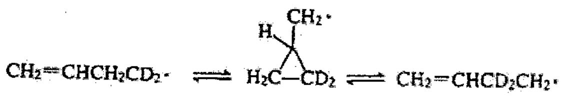
[7] J. K. Kochi, P. J. Krustic, and D. R. Eaton, *J. Am. Chem. Soc.* 91, 1877 (1969).

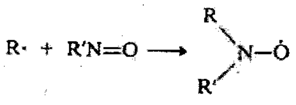
cyclopropyl radical is a very facile process, so that the lifetime of the cyclopropyl radical above −100°C is very short. The reversal of the ring opening can be detected by isotopic labeling experiments, which reveal the occurrence of deuterium migration:



The rates of both the ring opening ($k = 2 \times 10^8\ \mathrm{s}^{-1}$ at 25°C) and the ring closure ($k = 3 \times 10^3\ \mathrm{s}^{-1}$) have been measured and show that only a very small amount of the cyclopropylmethyl radical is present at equilibrium, in agreement with the EPR results.[8]

It is important to emphasize that direct studies such as those carried out on the cyclopropylmethyl radical can be done with low *steady-state* concentrations of the radical. In the case of the study of the cyclopropylmethyl radical, removal of the source of irradiation would lead to rapid disappearance of the EPR spectrum, because the radicals would react rapidly and not be replaced by continuing radical formation. Under many conditions, the steady-state concentration of a radical intermediate may be too low to permit direct detection. Failure to observe an EPR signal therefore cannot be taken as conclusive evidence against a radical intermediate.

A technique called *spin trapping* can sometimes be used to study radicals in this circumstance. A diamagnetic molecule that has the property of reacting rapidly with radicals to give a stable paramagnetic species is introduced into the reaction system being studied. As radical intermediates are generated, they are trapped by the reactive molecule to give more stable, detectable radicals. The most useful spin traps are nitroso compounds. They rapidly react with radicals to give stable nitroxide radicals.[9] Analysis of the EPR spectrum of the nitroxide radical product can often provide information about the structure of the original radical.



$$R\cdot + R'N{=}O \longrightarrow \begin{matrix} R \\ \quad\ \ \rangle N{-}\dot{O} \\ R' \end{matrix}$$

Another technique that is highly specific for radical processes is known as CIDNP, an abbreviation for *chemically induced dynamic nuclear polarization.*[10] The instrumentation required for such studied is a normal NMR spectrometer. CIDNP is observed as a strong perturbation of the intensity of NMR signals for products formed in certain types of free-radical reactions. The variation in intensity results

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[8] A. Eiffio, D. Griller, K. U. Ingold, A. L. J. Beckwith, and A. K. Serelis, *J. Am. Chem. Soc.* **102**, 1734 (1980); L. Mathew and J. Warkentin, *J. Am. Chem. Soc.* **108**, 7981 (1986).

[9] E. G. Janzen, *Acc. Chem. Res.* 4, 31 (1971); E. G. Janzen, in *Free Radicals in Biology*, W. A. Pryor (ed.), Vol. 4, Academic Press, New York, 1980, pp. 115–154.

[10] H. R. Ward, *Acc. Chem. Res.* 5, 18 (1972); R. G. Lawler, *Acc. Chem. Res.* 5, 25 (1972).

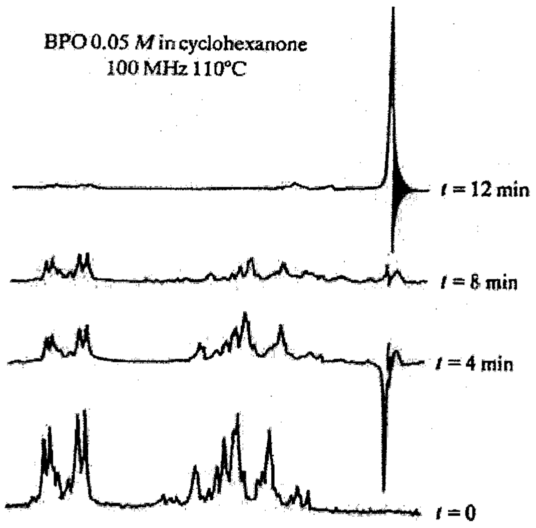
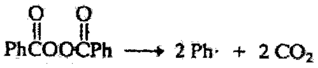


Fig. 12.3. NMR spectra recorded during thermal decomposition of dibenzoyl peroxide. Singlet at high field is due to benzene; other signals are due to dibenzoyl peroxide. [From H. Fischer and J. Bargon, *Acc. Chem. Res.* 2, 110 (1969). Reproduced by permission of the American Chemical Society.]

when the normal population of nuclear spin states dictated by the Boltzmann distribution is disturbed by the presence of an unpaired electron. The magnetic moment associated with an electron causes a redistribution of the nuclear spin states. Individual nuclei can become overpopulated in either the lower or upper spin state. If the lower state is overpopulated, an enhanced absorption signal is observed. If the upper state is overpopulated, an emission signal is observed. The CIDNP method is not as general as EPR spectroscopy because not all free-radical reactions can be expected to exhibit the phenomenon.[11]

Figure 12.3 shows the observation of CIDNP during the decomposition of dibenzoyl peroxide in cyclohexanone:



$$\mathrm{Ph\overset{O}{\overset{\|}{C}}O O\overset{O}{\overset{\|}{C}}Ph \longrightarrow 2\,Ph\cdot + 2\,CO_2}$$

$$\mathrm{Ph\cdot + S{-}H \longrightarrow C_6H_6 + S\cdot}$$

The emission signal corresponding to benzene confirms that it is formed by a free-radical process. As in steady-state EPR experiments, the enhanced emission and absorption are observed only as long as the reaction is proceeding. When the

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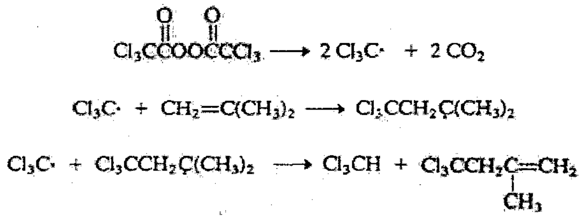
[11] For a discussion of the theory of CIDNP and the conditions under which spin polarization occurs, see G. L. Closs, *Adv. Magn. Reson.* 7, 157 (1974); R. Kaptein, *Adv. Free Radical Chem.* 5, 318 (1975); G. L. Closs, R. J. Miller, and O. D. Redwine, *Acc. Chem. Res.* 18, 196 (1985).

reaction is complete or is stopped in some way, the signals rapidly return to their normal intensity, because the equilibrium population of the two spin states is rapidly reached.

One aspect of both EPR and CIDNP studies that should be kept in mind is that either technique is capable of detecting very small amounts of radical intermediates. This aspect makes both techniques quite sensitive but can also present a pitfall. The most prominant features of either EPR or CIDNP spectra may actually be due to radicals that account for only minor products of the total reaction process. An example of this was found in a CIDNP study of the decomposition of trichloroacetyl peroxide in alkenes:



$$Cl_3C\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}CCl_3 \longrightarrow 2\,Cl_3C\cdot + 2\,CO_2$$

$$Cl_3C\cdot + CH_2{=}C(CH_3)_2 \longrightarrow Cl_3CCH_2\dot{C}(CH_3)_2$$

$$Cl_3C\cdot + Cl_3CCH_2\dot{C}(CH_3)_2 \longrightarrow Cl_3CH + Cl_3CCH_2\underset{CH_3}{\underset{|}{C}}{=}CH_2$$

In addition to the emission signals of $CHCl_3$ and $Cl_3CCH_2C(CH_3){=}CH_2$, which are the major products, a strong emission signal for Cl_3CCHCl_2 was identified. However, this compound is a very minor product of the reaction, and when the signals have returned to their normal intensity, Cl_3CCHCl_2 is present in such a small amount that it cannot be detected.[12]

12.1.4. Sources of Free Radicals

There are several reactions that are quite commonly used as sources of free radicals, both for the study of radical structure and reactivity and also in synthetic processes. Some of the most general methods are outlined here. Examples of many of these will be encountered again when specific reactions are discussed. For the most part, we will defer discussion of the reactions of the radicals until then.

Peroxides are a common source of radical intermediates. An advantage of the generation of radicals from peroxides is that reaction generally occurs at relatively low temperature. The oxygen–oxygen bond in peroxides is weak (~30 kcal/mol), and activation energies for radical formation are low. Diacyl peroxides are sources of alkyl radicals because the carboxyl radicals that are initially formed lose CO_2 very rapidly.[13] In the case of aroyl peroxides, products may be derived from the carboxyl radical or the radical formed by decarboxylation.[14]

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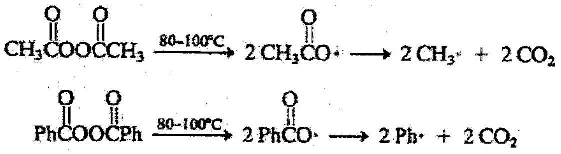
[12] H. Y. Loken, R. G. Lawler, and H. R. Ward, *J. Org. Chem.* **38**, 106 (1973).

[13] J. C. Martin, J. W. Taylor, and E. H. Drew, *J. Am. Chem. Soc.* **89**, 129 (1967); F. D. Greene, H. P. Stein, C.-C. Chu, and F. M. Vane, *J. Am. Chem. Soc.* **86**, 2080 (1964).

[14] D. F. DeTar, R. A. J. Long, J. Rendleman, J. Bradley, and P. Duncan, *J. Am. Chem. Soc.* **89**, 4051 (1967).



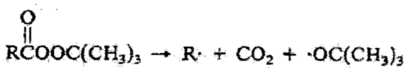
$$CH_3\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{80\text{–}100^\circ C} 2\,CH_3\overset{O}{\overset{\|}{C}}O\cdot \longrightarrow 2\,CH_3\cdot + 2\,CO_2$$

$$Ph\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}Ph \xrightarrow{80\text{–}100^\circ C} 2\,Ph\overset{O}{\overset{\|}{C}}O\cdot \longrightarrow 2\,Ph\cdot + 2\,CO_2$$

Alkyl hydroperoxides give alkoxy radicals and the hydroxyl radical. *t*-Butyl hydroperoxide is often used as a radical source. Detailed studies have been reported on the mechanism of the decomposition, which is a somewhat more complicated process than simple unimolecular decomposition.[15] Dialkyl peroxides decompose to give two alkoxy radicals.[16]

$$C_2H_5OOC_2H_5 \xrightarrow{80^\circ C} 2C_2H_5O\cdot$$

Peroxyesters are also sources of radicals. The acyloxy portion normally loses carbon dioxide, so peroxyesters yield an alkyl (or aryl) and an alkoxy radical.[17]



$$R\overset{O}{\overset{\|}{C}}OOC(CH_3)_3 \rightarrow R\cdot + CO_2 + \cdot OC(CH_3)_3$$

The decomposition of peroxides, which occurs thermally in the examples cited above, can also be readily accomplished by photochemical excitation. The alkyl hydroperoxides are also sometimes used in conjunction with a transition metal ion. Under these conditions, an alkoxy radical is produced, but the hydroxyl portion appears as hydroxide ion as a result of one-electron reduction by the metal ion.[18]

$$(CH_3)_3COOH + M^{2+} \rightarrow (CH_3)_3CO\cdot + {}^-OH + M^{3+}$$

The thermal decompositions described above are unimolecular reactions that should exhibit first-order kinetics. Under many conditions, peroxides decompose at rates faster than expected for unimolecular thermal decomposition, and with more complicated kinetics. This behavior is known as *induced decomposition* and occurs when part of the peroxide decomposition is the result of bimolecular reactions with radicals present in solution, as illustrated specifically for diethyl peroxide:

$$X\cdot + CH_3CH_2OOCH_2CH_3 \rightarrow CH_3\dot{C}HOOCH_2CH_3 + H{-}X$$
$$CH_3\dot{C}HOOCH_2CH_3 \rightarrow CH_3CH{=}O + \cdot OCH_2CH_3$$

The amount of induced decomposition that occurs depends on the concentration and reactivity of the radical intermediates and the susceptibility of the substrate to radical attack. The racial X· may be formed from the peroxide, but it can also be derived from subsequent reactions with the solvent. For this reason, both the structure

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[15] R. Hiatt, T. Mill, and F. R. Mayo, *J. Org. Chem.* 33, 1416 (1968), and accompanying papers.
[16] W. A. Pryor, D. M. Huston, T. R. Fiske, T. L. Pickering, and E. Ciuffarin, *J. Am. Chem. Soc.* 86, 4237 (1964).
[17] P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.* 80, 1398 (1958).
[18] W. H. Richardson, *J. Am. Chem. Soc.* 87, 247 (1965).

of the peroxide and the nature of the reaction medium are important in determining the extent of induced decomposition relative to unimolecular homolysis.

Another quite general source of free radicals is the decomposition of azo compounds. The products are molecular nitrogen and the radicals derived from the substituent groups.

$$R{-}N{=}N{-}R' \xrightarrow[h\nu]{\Delta \text{ or}} R\cdot + N{\equiv}N + \cdot R'$$

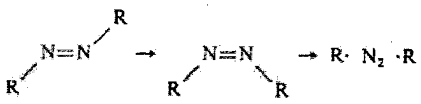
Both symmetrical and unsymmetrical azo compounds can be made so a single radical or two different ones may be generated. The energy for the decomposition can be either thermal or photochemical.[19] In the thermal decomposition, it has been established that the temperature at which decomposition occurs depends on the nature of the substituent groups. Azomethane does not decompose to methyl radicals and nitrogen until temperatures above 400°C are reached. Azo compounds that generate relatively stable radicals decompose at much lower temperatures. Azo compounds derived from allyl groups decompose somewhat above 100°C, for example:

$$CH_3CH_2CH_2N{=}NCH_2CH{=}CH_2 \xrightarrow{130°C} CH_3CH_2CH_2\cdot + N_2 + CH_2{=}CHCH_2\cdot \qquad \text{Ref. 20}$$

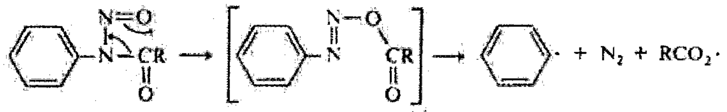
Unsymmetrical azo compounds must be used to generate phenyl radicals because azobenzene is very stable thermally. Phenylazotriphenylmethane decomposes readily because of the stability of the triphenylmethyl radical.

$$PhN{=}NC(Ph)_3 \xrightarrow{60°C} Ph\cdot + Ph_3C\cdot + N_2 \qquad \text{Ref. 21}$$

Many azo compounds also generate radicals when photolyzed. This can occur by a thermal decomposition of the *cis* azo compounds that are formed in the photochemical step.[22] The *cis* isomers are thermally much more labile than the *trans* isomers.



N-Nitrosoanilides are an alternative source of aryl radicals. There is a close mechanistic relationship between this route and the decomposition of azo compounds. The *N*-nitrosoanilides rearrange to an intermediate with a nitrogen-nitrogen double bond. This intermediate then decomposes to generate aryl radicals.[23]



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[19] P. S. Engel, *Chem. Rev.* **80**, 99 (1980).
[20] K. Takagi and R. J. Crawford, *J. Am. Chem. Soc.* **93**, 5910 (1971).
[21] R. F. Bridger and G. A. Russell, *J. Am. Chem. Soc.* **85**, 3754 (1963).
[22] M. Schmittel and C. Rüchardt, *J. Am. Chem. Soc.* **109**, 2750 (1987).
[23] C. Rüchardt and B. Freudenberg, *Tetrahedron Lett.*, 3623 (1964); J. I. G. Cadogan, *Acc. Chem. Res.* **4**, 186 (1971).

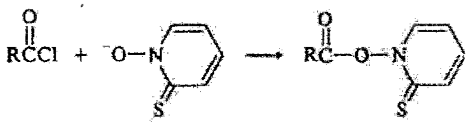
A technique that is a convenient source of radicals for study by EPR involves photolysis of a mixture of di-*t*-butyl peroxide, triethylsilane, and the alkyl bromide corresponding to the radical to be studied.[24] Photolysis of the peroxide gives *t*-butoxy radicals, which selectively abstract hydrogen from the silane. This reactive silicon radical in turn abstracts bromine, generating the alkyl radical at a steady-state concentration suitable for EPR study.

$$(CH_3)_3COOC(CH_3)_3 \xrightarrow{h\nu} 2\,(CH_3)_3CO\cdot$$

$$(CH_3)_3CO\cdot + (C_2H_5)_3SiH \longrightarrow (CH_3)_3COH + (C_2H_5)_3Si\cdot$$

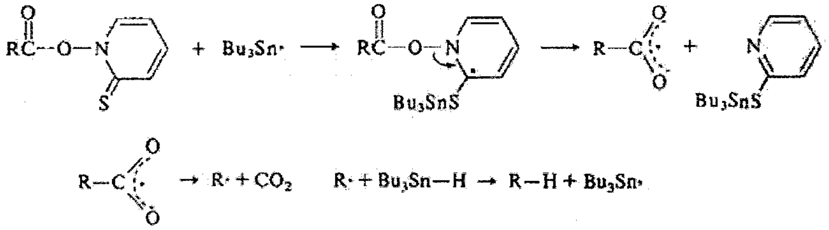
$$(C_2H_5)_3Si\cdot + RBr \longrightarrow (C_2H_5)_3SiBr + R\cdot$$

The acyl derivatives of *N*-hyroxypyridine-2-thione are a synthetically versatile source of free radicals.[25] These compounds are readily prepared from reactive acylating agents, such as acid chlorides, and a salt of the *N*-hydroxypyridine-2-thione.



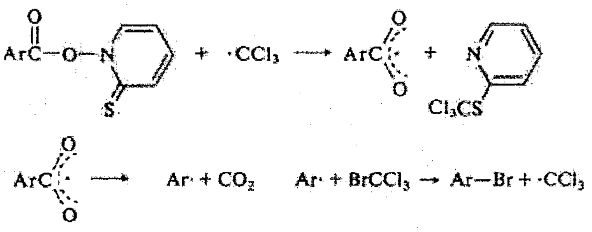
Radicals react at the sulfur, and decomposition generating an acyloxy radical ensues. The acyloxy radical undergoes decarboxylation. Usually, the radical then gives product and another radical, which can continue a chain reaction. The process can be illustrated by the reactions with tri-*n*-butylstannane and bromotrichloromethane.

(a) Reductive decarboxylation by reaction with tri-n-butylstannane



Ref. 26

(b) Conversion of aromatic carboxylic acid to aryl bromide by reaction with bromotrichloromethane



Ref. 27

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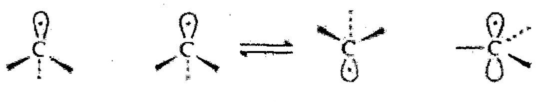
24. A. Hudson and R. A. Jackson, *J. Chem. Soc., Chem. Commun.*, 1323 (1969); D. J. Edge and J. K. Kochi, *J. Am. Chem. Soc.* 94, 7695 (1972).
25. D. H. R. Barton, D. Crich, and W. B. Motherwell, *Tetrahedron* 41, 3901 (1985).
26. D. H. R. Barton, D. Crich, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 939 (1983).
27. D. H. R. Barton, B. Lacher, and S. Z. Zard, *Tetrahedron Lett.* 26, 5939 (1985).

12.1.5. Structural and Stereochemical Properties of Radical Intermediates

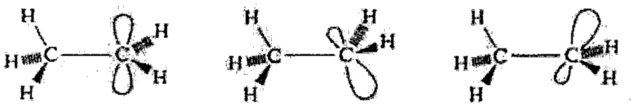
EPR studies and other physical methods have provided the basis for some insight into the detailed geometry of radical species.[28] Deductions about structure can also be drawn from the study of the stereochemistry of reactions involving radical intermediates. Several structural possibilities must be considered. If discussion is limited to alkyl radicals, the possibilities include a rigid pyramidal structure, rapidly inverting pyramidal structures, or a planar structure.



rigid pyramidal flexible pyramidal planar

Precise description of the pyramidal structures would also require that the bond angles be specified. The EPR spectrum of the methyl radical leads to the conclusion that its structure could be either planar or a very shallow pyramid.[29] The IR spectrum of methyl radical has been recorded at very low temperatures in frozen argon.[30] The IR spectrum puts a maximum of ~5° on the deviation from planarity.

The *t*-butyl radical has been studied extensively. While experimental results have been interpreted in terms of both planar and slightly pyramidal structures, theoretical calculations favor a pyramidal structure.[31] It appears that simple alkyl radicals are generally pyramidal, although the barrier to inversion is very small. *Ab initio* molecular orbital calculations suggest that two factors are of principal importance in favoring a pyramidal structure. One is a torsional effect in which the radical center tends to adopt a staggered conformation of the radical substituents. There is also a hyperconjugative interaction between the half-filled orbital and the hydrogen that is aligned with it. This hyperconjugation is stronger in the conformation in which the pyramidalization is such as to minimize eclipsing.[32] The theoretical results also indicate that the barrier to inversion is no more than 1–2 kcal/mol, so rapid inversion will occur.



planar preferred pyramidalization less stable pyramidalization

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[28] For a review, see J. K. Kochi, *Adv. Free Radicals Chem.* 5, 189 (1975).

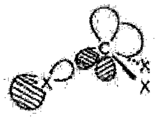
[29] M. Karplus and G. K. Fraenkel, *J. Chem. Phys.* 35, 1312 (1961).

[30] L. Andrews and G. C. Pimentel, *J. Chem. Phys.* 47, 3637 (1967).

[31] L. Bonazolla, N. Leroy, and J. Roncin, *J. Am. Chem. Soc.* 99, 8348 (1977); D. Griller, K. U. Ingold, P. J. Krusic, and H. Fischer, *J. Am. Chem. Soc.* 100, 6750 (1978); J. Pacansky and J. S. Chang, *J. Phys. Chem.* 74, 5539 (1978); B. Schrader, J. Pacansky, and U. Pfeiffer, *J. Phys. Chem.* 88, 4069 (1984).

[32] M. N. Paddon-Row and K. N. Houk, *J. Am. Chem. Soc.* 103, 5046 (1981); M. N. Paddon-Row and K. N. Houk, *J. Phys. Chem.* 89, 3771 (1985).

Radical geometry is significantly affected by substituent groups that can act as π donors. Addition of fluorine or oxygen substituents, in particular, favors a pyramidal structure. Analysis of the EPR spectra of the mono-, di-, and trifluoromethyl radicals indicates a progressive distortion from planarity.[33] Both EPR and IR studies of the trifluoromethyl radical show it to be pyramidal.[34] The basis of this structural effect has been probed by molecular orbital calculations and is considered to result from interactions of both the σ and the π type. There is a repulsive interaction between the singly occupied p orbital and the filled orbitals occupied by "lone pair" electrons on the fluorine or oxygen substituents. This repulsive interaction is minimized by adoption of a pyramidal geometry. The tendency for pyramidal geometry is reinforced by an interaction between the p orbital on carbon and the σ^* antibonding orbitals associated with the C—F or C—O bonds. The energy of the p orbital can be lowered by interaction with the σ^* orbital. This interaction increases electron density on the more electronegative fluorine or oxygen atom. This stabilizing p-σ^* interaction is increased with pyramidal geometry.



stabilizing interaction with σ^*

There have been many studies aimed at deducing the geometry of radical sites by examining the stereochemistry of radical reactions. The most direct kind of study involves the generation of a radical at a carbon that is a chiral center. A planar or rapidly inverting radical would lead to racemization, whereas a rigid pyramidal structure should lead to product of retained configuration. Some examples of reactions that have been subjected to this kind of study are shown in Scheme 12.2. In each case, racemic product is formed, indicating that alkyl radicals do not retain the tetrahedral geometry of their precursors.

Cyclic molecules also permit deductions about stereochemistry without the necessity of using resolved chiral compounds. The stereochemistry of a number of reactions of 4-substituted cyclohexyl radicals has been investigated.[35] In general, reactions starting from pure *cis* or *trans* stereoisomers give mixtures of *cis* and *trans* products. This result indicates that the radical intermediates do not retain the stereochemistry of the precursor. Radical reactions involving cyclohexyl radicals are not usually very stereoselective, but some show a preference for formation of the *cis* product. This has been explained in terms of a torsional effect. If the cyclohexyl radical is planar or a shallow pyramid, equatorial attack leading to *trans* product causes the hydrogen at the radical site to become eclipsed with the two

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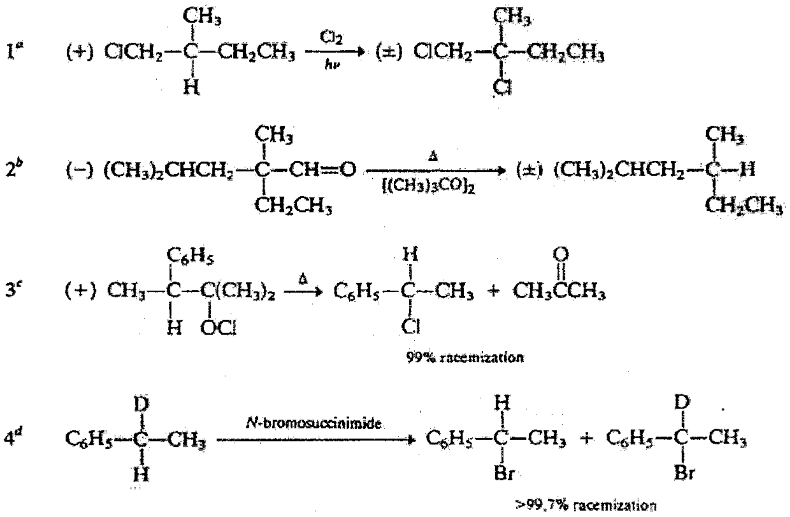
[33] P. J. Krusic and R. C. Bingham, *J. Am. Chem. Soc.* **98**, 230 (1976); F. Bernardi, W. Cherry, S. Shaik, and N. D. Epiotis, *J. Am. Chem. Soc.* **100**, 1352 (1978).

[34] R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.* **43**, 2704 (1965); G. A. Carlson and G. C. Pimentel, *J. Chem. Phys.* **44**, 4053 (1966).

[35] F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Am. Chem. Soc.* **90**, 5793 (1968).

Scheme 12.2. Stereochemistry of Radical Reactions at Chiral Carbon Atoms



$$\text{(+) } ClCH_2-C(CH_3)(H)-CH_2CH_3 \xrightarrow[h\nu]{Cl_2} (\pm)\ ClCH_2-C(CH_3)(Cl)-CH_2CH_3$$

$$(-)\ (CH_3)_2CHCH_2-C(CH_3)(CH_2CH_3)-CH{=}O \xrightarrow[[(CH_3)_3CO]_2]{\Delta} (\pm)\ (CH_3)_2CHCH_2-C(CH_3)(CH_2CH_3)-H$$

$$(+)\ CH_3-C(C_6H_5)(H)-C(CH_3)_2(OCl) \xrightarrow{\Delta} C_6H_5-C(H)(Cl)-CH_3 + CH_3\overset{O}{\overset{\|}{C}}CH_3$$

$$C_6H_5-C(D)(H)-CH_3 \xrightarrow{N\text{-bromosuccinimide}} C_6H_5-C(H)(Br)-CH_3 + C_6H_5-C(D)(Br)-CH_3$$

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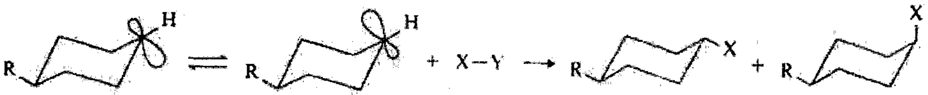
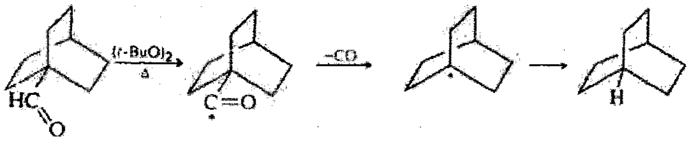
a. H. C. Brown, M. S. Kharasch, and T. H. Chao, *J. Am. Chem. Soc.* **62**, 3435 (1940).
b. W. von E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *J. Am. Chem. Soc.* 74, 3000 (1952).
c. F. D. Greene, *J. Am. Chem. Soc.* **81**, 2688 (1959); D. B. Denney and W. F. Beach, *J. Org. Chem.* **24**, 108 (1959).
d. H. J. Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.* **81**, 5404 (1959).

neighboring equatorial hydrogens. Axial attack does not suffer from this strain, since the hydrogen at the radical site moves away from the equatorial hydrogens toward the staggered conformation that is present in the chair conformation of the ring. The pyramidalization of the radical would be expected to be in the direction favoring axial attack.



Another approach to obtaining information about the geometric requirements of free radicals has been to examine bridgehead systems. It will be recalled that small bicyclic rings strongly resist formation of carbocations at bridgehead centers because the skeletal geometry prevents attainment of the preferred planar geometry by the carbocation. In an early study, the decarbonylation of bridgehead aldehydes by a free-radical reaction was found to proceed without difficulty[36]:



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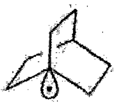
[36] W. v. E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *J. Am. Chem. Soc.* 74, 3000 (1952).

Subsequent rate studies have shown that there is significant rate retardation for reactions in which the norbornyl radical is generated in a rate-determining step.[37] Typically, such reactions proceed 500 to 1000 times slower than the corresponding reaction generating the *t*-butyl radical. This is a much smaller rate retardation than that of 10^{14} found in S_N1 solvolysis. Rate retardation is smaller for less strained bicyclic systems. The EPR spectra of the bridgehead radicals **A** and **B** are consistent with pyramidal geometry at the bridgehead carbon atoms.[38]

A

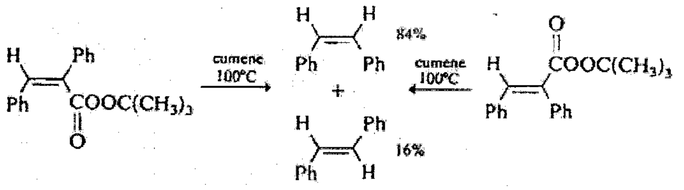


B

The general conclusion of all these studies is that alkyl radicals are shallow pyramids, and the barrier to inversion of the pyramidal structures is low. Radicals also are able to tolerate some geometric distortion associated with strained ring systems.

The allyl radical would be expected to be planar in order to maximize delocalization. Molecular structure parameters have been obtained from EPR, IR, and electron diffraction measurements and confirm that the radical is planar.[39]

There has also been study of the structure of vinyl free radicals.[40] Stereochemical results indicate that radicals formed at trigonal centers rapidly undergo interconversion with the geometric isomer. As a result, reactions proceeding through vinyl radical intermediates usually give rise to the same mixture from both the *cis* and *trans* precursors.



Ref. 41

In this particular case, there is evidence from EPR spectra that the radical is not linear in its ground state, but is an easily inverted bent species.[42] The barrier to

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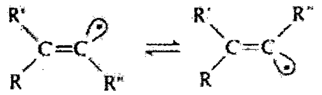
37. A. Oberlinner and C. Rüchardt, *Tetrahedron Lett.*, 4685 (1969); L. B. Humphrey, B. Hodgson, and R. E. Pincock, *Can. J. Chem.* **46**, 3099 (1968); D. E. Applequist and L. Kaplan, *J. Am. Chem. Soc.* **87**, 2194 (1965).
38. P. J. Krusic, T. A. Rettig, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **94**, 995 (1972).
39. R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.* **39**, 2147 (1963); A. K. Maltsev, V. A. Korolev, and O. M. Nefedov, *Izd. Akad. Nauk SSSR, Ser. Khim.*, 555 (1984); E. Vajda, J. Tremmel, B. Rozandai, I. Hargittai, A. K. Maltsev, N. D. Kagrammanov, and O. M. Nefedov, *J. Am. Chem. Soc.* **108**, 4352 (1986).
40. For reviews of the structure and reactivity of vinyl radicals, see W. G. Bentrude, *Annu. Rev. Phys. Chem.* **18**, 283 (1967); L. A. Singer, in *Selective Organic Transformations*, Vol II, B. S. Thyagarajan (ed.), John Wiley, New York, 1972, p. 239; O. Simamura, *Top. Stereochem.* **4**, 1 (1969).
41. L. A. Singer and N. P. Kong, *J. Am. Chem. Soc.* **88**, 5213 (1966); J. A. Kampmeier and R. M. Fantazier, *J. Am. Chem. Soc.* **88**, 1959 (1966).
42. R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.* **39**, 2147 (1963).

Table 12.1. Oxidation and Reduction Potentials for Some Aromatic Hydrocarbons[a]

Hydrocarbon	$\text{Ar—H} \xrightarrow{+e^-} \text{Ar—H}^{\cdot-}$	$\text{Ar—H} \xrightarrow{-e^-} \text{Ar—H}^{\cdot+}$
Benzene	−3.42[b]	+2.06
Naphthalene	−2.95	+1.33
Anthracene	−2.36	+0.89
Phenanthrene	−2.87	+1.34
Tetracene	−1.92	+0.57

a. Except where noted otherwise, the data are from C. Madec and J. Courtot-Coupez, *J. Electroanal. Chem. Interfacial Electrochem.* 84, 177 (1977).
b. J. Mortensen and J. Heinze, *Angew. Chem. Int. Ed. Engl.* 23, 84 (1984).

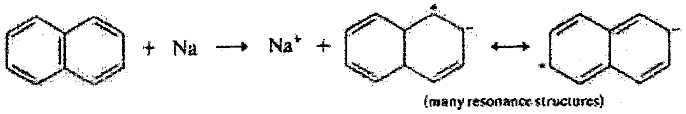
inversion is very low (~2 kcal), so that the lifetime of the individual isomers is very short (~10^{-9} s).



12.1.6. Charged Radical Species

Unpaired electrons can be present in charged species as well as in the neutral systems that have been considered up to this point. There have been many studies of such radical cations and radical anions, and we will consider some representative examples in this section.

Various aromatic and conjugated polyunsaturated hydrocarbons undergo one-electron reduction by alkali metals.[43] Benzene and naphthalene are examples. The EPR spectrum of the benzene radical anion was shown in Fig. 12.2a (p. 657). These reductions must be carried out in aprotic solvents, and ethers are usually used. The ease of formation of the radical anion increases as the number of fused rings increases. The electrochemical reduction potentials of some representitive compounds are given in Table 12.1. The potentials correlate with the energy of the LUMO as calculated by simple Hückel MO theory.[44] A correlation that includes a more extensive series of compounds can be observed with the use of somewhat more sophisticated molecular orbital methods.[45]



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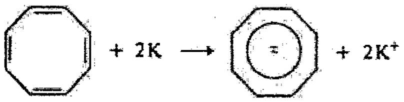
[43] D. E. Paul, D. Lipkin, and S. I. Weissman, *J. Am. Chem. Soc.* **78**, 116 (1956); T. R. Tuttle, Jr., and S. I. Weissman, *J. Am. Chem. Soc.* **80**, 5342 (1958).

[44] E. S. Pysh amd N. C. Yang, *J. Am. Chem. Soc.* **85**, 2124 (1963); D. Bauer and J. P. Beck, *Bull. Soc. Chim. Fr.*, 1252 (1973); C. Madec and J. Courtot-Coupez, *J. Electroanal. Chem. Interfacial Electrochem.* **84**, 177 (1977).

[45] C. F. Wilcox, Jr., K. A. Weber, H. D. Abruna, and C. R. Cabrera, *J. Electroanal. Chem. Interfacial Electrochem.* **198**, 99 (1986).

In the presence of a proton source, the radical anion is protonated and further reduction occurs (the Birch reduction, Part B, Section 5.5). In general, when no proton source is present, it is relatively difficult to add a second electron. Solutions of the radical anions of aromatic hydrocarbons can be maintained for relatively long periods in the absence of oxygen or protons.

Cyclooctatetraene provides a significant contrast to the usual preference of aromatic hydrocarbons for one-electron reduction. It is converted to a diamagnetic dianion by addition of two electrons.[46] It is easy to understand the ease with which the cyclooctatetraene radical accepts a second electron because of the aromaticity of the 10-π-electron system that results.



Radical cations can be derived from aromatic hydrocarbons or alkenes by one-electron oxidation. Antimony trichloride and pentachloride are among the chemical oxidants that have been used.[47] Photodissociation and γ radiation also generate radical cations from aromatic hydrocarbons.[48] Most radical cations derived from hydrocarbons have limited stability, but EPR spectral parameters have permitted structural characterization.[49] The radical cations can be generated electrochemically, and the oxidation potentials are included in Table 12.1. The potentials correlate with the HOMO levels of the hydrocarbons. The higher the HOMO, the more easily oxidized is the hydrocarbon.

Two classes of charged radicals derived from ketones have been well studied. *Ketyls* are radical anions formed by one-electron reduction of carbonyl compounds. The formation of the benzophenone radical anion by reduction with sodium metal is an example. This radical anion is deep blue in color and is very reactive toward both oxygen and protons. Many detailed studies on the structure and spectral properties of this and related radical anions have been carried out.[50] A common chemical reaction of the ketyl radicals is coupling to form a diamagnetic dianion. This occurs reversibly for simple aromatic ketyls. The dimerization is promoted by protonation of one or both of the ketyls since the electrostatic repulsion is then removed. The coupling process leads to reductive dimerization of carbonyl com-

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[46] T. J. Katz, *J. Am. Chem. Soc.* **82**, 3784 (1960).

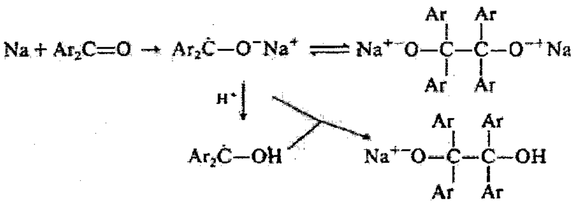
[47] I. C. Lewis and L. S. Singer, *J. Chem. Phys.* **43**, 2712 (1965); R. M. Dessau, *J. Am. Chem. Soc.* **92**, 6356 (1970).

[48] R. Gschwind and E. Haselbach, *Helv. Chim. Acta* **62**, 941 (1979); T. Shida, E. Haselbach, and T. Bally, *Acc. Chem. Res.* **17**, 180 (1984); M. C. R. Symons, *Chem. Soc. Rev.* **13**, 393 (1984).

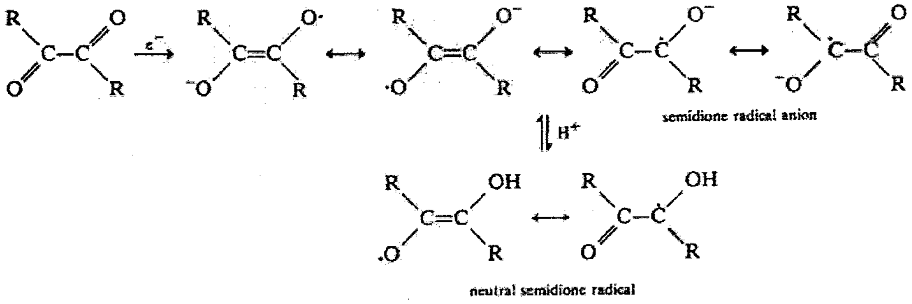
[49] J. L. Courtneidge and A. G. Davies, *Acc. Chem. Res.* **20**, 90 (1987).

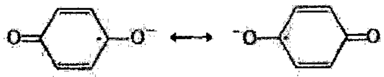
[50] For a summary, see N. Hirota, in *Radical Ions*, E. T. Kaiser and L. Kevan (eds.), Interscience, New York, 1968, pp. 35–85.

pounds, a reaction that will be discussed in detail in Part B, Section 5.5.



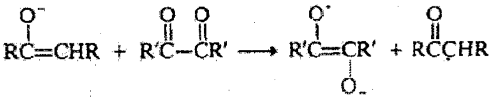
One-electron reduction of α-dicarbonyl compounds gives radical anions known as *semidiones*.[51] Closely related are the one-electron reduction products of aromatic quinones, the *semiquinones*. Both the semidiones and the semiquinones can be protonated to give neutral radicals which are relatively stable.





semiquinone radical anion

Reductants such as zinc or sodium dithionite generate the semidione from diketones. Electrolytic reduction can also be used. Enolates can reduce diones to semidiones by electron transfer:



$$R\overset{O^-}{\overset{|}{C}}{=}CHR + R'\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}R' \longrightarrow R'\overset{O^\cdot}{\overset{|}{C}}{=}\underset{\underset{O^-}{|}}{C}R' + R\overset{O}{\overset{\|}{C}}\dot{C}HR$$

The radicals formed from the enolate in this process are rapidly destroyed so that only the stable semidione species remains detectable for EPR study.

Semidiones can also be generated oxidatively from ketones by reaction with oxygen in the presence of base[52].

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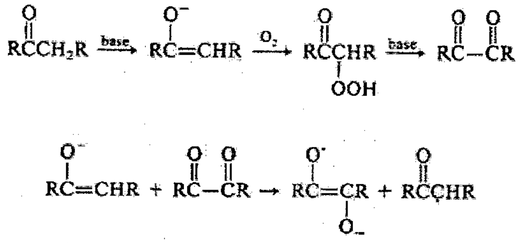
[51] G. A. Russell, in *Radical Ions*, E. T. Kaiser and L. Kevan (eds.), Interscience, New York, 1968, pp. 87–150.

[52] G. A. Russell and E. T. Strom, *J. Am. Chem. Soc.* 86, 744 (1964).



$$\mathrm{R\overset{O}{\overset{\|}{C}}CH_2R \xrightarrow{base} R\overset{O^-}{\overset{|}{C}}{=}CHR \xrightarrow{O_2} R\overset{O}{\overset{\|}{C}}\underset{\underset{OOH}{|}}{C}HR \xrightarrow{base} R\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}R}$$

$$\mathrm{R\overset{O^-}{\overset{|}{C}}{=}CHR + R\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}R \rightarrow R\overset{O^\cdot}{\overset{|}{C}}{=}\underset{\underset{O^-}{|}}{C}R + R\overset{O}{\overset{\|}{C}}\dot{C}HR}$$

The diketone is presumably generated oxidatively and then reduced to the semidione via reduction by the enolate derived from the original ketone.

The EPR spectra of semidione radical anions can provide information on the spin density at the individual atoms. The semidione derived from 2,3-butane dione, for example, has a spin density of 0.22 at each oxygen and 0.23 at each carbonyl carbon. The small amount of remaining spin density is associated with the methyl groups. This extensive delocalization is consistent with the resonance picture of the semidione radical anion.

12.2. Characteristics of Reaction Mechanisms Involving Radical Intermediates

12.2.1. Kinetic Characteristics of Chain Reactions

Certain aspects of free-radical reactions are unique in comparison with other reaction types that have been considered to this point. The underlying difference is that many free-radical reactions are chain reactions; that is, the reaction mechanism consists of a cycle of repetitive steps which form many product molecules for each initiation event. The hypothetical mechanism below illustrates a typical chain reaction.

$$\begin{array}{llcll}
 & \mathrm{A{-}A} & \xrightarrow{k_i} & \mathrm{2A\cdot} & \text{initiation} \\
\text{repeated} & \left\{\begin{array}{l}\mathrm{A\cdot + B{-}C} \\ \mathrm{C\cdot + A{-}A} \\ \mathrm{A\cdot + B{-}C} \\ \mathrm{C\cdot + A{-}A}\end{array}\right. & \begin{array}{c}\xrightarrow{k_{p1}} \\ \xrightarrow{k_{p2}} \\ \xrightarrow{k_{p1}} \\ \xrightarrow{k_{p2}}\end{array} & \left.\begin{array}{l}\mathrm{A{-}B + C\cdot} \\ \mathrm{A{-}C + A\cdot} \\ \mathrm{A{-}B + C\cdot} \\ \mathrm{A{-}C + A\cdot}\end{array}\right\} & \text{propagation} \\
\text{many times} & & & & \\
 & \begin{array}{l}\mathrm{2A\cdot} \\ \mathrm{2C\cdot} \\ \mathrm{A\cdot + C\cdot}\end{array} & \begin{array}{c}\xrightarrow{k_{t1}} \\ \xrightarrow{k_{t2}} \\ \xrightarrow{k_{t3}}\end{array} & \left.\begin{array}{l}\mathrm{A{-}A} \\ \mathrm{C{-}C} \\ \mathrm{A{-}C}\end{array}\right\} & \text{termination} \\
\text{overall reaction} & \mathrm{A{-}A + B{-}C} & \longrightarrow & \mathrm{A{-}B + A{-}C} &
\end{array}$$

The step in which the reactive intermediate, in this case A·, is generated is called the *initiation step.* In the next four equations in the example, a sequence of two reactions is repeated; this is the *propagation phase.* Chain reactions are characterized by a *chain length,* which is the number of propagation steps that take place per initiation step. Finally, there are *termination steps.* These include any reactions that destroy one of the reactive intermediates necessary for the propagation of the chain. Clearly, the greater the frequency of termination steps, the lower the chain length will be.

The overall rate of a chain process is determined by the rates of initiation, propagation, and termination reactions. Analysis of the kinetics of chain reactions normally depends on application of the steady-state approximation to the radical intermediates. Such intermediates are highly reactive, and their concentrations are low and nearly constant throughout the course of the reaction:

$$\frac{d[\mathrm{A}\cdot]}{dt}=\frac{d[\mathrm{C}\cdot]}{dt}=0$$

The result of the steady-state condition is that the overall rate of initiation must equal the total rate of termination. The application of the steady-state approximation and the resulting equality of the initiation and termination rates permits formulation of a rate law for the reaction mechanism above. The overall stoichiometry of a free-radical chain reaction is independent of the initiating and termination steps because the reactants are consumed and products formed almost entirely in the propagation steps.

$$\mathrm{A_2 + B{-}C \rightarrow A{-}B + A{-}C}$$

The overall reaction rate is given by

$$\text{rate}=\frac{d[\mathrm{A{-}B}]}{dt}=\frac{d[\mathrm{A{-}C}]}{dt}=\frac{-d[\mathrm{A_2}]}{dt}=\frac{-d[\mathrm{B{-}C}]}{dt}$$

Setting the rate of initiation equal to the rate of termination and assuming that k_{t2} is the dominant termination process gives

$$k_i[\mathrm{A_2}]=2k_{t2}[\mathrm{C}\cdot]^2$$

$$[\mathrm{C}\cdot]=\left(\frac{k_i}{2k_{t2}}\right)^{1/2}[\mathrm{A_2}]^{1/2}$$

In general, the rate constants for termination reactions involving coupling of two radicals are very large. Since the concentration of the reactive intermediates is very low, however, the overall rate of termination is low enough that the propagation steps can compete since these steps involve the reactants, which are present at much higher concentration. The rate of the overall reaction is that of either propagation step:

$$\text{rate}=k_{p2}[\mathrm{C}\cdot][\mathrm{A_2}]$$

Both propagation steps must proceed at the same rate or the concentration of A· or C· would build up. By substituting for the concentration of the intermediate C·, we obtain:

$$\text{rate}=k_{p2}\left(\frac{k_i}{2k_t}\right)_2^{1/2}[\mathrm{A_2}]^{3/2}=k_{obs}[\mathrm{A_2}]^{3/2}$$

The observed rate law is then three-halves order in the reagent A_2.

In most real systems, the situation would be complicated by the possibility that more than one termination reaction makes a contribution to the total termination rate. A more complete discussion of the effect of termination steps on the form of the rate law has been given by Huyser.[53]

The overall rates of chain reactions can be greatly modified by changing the rate at which initiation or termination steps occur. The idea of initiation has been touched on in Section 12.1.4, where sources of free radicals were discussed. Many chain reactions of interest in organic chemistry depend on the presence of an *initiator*, which is a source of free radicals to start chain sequences. Peroxides are frequently used as initiators, since they give radicals by thermal decomposition at relatively low temperatures. Azo compounds are another very useful class of initiators, with azoisobutyronitrile, AIBN, being the most commonly used compound. Initiation by irradiation of a photosensitive compound that generates radical products is also a common procedure. Conversely, chain reactions can be greatly retarded by *inhibitors*. A compound can act as an inhibitor if it is sufficiently reactive toward a radical involved in the chain process that it effectively traps the radical, thus terminating the chain. The sensitivity of the rates of free-radical chain reactions to both initiators and inhibitors can be used in mechanistic studies to distinguish radical chain reactions from polar or concerted processes. Certain stable free radicals, for example, galvinoxyl (see entry 6, Scheme 12.1), are used in this way. Since they contain an unpaired electron, they are usually very reactive toward radical intermediates.

Free-radical chain inhibitors are of considerable economic importance. The term *antioxidant* is commonly applied to inhibitors that retard the free-radical chain oxidations that can cause relatively rapid deterioration of many commercial materials derived from organic molecules, including foodstuffs, petroleum products, and many plastics. The chain mechanism for autoxidation of hydrocarbons is

$$\begin{array}{ll} \text{initiation} & \mathrm{In\cdot + R{-}H \rightarrow R\cdot + In{-}H} \\ \text{propagation} & \mathrm{R\cdot + O_2 \rightarrow ROO\cdot} \\ & \mathrm{ROO\cdot + R{-}H \rightarrow ROOH + R\cdot} \end{array}$$

The function of an antioxidant is to divert the peroxy radicals and thus prevent a chain process. Other antioxidants function by reacting with potential initiators and thus retard oxidative degradation by preventing the initiation of autoxidation chains. The hydroperoxides generated by autoxidation are themselves potential chain initiators, and autoxidations therefore have the potential of being autocatalytic. Certain antioxidants function by reducing such hydroperoxides and thereby preventing their accumulation. Other antioxidants function by diverting intermediates in the chain process. They function in the same way as free-radical inhibitors. Such antioxidants are frequently called *free-radical scavengers*.

Molecular oxygen is an important participant in chain oxidative degradation. The oxygen molecule, with its two unpaired electrons, is extremely reactive toward most free-radical intermediates. The product that is formed is a reactive peroxyl

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[53] E. S. Huyser, *Free Radical Chain Reactions*, Wiley-Interscience, New York, 1970, pp. 39–54.

radical, which can propagate a chain reaction.

$$R\cdot + O_2 \rightarrow R{-}O{-}O\cdot$$

The presence of oxygen frequently can modify the course of a free-radical chain reaction. This occurs if a radical intermediate is diverted by reaction with molecular oxygen.

12.2.2. Structure–Reactivity Relationships

Structure–reactivity relationships can be probed by measurements of rates and equilibria, as was discussed in Chapter 4. Direct kinetic measurements have been used relatively less often in the study of radical reactions than for heterolytic reactions. Instead, *competition methods* have frequently been used. The basis of competition methods lies in the rate expression for a reaction, and the results obtained can be just as valid a basis for comparison of relative reactivity as directly measured rates, *provided the two competing processes are of the same kinetic order.* Suppose it is desired to compare the reactivity of two related compounds, B—X and B—Y, in a hypothetical sequence:

$$A{-}A \longrightarrow 2A\cdot$$

$$A\cdot + B{-}X \xrightarrow{k_X} A{-}B + X\cdot$$

$$X\cdot + A{-}A \rightarrow A{-}X + A\cdot$$

and

$$A\cdot + B{-}Y \xrightarrow{k_Y} A{-}B + Y\cdot$$

$$Y\cdot + A{-}A \rightarrow A{-}Y + A\cdot$$

The data required are the relative magnitudes of k_X and k_Y. When both B—X and B—Y are present in the reaction system, they will be consumed at rates that are a function of their reactivity and concentration:

$$\frac{-d[B{-}X]}{dt} = k_X[A\cdot][B{-}X]$$

$$\frac{-d[B{-}Y]}{dt} = k_Y[A\cdot][B{-}Y]$$

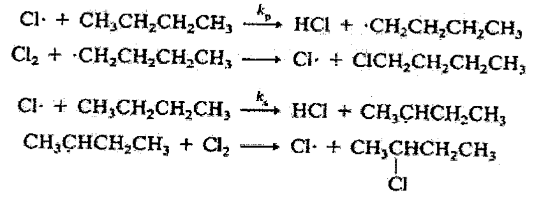
$$\frac{k_X}{k_Y} = \frac{d[B{-}X]/[B{-}X]}{d[B{-}Y]/[B{-}Y]}$$

Integration of this expression with the limits $[B{-}X] = [B{-}X]_{in}$ to $[B{-}X]_t$, where t is a point in time during the course of the reaction, gives

$$\frac{k_X}{k_Y} = \frac{\ln([B{-}X]_{in}/[B{-}X]_t)}{\ln([B{-}Y]_{in}/[B{-}Y]_t)}$$

This relationship permits the measurement of the ratio k_X/k_Y. The initial concentrations $[B{-}X]_{in}$ and $[B{-}Y]_{in}$ are known from the conditions of the experiment. The reaction can be stopped at some point when some of both B—X and B—Y remain unreacted, or an excess of B—X and B—Y can be used so that neither is completely consumed when A—A has completely reacted. Determination of $[B{-}X]_t$ and $[B{-}Y]_t$ then provides the information needed to calculate k_X/k_Y. Is it clear why the reactions being compared must be of the same order? If they were not, division of the two rate expressions would leave uncanceled concentration terms.

Another experiment that can be considered to be of the competition type involves the comparison of the reactivity of different atoms in the same molecule. For example, gas phase chlorination of butane can lead to 1- or 2-chlorobutane. The relative reactivity (k_p/k_s) of the primary and secondary hydrogens is the sort of information that helps to characterize the details of the reaction process.



$$Cl\cdot + CH_3CH_2CH_2CH_3 \xrightarrow{k_p} HCl + \cdot CH_2CH_2CH_2CH_3$$
$$Cl_2 + \cdot CH_2CH_2CH_2CH_3 \longrightarrow Cl\cdot + ClCH_2CH_2CH_2CH_3$$
$$Cl\cdot + CH_3CH_2CH_2CH_3 \xrightarrow{k_s} HCl + CH_3\dot{C}HCH_2CH_3$$
$$CH_3\dot{C}HCH_2CH_3 + Cl_2 \longrightarrow Cl\cdot + CH_3\underset{Cl}{\underset{|}{C}}HCH_2CH_3$$

The value of k_p/k_s can be determined by measuring the ratio of the products, 1-chlorobutane:2-chlorobutane, during the course of the reaction. A statistical correction must be made to take account of the fact that the primary hydrogens outnumber the secondary ones by 3:2. This calculation provides the relative reactivity of chlorine atoms toward the primary and secondary hydrogens in butane.

$$\frac{k_p}{k_s} = \frac{2[\text{1-chlorobutane}]_t}{3[\text{2-chlorobutane}]_t}$$

Recent developments of techniques for measuring the rates of very fast reactions have permitted absolute rates to be measured for some fundamental types of free-radical reactions. Some examples where absolute rates and E_a values are available are given in Table 12.2.

The strength of the bond to the reacting hydrogen is a major determinant of the rate at which hydrogen atom abstraction occurs. It is for this reason that trisubstituted stannanes are among the most useful reagents as hydrogen atom donors. As indicated by entries 6–8 in Table 12.2, hydrogen abstractions from stannanes proceed with rates greater than $10^6\ M^{-1}\,s^{-1}$ and have very low activation energies. This high reactivity correlates with the low bond strength of the Sn—H bond (74 kcal/mol, Table 12.4, p. 683). For comparison, entries 1–3 give the rates of hydrogen abstraction from two of the more reactive C-H hydrogen atom donors, tetrahydrofuran and isopropylbenzene. For the directly comparable reactions with the phenyl radical (entries 1 and 8), tri-*n*-butylstannane is about 100 times more reactive than tetrahydrofuran as a hydrogen atom donor.

Table 12.2. Absolute Rates of Some Free-Radical Reactions[a]

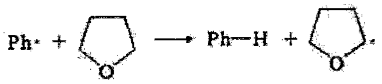
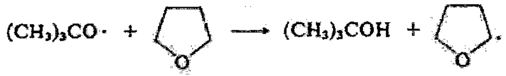
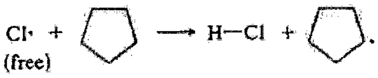
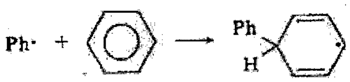
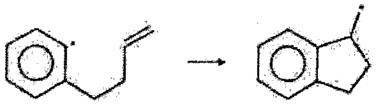
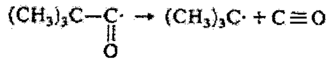
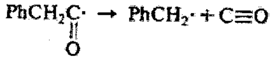
	Reaction		Ref.
A.	Hydrogen atom abstraction		
1		$k = 4.8 \times 10^6 M^{-1} s^{-1}$	b
2		$k = 8.7 \times 10^5 M^{-1} s^{-1}$	c
3		$k = 8.3 \times 10^6 M^{-1} s^{-1}$	c
4	 (free)	$k = 4.7 \times 10^9 M^{-1} s^{-1}$	d
5	 (benzene complex)	$k = 4.3 \times 10^7 M^{-1} s^{-1}$	d
6	$CH_3\cdot + Bu_3Sn{-}H \rightarrow CH_4\cdot + Bu_3Sn\cdot$	$k = 1.0 \times 10^7 M^{-1} s^{-1}$ $E_a = 3.2$ kcal	e
7	$(CH_3)_3C\cdot + Bu_3Sn{-}H \rightarrow (CH_3)_3CH + Bu_3Sn\cdot$	$k = 1.8 \times 10^6 M^{-1} s^{-1}$ $E_a = 2.95$ kcal	e
8	$Ph\cdot + Bu_3Sn{-}H \rightarrow Ph{-}H + Bu_3Sn\cdot$	$k = 5.9 \times 10^8 M^{-1} s^{-1}$	f
9	$PhCH_2\cdot + PhSH \rightarrow PhCH_3 + PhS\cdot$	$k = 3.1 \times 10^5 M^{-1} s^{-1}$	g
B.	Additions to alkenes and aromatics		
10	$Ph\cdot + PhCH{=}CH_2 \rightarrow Ph\underset{\cdot}{C}H{-}CH_2Ph$	$k = 1.1 \times 10^8 M^{-1} s^{-1}$	b
11		$k = 4.5 \times 10^5 M^{-1} s^{-1}$	b
12	$(CH_3)_3CO\cdot + CH_2{=}CH(CH_2)_5CH_3$ $(CH_3)_3COCH_2CH(CH_2)_5CH_3$	$k = 1.5 \times 10^6 M^{-1} s^{-1}$	c
C.	Cyclization and ring opening		
13		$k = 2.1 \times 10^8 s^{-1}$ $E_a = 7.6$ kcal	h

Table 12.2. continued.

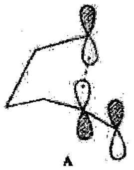
	Reaction		Ref.
14		$k = 1.0 \times 10^5\ s^{-1}$ $E_a = 6.1$ kcal	i
15		$k = 4.0 \times 10^8\ s^{-1}$ $E_a = 3.6$ kcal	f
16		$k = 1.5 \times 10^5\ s^{-1}$ $E_a = 7.3$ kcal	j
17		$k = 2 \times 10^{-1}\ s^{-1}$ $E_a = 16.3$ kcal	k
18		$k = 2.8 \times 10^4\ s^{-1}$ $E_a = 8.3$	l
D.	Other reactions		
19	$(CH_3)_3C\cdot + O_2 \rightarrow (CH_3)_3C{-}O{-}O\cdot$	$k = 4.9 \times 10^9 M^{-1}\ s^{-1}$	f
20	$PhCH_2\cdot + O_2 \rightarrow PhCH_2{-}O{-}O\cdot$	$k = 2.4 \times 10^9 M^{-1}\ s^{-1}$	f
21	 $(CH_3)_3C{-}\underset{\|\|}{\overset{}{C}}\cdot \rightarrow (CH_3)_3C\cdot + C{\equiv}O$ (C=O)	$k = 1.2 \times 10^5\ s^{-1}$ $E_a = 9.3$ kcal	i
22	 $PhCH_2\underset{O}{\underset{\|\|}{C}}\cdot \rightarrow PhCH_2\cdot + C{\equiv}O$	$k = 5.2 \times 10^7\ s^{-1}$ $E_a = 7.2$ kcal	i

a. Rates quoted are for temperatures near 300 K. The original literature should be consulted for precise temperatures and other conditions.
b. J. C. Scaiano and L. C. Stewart, *J. Am. Chem. Soc.* **105**, 3609 (1983).
c. A. Baignee, J. A. Howard, J. C. Scaiano, and L. C. Stewart, *J. Am. Chem. Soc.* **105** 6120 (1983).
d. N. J. Bunce, K. U. Ingold, J. P. Landers, J. Lusztyk, and J. Scaiano, *J. Am. Chem. Soc.* **107**, 564 (1985).
e. C. Chatgilialoglu, K. U. Ingold, and J. C. Scaiano, *J. Am. Chem. Soc.* **103**, 7739 (1981).
f. L. J. Johnson, J. Lusztyk, D. D. M. Wayner, A. N. Abeywickreyma, A. L. Beckwith, J. C. Scaiano, and K. U. Ingold, *J. Am. Chem. Soc.* **107**, 4594 (1985).
g. J. A. Franz, N. K. Suleman, and M. S. Alnajjar, *J. Org. Chem.* **51**, 19 (1986).
h. L. Mathew and J. Warkentin, *J. Am. Chem. Soc.* **108**, 7981 (1986).
i. D. Griller and K. U. Ingold, *Acc. Chem. Res.* **13**, 317 (1980).
j. J. A. Franz, R. D. Barrows, and D. M. Camaioni, *J. Am. Chem. Soc.* **106**, 3964 (1984).
k. J. A. Franz, M. S. Alnajjar, R. D. Barrows, D. L. Kaisaki, D. M. Camaioni, and N. K. Suleman, *J. Org. Chem.* **51**, 1446 (1986).
l. A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron Lett.* **26**, 373 (1985).
m. B. Maillard, K. U. Ingold, and J. C. Scaiano, *J. Am. Chem. Soc.* **105**, 5095 (1983).

Entries 4 and 5 point to another important aspect of free-radical reactivity. The data given illustrate that the observed reactivity of the chlorine atom is strongly influenced by the presence of benzene. Evidently, a complex is formed that attenuates the reactivity of the chlorine atom. This is probably a general feature of radical chemistry, but there are relatively few data available on solvent effects on either absolute or relative reactivity of radical intermediates.

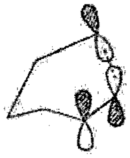
Section C of Table 12.2 shows some reactions involving cyclization of unsaturated radicals. This type of reaction has become an important application of free-radical chemistry in synthesis and will be discussed more thoroughly in Section 10.3.4 of Part B. Rates of cyclization reactions have also proved useful in mechanistic studies, where they can serve as reference points for comparison with other reaction rates.

The remaining entries in part C of Table 12.2 are examples of ring closures of unsaturated radicals. They all display a feature that is common to such cyclizations, namely, there is a preference for five-membered ring formation over six-membered ring formation.[54] This is observed even though it results in formation of a less stable primary radical. The cause for this preference has been traced to stereoelectronic effects. In order for a bonding interaction to occur, the radical center must interact with the π^* orbital of the alkene. Bond formation takes place as the result of initial interaction with the LUMO, which is the π^* orbital. According to MO calculations, the preferred direction of attack is from an angle of about 70° with respect to the plane of the double bond.[55]



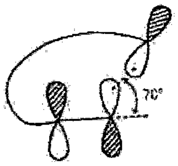
A

exo



B

endo



When this stereoelectronic requirement is combined with a calculation of the steric and angle strain imposed on the transition state, as determined by molecular mechanics calculations, preferences for the *exo* versus *endo* modes of cyclization are predicted to be as summarized in Table 12.3.

The observed results show at least the correct qualitative trend. The observed preference for ring formation is 5 > 6, 6 > 7, and 8 > 7, which is in agreement with the calculated preference. The relationship only holds for terminal double bonds. An additional alkyl substituent at either end of the double bond reduces the relative reactivity by a steric effect.

The relatively low rate and high activation energy noted for entry 17 in Table 12.2 also reflects a stereoelectronic effect. The preference for delocalization at the radical center requires coplanarity of the substituents at the radical site. In view of

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[54] A. L. J. Beckwith, C. J. Eaton, and A. K. Serelis, *J. Chem. Soc., Chem. Commun.*, 482 (1980); A. L. J. Beckwith, T. Lawrence, and A. K. Serelis, *J. Chem. Soc., Chem. Commun.*, 484 (1980); A. L. J. Beckwith, *Tetrahedron* **37**, 3073 (1981).

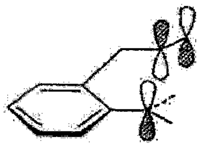
[55] M. J. S. Dewar and S. Olivella, *J. Am. Chem. Soc.* **100**, 5290 (1978); D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.* **52**, 959 (1987); A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron* **41**, 3925 (1985).

Table 12.3. Regioselectivity of Radical Cyclization as a Function of Ring Size[a]

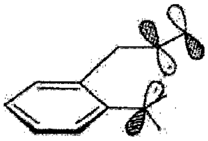
Ring size	*n*	exo:endo Ratio Calc.	exo:endo Ratio Found
5:6	2	10:1	50:1
6:7	3	>100:1	10:1
7:8	4	1:5.8	<1:100

a. D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.* **52**, 959 (1987).

the restrictions on the mode of approach of the radical to the double bond, significant strain develops at the transition state, and this requires rotation of the benzylic methylene group out of its preferred coplanar alignment.[56]



poor alignment in planar conformation



optimal alignment disrupts benzylic conjugation

Some general remarks about structure-reactivity relationships in radical reactions can be made at this point. The reactivity of C—H groups toward radicals that abstract hydrogen is usually primary < secondary < tertiary. Vinyl and phenyl substituents at a reaction site increase the reactivity toward radicals. This reactivity order reflects the bond dissociation energies of the various C—H bonds, which are in the order allyl ~ benzyl < tertiary < secondary < primary.[57] The relative reactivity of primary, secondary, and tertiary positions in aliphatic hydrocarbons toward hydrogen abstraction by methyl radicals is 1:4.3:46.[58] The relative reactivity toward the *t*-butoxy radical is 1:10:44.[59] An allylic or benzylic hydrogen is more reactive toward a methyl radical by a factor of about 9, compared to a corresponding unactivated hydrogen.[58] Data for other types of radicals have been obtained and tabulated.[59] The trend of reactivity tertiary > secondary > primary is consistently observed, and the range of reactivity is determined by the nature of the reacting radical. In the gas phase, the bromine atom, for example, is very selective, with relative reactivities of 1:250:6,300 for primary, secondary, and tertiary hydrogens.[60]

The stabilizing effects of vinyl groups (in allylic radicals) and phenyl groups (in benzyl radicals) are very significant and can be satisfactorily rationalized in

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[56] J. A. Franz, N. K. Suleman, and M. S. Alnajjar, *J. Org. Chem.* **51**, 19 (1986).
[57] J. A. Kerr, *Chem. Rev.* **66**, 465 (1966).
[58] W. A. Pryor, D. L. Fuller, and J. P. Stanley, *J. Am. Chem. Soc.* **94**, 1632 (1972).
[59] C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.* **82**, 6108 (1960).
[60] A. F. Trotman-Dickenson, *Adv. Free Radical Chem.* **1**, 1 (1965).

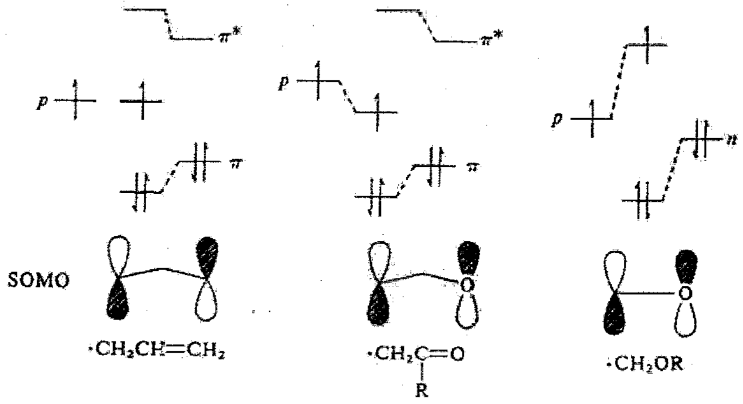
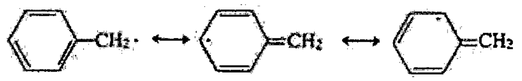


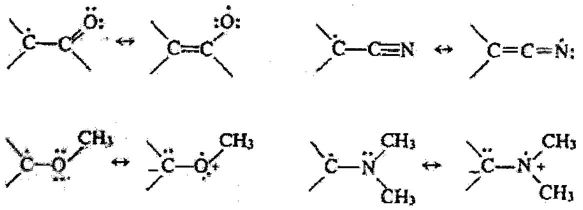
Fig. 12.4. PMO representation of *p*-orbital interactions with (a) C=C, (b) C=O, and (c) ŌR substituents. Form of SOMO (singly occupied molecular orbital) is shown.

resonance terminology:

$$CH_2{=}CH{-}CH_2\cdot \leftrightarrow \cdot CH_2{-}CH{=}CH_2$$



The stabilizing role of other functional groups can also be described in resonance terms. Both electron-attracting groups such as carbonyl and cyano and electron-donating groups such as methoxy and dimethylamino have a stabilizing effect on a radical intermediate at an adjacent carbon. The resonance structures that depict these interactions indicate delocalization of the unpaired electron onto the adjacent substituents:

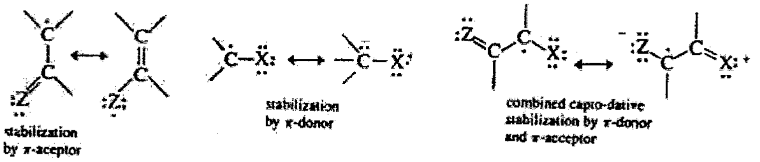


A description of the radical-stabilizing effect of both types of substituents can also be presented in MO terms. In this case, the question we ask is how will the unpaired electron in a *p* orbital interact with the orbitals of the adjacent substituent, such as vinyl, carbonyl, or methoxy? Figure 12.4 presents a qualitative description of the situation.

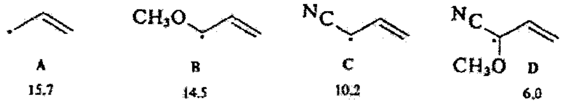
For the vinyl substituent, we can analyze the stabilization in terms of simple Hückel MO theory. The interaction of a *p* orbital with an adjacent vinyl group creates the allyl radical. In Hückel calculations, the resulting orbitals have energies of $\alpha + 1.4\beta$, α, and $\alpha - 1.4\beta$. Thus, the interaction of the p orbital with both the π and π^* orbitals leaves it at the same energy level but the π and π^* levels are transformed to ψ_1 and ψ_3 of the allyl radical. There is a net stabilization of 0.4β. The stabilization of the allyl radical has been estimated to be about 14 kcal/mol.[61] Since the stabilizing interaction is maximum in a planar structure, there is a barrier to rotation of either of the terminal methylene groups with respect to the rest of the molecule. The measured barrier is 15.7 kcal/mol.

The basic tenet of PMO theory that the orbitals which are closest in energy will interact most strongly is employed in the analysis of the effect of electron-withdrawing and electron-donating substituents. In the case of an electron-accepting substituent, such as a carbonyl group, the strongest interaction is with the carbonyl LUMO, π^*. This results in a lowering of the energy of the orbital containing the unpaired electron, that is, the radical is stabilized. For an electron-donating substituent, the strongest interaction is between the electron in the p orbital and a nonbonding pair on the electron donor. This interaction results in lowering of the energy of the orbital occupied by the electron pair and raising of the energy of the orbital occupied by the single electron. The net effect is still stabilizing since there are two electrons in the stabilized orbital and only one in the destabilized one.

Radicals are particularly strongly stabilized when both an electron-attracting and an electron-donating substituent are present at the radical site. This has been called "*mero-stabilization*"[62] or "*capto-dative stabilization*."[63] This type of stabilization results from mutual reinforcement of the two substituent effects. Scheme 12.3 gives some information on the stability of this type of radical.



A comparison of the rotational barriers in allylic radicals **A**–**D** provides evidence for the stabilizing effect of the capto-dative combination:



The decreasing barrier at the formal single bond along the series **A** to **D** implies decreasing π-allyl character of this bond. The decrease in the importance of the π bonding in turn reflects a diminished degree of interaction of the radical center with the adjacent double bond. The fact that the decrease from **C** to **D** is greater than that from **A** to **B** indicates a synergistic effect, as implied by the capto-dative

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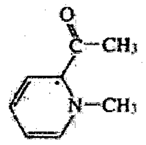
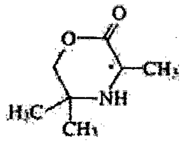
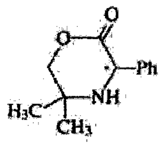
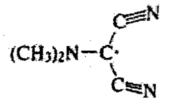
[61] H. G. Korth, H. Trill, and R. Sustmann, *J. Am. Chem. Soc.* **103**, 4483 (1981).
[62] R. W. Baldock, P. Hudson, A. R. Katritzky, and F. Soti, *J. Chem. Soc., Perkin Trans. 1*, 1422 (1974).
[63] H. G. Viehe, R. Merenyi, L. Stella, and Z. Janousek, *Angew Chem. Int. Ed. Engl.* **18**, 917 (1979).

Scheme 12.3. Radicals with Capto-dative Stabilization

1[a]		Wurster's salts. Generated by one-electron oxidation of the diamine. Indefinitely stable.
2[b]		Generated by one-electron reduction of the pyridinium salt. Stable, distillable, and only moderately reactive to oxygen.
3[c]		Stable and distillable. A small amount of dimer is present in equilibrium with the radical.
4[d]		Generated by spontaneous dissociation of the dimer. In equilibrium with dimer.
5[e]		Generated by spontaneous dissociation of the dimer. Stable for several days at room temperature. Oxidized by oxygen.
6[f]		Generated spontaneously from dimethyl-amino-malononitrile at room temperature. Observed to be persistent over many hours by EPR.

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[a] A. R. Forrester, J. M. Hay, and R. H. Thompson, *Organic Chemistry of Stable Free Radicals*, Academic Press, New York, 1968, pp. 254–261.

[b] J. Hermolin, M. Levin, and E. M. Kosower, *J. Am. Chem. Soc.* **103**, 4808 (1981).

[c] J. Hermolin, M. Levin, Y. Ikegami, M. Sawayangai, and E. M. Kosower, *J. Am. Chem. Soc.* **103**, 4795 (1981).

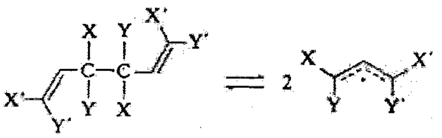
[d] T. H. Koch, J. A. Oleson, and J. DeNiro, *J. Am. Chem. Soc.* **97**, 7285 (1975).

[e] J. M. Burns, D. L. Wharry, and T. H. Koch, *J. Am. Chem. Soc.* **103**, 849 (1981).

[f] L. de Vries, *J. Am. Chem. Soc.* **100**, 926 (1978).

formulation. The methoxy group is more stabilizing when it can interact with the cyano group than as an isolated substituent, as it is in **B**.[64]

The capto-dative effect has also been demonstrated by studying the bond dissociation process in a series of 1,5-dienes substituted at C-3 and C-4.



X	Y	X'	Y'	H
CO_2R	CO_2R	CO_2R	CO_2R	38.1
CO_2R	CO_2R	CO_2R	OR	28.2
CN	OR	CN	OR	24.5
CN	NR_2	CN	NR_2	8.1

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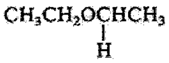
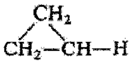
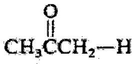
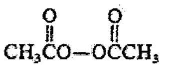
[64] H.-G. Korth, P. Lommes, and R. Sustmann, *J. Am. Chem. Soc.* **106**, 663 (1984).

Table 12.4. Bond Dissociation Energies (kcal/mol)[a]

Bond	D.E.	Bond	D.E.
CH_3-H	104	$H-Br$	87.5
CH_3CH_2-H	98	$H-I$	71
$(CH_3)_2CH-H$	94.5	$HOCH_2-H$	92
$(CH_3)_3C-H$	91	 $CH_3CH_2O\underset{H}{C}HCH_3$	92[b]
$CH_2=CH-H$	104		
	101	 $CH_3\overset{O}{C}CH_2-H$	92
$PhCH_2-H$	85	$N\equiv CCH_2-H$	86
$CH_2=CHCH_2-H$	85	$PhS-H$	82[c]
		$(CH_3)_3Si-H$	90[d]
	73[b]	$(CH_3)_3Ge-H$	82[d]
		$(C_4H_9)_3Sn-H$	74[b]
F_3C-H	106		
Cl_3C-H	96	 $CH_3\overset{O}{C}O-O\overset{O}{C}CH_3$	30
C_2H_5-F	106		
C_2H_5-Cl	81	$(CH_3)_3CO-OH$	44
C_2H_5-Br	69	$F-F$	38
C_2H_5-I	53	$Cl-Cl$	58
$H-F$	136	$Br-Br$	46
$H-Cl$	103	$I-I$	36

a. Except where noted otherwise, data are from J. A. Kerr, *Chem. Rev.* **66**, 465 (1966); S. W. Benson, *J. Chem. Educ.* **42**, 502 (1965).
b. T. J. Burkey, M. Majewski, and D. Griller, *J. Am. Chem. Soc.* **108**, 2218 (1986).
c. S. W. Benson, *Chem. Rev.* **78**, 23 (1978).
d. R. A. Jackson, *J. Organomet. Chem.* **166**, 17 (1979).

When one or both of the combinations X, Y and X′, Y′ are of the capto-dative type, as is the case for an alkoxy and an ester group, the enthalpy of bond dissociation is 10–15 kcal lower than when all four groups are electron-attracting. When the captodative combination CN/NR_2 occupies both X, Y and X′, Y′ positions, the enthalpy for dissociation of the C-3—C-4 bond is less than 10 kcal/mol.[65]

The radical stabilization provided by various functional groups results in reduced bond dissociation energies for bonds to the stabilized radical center. Some bond dissociation energy values are given in Table 12.4. As an example of the substituent effect on bond dissociation energies, it can be seen that the primary C—H bonds in acetonitrile (86 kcal/mol) and acetone (92 kcal/mol) are significantly weaker than a primary C—H bond in ethane (98 kcal/mol).

By analysis of heats of formation of compounds incorporating radical fragments and assignment of standard sets of bond energies, it is possible to arrive at energies corresponding to the stabilization of the radical fragment. This energy then reflects

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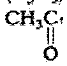
[65] M. Van Hoecke, A. Borghese, J. Pennelle, R. Merenyi, and H. G. Viehe, *Tetrahedron Lett.* **27**, 4569 (1986).

Table 12.5. Thermochemical Stabilization Energies for Some Substituted Radicals

	SE^{0a}	SE^{b}
$\dot{C}H_3$	−1.67	−3.9
$CH_3\dot{C}H_2$	2.11	−1.5
$CN\dot{C}H_2$	6.50	
$NH_2\dot{C}H_2$	3.92	
$CH_3NH\dot{C}H_2$	12.18	
$(CH_3)_2N\dot{C}H_2$	14.72	
$HO\dot{C}H_2$	3.13	1.7
$CH_3O\dot{C}H_2$	3.64	
$F\dot{C}H_2$	−1.89	−0.7
$(CH_3)_2\dot{C}H$	2.57	
$(CN)_2\dot{C}H$	5.17	
$(HO)_2\dot{C}H$	−2.05	
$(CN)(NH_2)\dot{C}H$	12.94	
$(CN)(OH)\dot{C}H$	2.15	
$(CN)F\dot{C}H$	−2.79	
$F_2\dot{C}H$	−4.11	1.7
$(CH_3)_3\dot{C}$	4.35	
$CH_3\dot{C}(CN)_2$	3.92	
$CH_3\dot{C}(OH)_2$	0.15	
$CH_3\dot{C}(CN)(OH)$	2.26	
$\dot{C}F_3$	−4.17	
$\dot{C}Cl_3$	−13.79	
$CH_2{=}CH{-}\dot{C}H_2$	13.28	10.5
$C_6H_5{-}\dot{C}H_2$	12.08	13.9
$CH_2{=}\dot{C}H$	−6.16	−10.0
$HC{\equiv}C^{\cdot}$	−15.57	
$(C_6H_5)^{\cdot}$	−10.27	−12.3
$(C_5H_5)^{\cdot}$	19.24	
 $CH_3\underset{\underset{O}{\Vert}}{C}\cdot$	7.1	
 $H\underset{\underset{O}{\Vert}}{C}\cdot$		5.8

a. Stabilization energy as defined by C. Leroy, D. Peeters, and C. Wilante, *Theochem* 5, 217 (1982).
b. Reorganization energy as defined by R. T. Sanderson, *J. Org. Chem.* 47, 3835 (1982) but given here as a stabilization energy of opposite sign.

the stabilization or destabilization of the radical center in the particular structural environment. Table 12.5 lists values assigned by two such approaches. Although the two sets of values differ by a few kilocalories, the trends are consistent with the qualitative predictions of radical stability based on PMO theory. These data reveal the familiar stabilization of allyl and benzyl radicals, which appears as positive stabilization energies. The trend of increasing stability of alkyl radicals in the order tertiary > secondary > primary > methyl is also apparent. According to this analysis, donor substituents, such as hydroxy, are not as strongly stabilizing as acceptor substituents, such as the carbonyl group. The assignment of significantly negative stabilization energies (i.e., destabilization) implies that the substituent will increase the bond energy of adjacent bonds. The phenyl and vinyl radicals are examples of radicals having negative stabilization energies, implying that there will be an increase in the bond energy to the substituents. These negative values are in agreement with the relative instability of phenyl and vinyl radicals and the difficulty of abstracting a hydrogen atom from aromatic rings or double bonds.

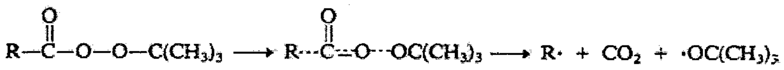
Bond dissociation energies such as those in Table 12.4 are also useful for estimation of the energy balance in individual steps in a free-radical reaction sequence. This is an important factor in assessing the feasibility of chain reaction sequences since only reactions with low activation energies are rapid enough to sustain a chain process. If individual steps are identified as being endothermic by more than a few kilocalories, it is very unlikely that a chain mechanism can operate.

Example 12.1. Calculate the enthalpy for each step in the bromination of ethane by bromine atoms from molecular bromine. Determine the overall enthalpy of the reaction.

Initiation	$Br{-}Br \longrightarrow 2\,Br\cdot$	Br–Br	+46 kcal/mol
propagation	$Br\cdot + CH_3{-}CH_3 \longrightarrow H{-}Br + \cdot CH_2{-}CH_3$	H–Br	−87
		H–C	+98
			+11
	$Br{-}Br + \cdot CH_2{-}CH_3 \longrightarrow BrCH_2{-}CH_3 + Br\cdot$	Br–Br	+46
		Br–C	−69
			−23
		total	−12 kcal/mol

The enthalpy of the reaction is given by the sum of the propagation steps and is −12 kcal/mol. Analysis of the enthalpy of the individual steps indicates the first step is somewhat endothermic. This endothermicity is the lower limit of the activation energy for the step. Radical chain processes depend on a series of rapid steps that maintain the reactive intermediates at low concentration. Since termination reactions are usually very fast, the presence of an endothermic step in a chain sequence means that the chains will be short. The value for ethane is borderline and suggests that radical bromination of ethane would exhibit only short chain lengths. Since the enthalpies of the corresponding steps for abstraction of secondary or tertiary hydrogen are less positive, the bromination selects for hydrogens in the order tertiary > secondary > primary in compounds with more than one type of hydrogen. Enthalpy calculations cannot give a direct evaluation of the activation energy of either exothermic or endothermic steps. These will depend on the energy of the transition state. The bond dissociation energies can therefore provide only permissive, not definitive, conclusions.

Radical stability is reflected in a variety of ways in addition to the bond dissociation energy of the corresponding C—H bond. It has already been indicated that radical structure and stability determines the temperature at which azo compounds undergo decomposition with elimination of nitrogen (Section 12.1.4). Similar trends have been established in other radical-forming reactions. Rates of thermal decomposition of *t*-butyl peroxyesters, for example, vary over a wide range, depending on the structure of the carbonyl substituent.[66] This clearly indicates that the bonding changes involved in the rate-determining step are not completely localized in the O—O bond. Radical character must also be developing at the alkyl group by partial cleavage of the alkyl–carbonyl bond.



$$R-\overset{O}{\overset{\|}{C}}-O-O-C(CH_3)_3 \longrightarrow R\cdots\overset{O}{\overset{\|}{C}}\cdots O\cdots OC(CH_3)_3 \longrightarrow R\cdot + CO_2 + \cdot OC(CH_3)_3$$

R	Relative rate at 60°C
CH_3	1
Ph	17
$PhCH_2$	290
$(CH_3)_3C$	1,700
Ph_2CH	19,300
$Ph(CH_3)_2C$	41,500
$PhCHCH{=}CH_2$	125,000

The same is true for decarbonylation of acyl radicals. The rates of decarbonylation have been measured over a very wide range of structural types.[67] There is a very strong dependence of the rate on the stability of the radical that results from decarbonylation. For example, decarbonylations giving tertiary benzylic radicals are on the order of $10^8\ s^{-1}$, whereas the benzoyl radical decarbonylates with a rate on the order of $1\ s^{-1}$.

Free-radical reactions written in the simplest way imply no separation of charge. The case of toluene bromination can be used to illustrate this point:

$$Br\cdot + H-CH_2Ph \longrightarrow Br\cdots H\cdots CH_2Ph \longrightarrow Br-H + \cdot CH_2Ph$$

$$PhCH_2\cdot + Br-Br \longrightarrow PhCH_2\cdots Br\cdots Br \longrightarrow PhCH_2Br + Br\cdot$$

Nevertheless, many free-radical processes respond to introduction of polar substituents, just as do heterolytic processes that involve polar or ionic intermediates. The substituent effects on toluene bromination, for example, are correlated by the Hammett equation, and the correlation gives a ρ value of -1.4, indicating that the benzene ring acts as an electron donor in the transition state.[68] Other radicals, for

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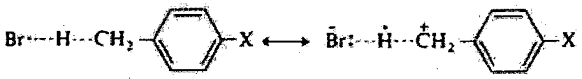
[66] P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.* **80**, 1398 (1958).

[67] H. Fischer and H. Paul, *Acc. Chem. Res.* **20**, 200 (1987).

[68] J. Hradil and V. Chvalovsky, *Collect. Czech. Chem. Commun.* **33**, 2029 (1968); S. S. Kim, S. Y. Choi, and C. H. Kong, *J. Am. Chem. Soc.* **107**, 4234 (1985); G. A. Russell, C. DeBoer, and K. M. Desmond, *J. Am. Chem. Soc.* **85**, 365 (1963); C. Walling, A. L. Rieger, and D. D. Tanner, *J. Am. Chem. Soc.* **85**, 3129 (1963).

example, the *t*-butyl radical, show a positive ρ for hydrogen abstraction reactions involving toluene.[69]

Why do free-radical reactions involving neutral reactants and intermediates respond to substituent changes that modify electron distribution? One explanation has been based on the idea that there would be some polar character in the transition state because of the electronegativity differences of the reacting atoms.[70]:



This idea receives general support from the fact that the most negative ρ values are found for reactions of more electronegative radicals such as Br·, Cl· and Cl_3C·. There is, however no simple correlation with a single property, and this probably reflects the fact that the *selectivity* of the radicals is also different. Furthermore, in hydrogen abstraction reactions, where many of the quantitative measurements have been done, the C—H bond dissociation energy is also subject to a substituent effect.[71] Thus, the extent of bond cleavage and formation at the transition state may be different for different radicals. Successful interpretation of radical reactions therefore requires consideration of factors such as the electronegativity and polarizability of the radicals and the bond energy of the reacting C—H bond. The relative importance of these effects may vary from system to system. As a result, substituent effect trends in radical reactions appear to be more complicated than those for heterolytic reactions, where substituent effects are usually dominated by the electron-withdrawing or electron-donating capacity of the substituent.[72]

Despite their overall electrical neutrality, carbon-centered radicals show pronounced electrophilic or nucleophilic character, depending on the substituents present. This electrophilic or nucleophilic character is then reflected in rates of reaction with nonradical species, for example, in additions to substituted alkenes. Unsubstituted alkyl radicals and α-alkoxyalkyl radicals are nucleophilic in character and react most rapidly with alkenes having electron-attracting substituents.[73] Radicals having electron-attracting groups, such as the radicals derived from malonate esters, react preferentially with double bonds having electron-releasing substituents.[74] Some representative data are given in Table 12.6.

These reactivity trends are in line with what would be expected from a frontier orbital interpretation. As shown in Fig. 12.5, electron-releasing substituents will

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[69] W. A. Pryor, F. Y. Tang, R. H. Tang, and D. F. Church, *J. Am. Chem. Soc.* **104**, 2885 (1982); R. W. Henderson and R. O. Ward, Jr., *J. Am. Chem. Soc.* **96**, 7556 (1974); W. A. Pryor, D. F. Church, F. Y. Tang, and T. H. Tang, in *Frontiers of Free Radical Chemistry*, W. A. Pryor (ed.), Academic Press, New York, 1980, pp. 355-379.

[70] E. S. Huyser, *Free Radical Chain Reactions*, Wiley-Interscience, New York, 1970, Chapter 4; G. A. Russell, in *Free Radicals*, J. Kochi (ed.), Vol. 1, Wiley, New York, 1973, Chapter 7.

[71] A. A. Zavitsas and J. A. Pinto, *J. Am. Chem. Soc.* **94**, 7390 (1972).

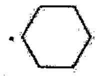
[72] W. H. Davis, Jr., and W. A. Pryor, *J. Am. Chem. Soc.* **99**, 6365 (1977); W. H. Davis, Jr., J. H. Gleason, and W. A. Pryor, *J. Org. Chem.* **42**, 7 (1977); W. A. Pryor, G. Gojon, and D. F. Church, *J. Org. Chem.* **43**, 793 (1978).

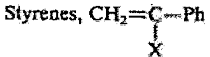
[73] B. Giese, *Angew. Chem. Int. Ed. Engl.* **22**, 753 (1983).

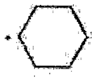
[74] B. Giese, H. Horler, and M. Leising, *Chem. Ber.* **119**, 444 (1986).

Table 12.6. Relative Rates of Radical Addition as a Function of Alkene Substitution[a]

A. Addition to Substituted Ethenes, $CH_2{=}CH{-}X$

X	$\cdot CH_3$	$\cdot C_2H_5$	
CN	2.2	5.1	24
$COCH_3$	2.3		13
CO_2CH_3	1.3	1.9	6.7
Ph	1.0	1.0	1.0
O_2CCH_3		0.05	0.016

B. Addition to Substituted Styrenes,  $CH_2{=}\underset{X}{C}{-}Ph$

X		$\cdot CH(CO_2C_2H_5)_2$
CN	122	
$CO_2C_2H_5$	11.7	0.28
Ph	1.0	1.0
CH_3	0.28	1.06
OCH_3		0.78
$N(CH_3)_2$		6.6

a. Data from B. Giese, H. Horler, and M. Leising, *Chem. Ber.* **119**, 444 (1986); B. Giese, *Angew. Chem. Int. Ed. Engl.* **22**, 753 (1983).

raise the energy of the singly occupied molecular orbital (SOMO) and increase the strength of interaction with the relatively low-lying LUMO of alkenes having electron-withdrawing groups. When the radical site is substituted by an electron-attracting group, the SOMO is lower, and the strongest interaction will be with the HOMO of the alkene. This interaction is strengthened by donor substituents on the alkene.

12.3. Free-Radical Substitution Reactions

12.3.1. Halogenation

Free-radical bromination is an important method of selective functionalization of hydrocarbons.[75] The process is a chain reaction involving the following steps:

initiation $\quad Br{-}Br \longrightarrow 2\,Br\cdot$

propagation $\quad Br\cdot + R_3CH \longrightarrow R_3C\cdot + HBr$

$R_3C\cdot + Br_2 \longrightarrow R_3CBr + Br\cdot$

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[75] W. A. Thaler, *Methods Free Radical Chem.* **2**, 121 (1969); A. Nechvatal, *Adv. Free Radical Chem.* **4**, 175 (1972).

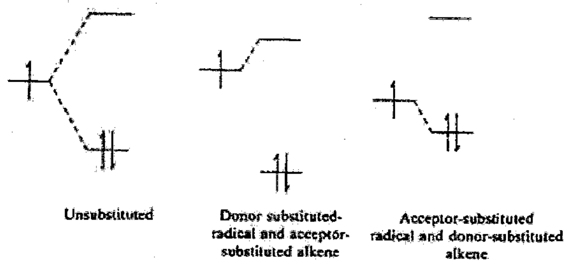
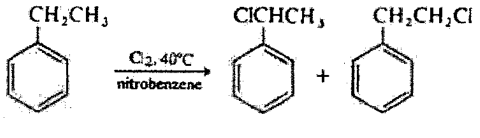


Fig. 12.5. Frontier orbital interactions between different combinations of substituted radicals and alkenes.

The reaction is often initiated by photolysis of bromine. The hydrogen atom abstraction step is rate-limiting, and the product composition is governed by the selectivity of the hydrogen abstraction step. The enthalpy requirements for abstraction of hydrogen from methane, ethane (primary), propane (secondary), and isobutane (tertiary) by bromine atoms are +16.5, +10.5, +7.0, and +3.5 kcal/mol, respectively.[76] These difference are reflected in the activation energies, and there is a substantial kineric preference for hydrogen abstraction in the order tertiary > secondary > primary. Substituents that promote radical stability, such as phenyl, vinyl, or carbonyl groups, also lead to kinetic selectivity in radical brominations. Bromination at benzylic positions is a particularly efficient process, as illustrated by entries 2 and 4 in Scheme 12.4.

There are important differences in the reactions of other halogens relative to bromination. In the case of chlorination, although the same chain mechanism as for bromination is operative, there is a key difference in the *greatly diminished selectivity of the chlorination.* Because of the greater reactivity of the chlorine atom, abstractions of primary, secondary, and tertiary hydrogens are all *exothermic.* As a result of this exothermicity, the stability of the product radical has less influence on the activation energy. In terms of the Hammond postulate, the transition state would be expected to be very *reactant-like.* As an example of the low selectivity, ethylbenzene is chlorinated at both the methyl and the methylene positions, despite the much greater stability of the benzyl radical.[77]



Radical chlorination reactions show a substantial polar effect. Positions substituted by electron-withdrawing groups are relatively unreactive toward chlorination, even though the substituents may be potentially capable of stabilizing the

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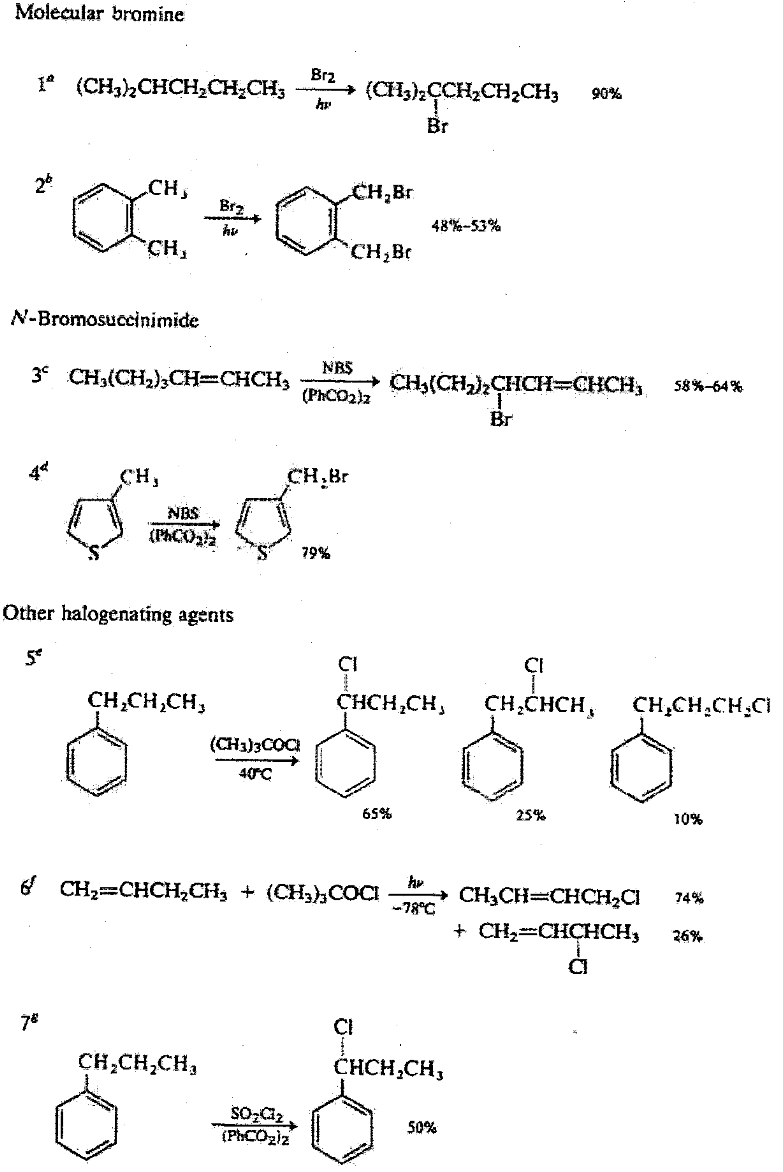
[76] E. S. Huyser, *Free Radical Chain Reactions,* Wiley-Interscience, New York, 1970, p. 91.
[77] G. A. Russell, A. Ito, and D. G. Hendry, *J. Am. Chem. Soc.* 86, 2976 (1963).

Scheme 12.4. Radical Halogenations



Molecular bromine

1[a] $(CH_3)_2CHCH_2CH_2CH_3 \xrightarrow[h\nu]{Br_2} (CH_3)_2C(Br)CH_2CH_2CH_3$ 90%

N-Bromosuccinimide

3[c] $CH_3(CH_2)_3CH{=}CHCH_3 \xrightarrow[(PhCO_2)_2]{NBS} CH_3(CH_2)_2CH(Br)CH{=}CHCH_3$ 58%–64%

Other halogenating agents

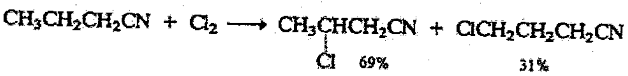
6[f] $CH_2{=}CHCH_2CH_3 + (CH_3)_3COCl \xrightarrow[-78°C]{h\nu} CH_3CH{=}CHCH_2Cl$ 74%

$+\ CH_2{=}CHCH(Cl)CH_3$ 26%

---

a. G. A. Russell and H. C. Brown, *J. Am. Chem. Soc.* **77**, 4025 (1955).
b. E. F. M. Stephenson, *Org. Synth.* **IV**, 984 (1963).
c. F. L. Greenwood, M. D. Kellert, and J. Sedlak, *Org. Synth.* **IV**, 108 (1963).
d. E. Campaigne and B. F. Tullar, *Org. Synth.* **IV**, 921 (1963).
e. C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.* **82**, 6108 (1960).
f. C. Walling and W. Thaler, *J. Am. Chem. Soc.* **83**, 3877 (1961).
g. H. C. Brown and A. B. Ash, *J. Am. Chem. Soc.* **77**, 4019 (1955).

free-radical intermediate.[78]



$$CH_3CH_2CH_2CN + Cl_2 \longrightarrow \underset{69\%}{CH_3\underset{Cl}{C}HCH_2CN} + \underset{31\%}{ClCH_2CH_2CH_2CN}$$

The polar effect is attributed to the fact that the chlorine atom is an electrophilic species, and the relatively electron-deficient carbon atoms adjacent to the electron-withdrawing groups are avoided. Similarly, carboxylic acid and ester groups tend to direct chlorination to the β and γ positions, because attack at the α position is electronically disfavored. The effect of an electron-withdrawing substituent is to decrease the electron density at the potential radical site, even though there would be a net stabilization of the radical that would be eventually formed. Since the chlorine atom is highly reactive, the reaction would be expected to have a very early transition state. The polar substituent effect dominates the *kinetic selectivity* of the reaction, and the stability of the radical intermediate has relatively little influence.

Radical substitution reactions by iodine are not practical because the abstraction of hydrogen from hydrocarbons by iodine is highly endothermic, even for stable radicals. The enthalpy of the overall reaction is also slightly endothermic. Thus, both because of the kinetic problem excluding a chain reaction and an unfavorable equilibrium constant for substitution, iodination cannot proceed by a radical chain mechanism.

Fluorination presents problems of the other extreme. Both steps in the substitution chain reaction are so exothermic that the reaction is violent if not performed under carefully controlled conditions. Furthermore, fluorine atoms are capable of cleaving carbon–carbon bonds:

$$F\cdot + CH_3CH_3 \rightarrow CH_3F + CH_3\cdot$$

Saturated hydrocarbons such as neopentane, norbornane, and cyclotane have been converted to the corresponding perfluoro derivatives in 10–20% yield by gas phase reaction with fluorine gas diluted with helium at −78°C.[79] Simple ethers can be completely fluorinated under similar conditions.[80] Crown polyethers can be fluorinated by passing a F_2/He stream over a solid mixture of sodium fluoride and the crown ether.[81] Liquid phase fluorination of hydrocarbons has also been observed, but the reaction is believed to be ionic, rather than radical, in character.[82]

Halogenations of organic molecules can also be carried out with several other chemical reagents in addition to the molecular halogens. *N*-Bromosuccinimide (NBS) has been used extensively, especially for allylic and benzylic bromination. Mechanistic investigations have established that molecular bromine is the active

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[78] A. Bruylants, M. Tits, C. Dieu, and R. Gauthier, *Bull. Soc. Chim. Belg.* **61**, 266 (1952); A. Bruylants, M. Tits, and R. Danby, *Bull. Soc. Chim. Belg.* **58**, 210 (1949); M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.* **62**, 925 (1940).

[79] N. J. Maraschin, D. B. Catsikis, L. H. Davis, G. Jarvinen, and R. J. Lagow, *J. Am. Chem. Soc.* **97**, 513 (1975).

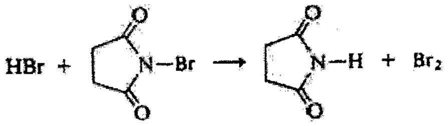
[80] D. F. Persico, H.-N. Huang, R. J. Lagow, Jr., and L. C. Clark, *J. Org. Chem.* **50**, 5156 (1985).

[81] W.-H. Lin, W. I. Bailey, Jr., and R. J. Lagow, *J. Chem. Soc., Chem. Commun.*, 1350 (1985).

[82] C. Gal and S. Rozen, *Tetrahedron Lett.* **25**, 449 (1984).

halogenating agent under the usual conditions used for NBS bromination.[83] Molecular bromine is maintained at a low concentration throughout the course of the reaction by formation from NBS and hydrogen bromide.

$$Br\cdot + H\text{-}R \longrightarrow HBr + R\cdot$$

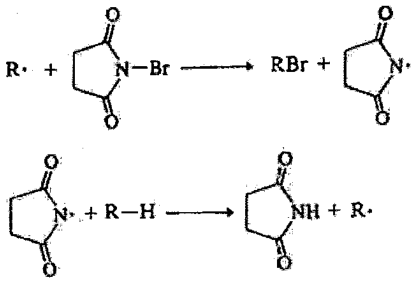


$$Br_2 + R\cdot \longrightarrow RBr + Br\cdot$$

The fact that the bromine concentration remains at very low levels is important to the success of the allylic halogenation process. Substitution at the allylic position in preference to addition is the result of the reversibility of electrophilic attack by bromine at the double bond. With a low concentration of bromine, the rate of bromine addition is low enough to permit hydrogen atom abstraction to compete successfully.

N-Bromosuccinimide can also be used to brominate alkanes. For example, cyclopropane, cyclopentane, and cyclohexane give the corresponding bromides when irradiated with NBS in dichloromethane.[84] Under these conditions, the succinimidyl radical appears to be involved as the hydrogen-abstracting intermediate.

$$Br\cdot + R{-}H \longrightarrow R\cdot + HBr$$



Another reagent that effects chlorination by a radical mechanism is *t*-butyl hypochlorite. The hydrogen-abstracting species in the chain mechanism is the *t*-butoxy radical.

$$(CH_3)_3CO\cdot + H\text{-}R \longrightarrow (CH_3)_3COH + R\cdot$$
$$R\cdot + (CH_3)_3COCl \longrightarrow (CH_3)_3CO\cdot + RCl$$

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83. R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.* **85**, 354, 3142 (1963); G. A. Russell, C. DeBoer, and K. M. Desmone, *J. Am. Chem. Soc.* **85**, 365 (1963); J. H. Incremona and J. C. Martin, *J. Am. Chem. Soc.* **92**, 627 (1970); J. C. Day, M. J. Lindstrom, and P. S. Skell, *J. Am. Chem. Soc.* **96**, 5616 (1974).

84. J. G. Traynham and Y.-S. Lee, *J. Am. Chem. Soc.* **96**, 3590 (1974).

Table 12.7. Relative Reactivities of Some Aromatic Hydrocarbons toward Oxygen[a]

$PhCH(CH_3)_2$	1.0	$PhCH_2CH_3$	0.18
$PhCH_2CH{=}CH_2$	0.8	$PhCH_3$	0.015
$(Ph)_2CH_2$	0.35		

a. Data from G. A. Russell, *J. Am. Chem. Soc.* 78, 1047 (1956).

This radical is intermediate in selectivity between chlorine and bromine atoms. The selectivity is also solvent and temperature dependent. A typical ratio, in chlorobenzene as solvent, is tertiary: secondary: primary = 60:10:1.[85] Scheme 12.4 (p. 690) gives a number of specific halogenation reactions that proceed by radical chain mechanisms.

12.3.2. Oxidation

Free-radical chain oxidation of organic molecules by molecular oxygen is often referred to as *autoxidation*. The general mechanism is outlined below:

initiation $\quad In\cdot + R{-}H \longrightarrow In{-}H + R\cdot$

propagation $\quad R\cdot + O_2 \longrightarrow R{-}O{-}O\cdot$

$$R{-}O{-}O\cdot + R{-}H \longrightarrow R{-}O{-}O{-}H + R\cdot$$

The rate of reaction of oxygen with most radicals is very rapid because of the triplet character of molecular oxygen. The ease of autoxidation is therefore largely governed by the ease of hydrogen abstraction in the second step of the propagation sequence. The alkylperoxy radicals that act as the chain carrier are fairly selective. Substrates that are relatively electron-rich or that provide particularly stable radicals are the most easily oxidized. Benzylic, allylic, and tertiary positions are especially susceptible to oxidation. This selectivity make radical chain oxidation a preparatively useful reaction in some cases.

The reactivities of a series of hydrocarbons toward oxygen measured under a standard set of conditions can give some indication of the susceptibility of various structural units to autoxidation.[86] Table 12.7 gives the results for a series of aromatic hydrocarbons. These data illustrate the activating effect of alkyl, vinyl, and phenyl substituents.

The best preparative results from autoxidation are encountered when only one relatively reactive hydrogen is available for abstraction. The oxidation of isopropylbenzene (cumene) is carried out on an industrial scale, with the ultimate products

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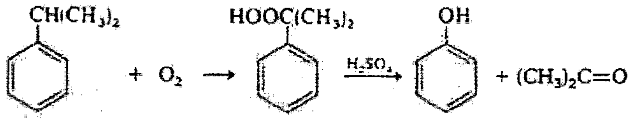
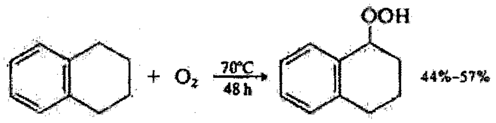
[85] C. Walling and P. J. Wagner, *J. Am. Chem. Soc.* 86, 3368 (1964).

[86] G. A. Russell, *J. Am. Chem. Soc.* 78, 1047 (1956).

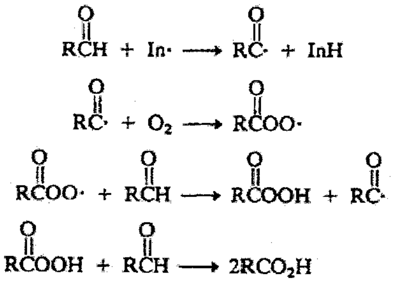
being acetone and phenol.



The benzylic position in tetralin is selectively oxidized to the hydroperoxide.[87]



Functional groups that stabilize radicals would be expected to increase susceptibility to autoxidation. This is illustrated by two cases that have been relatively well studied. Aldehydes, in which abstraction of the aldehyde hydrogen is facile, are easily autoxidized. The autoxidation initially forms a peroxycarboxylic acid, but usually the corresponding carboxylic acid is isolated because the peroxy acid oxidizes additional aldehyde in a parallel reaction.



$$\mathrm{R\overset{O}{\overset{\|}{C}}H + In\cdot \longrightarrow R\overset{O}{\overset{\|}{C}}\cdot + InH}$$

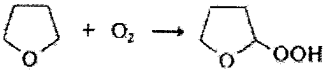
$$\mathrm{R\overset{O}{\overset{\|}{C}}\cdot + O_2 \longrightarrow R\overset{O}{\overset{\|}{C}}OO\cdot}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}OO\cdot + R\overset{O}{\overset{\|}{C}}H \longrightarrow R\overset{O}{\overset{\|}{C}}OOH + R\overset{O}{\overset{\|}{C}}\cdot}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}OOH + R\overset{O}{\overset{\|}{C}}H \longrightarrow 2RCO_2H}$$

The final step is not a radical reaction but is an example of the Baeyer–Villiger reaction, which will be discussed in Part B, Section 12.5.2.

Similarly, the α position in ethers is autoxidized quite readily to give α-hydroperoxy ethers.



This reaction is the basis of a widely recognized laboratory hazard. The peroxides formed from several commonly used ethers such as diethyl ether and tetrahydrofuran are explosive. Appreciable amounts of such peroxides can build up in ether samples that have been exposed to the atmosphere. Since the hydroperoxides are less volatile than the ethers, they are concentrated by evaporation or distillation, and the

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[87] H. B. Knight and D. Swern, *Org. Synth.* IV, 895 (1963).

concentrated peroxide solutions may explode. For this reason, extended storage of ethers that have been exposed to oxygen is extremely hazardous.

12.4. Free-Radical Addition Reactions

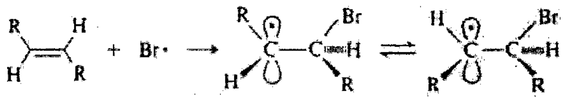
12.4.1. Addition of Hydrogen Halides

The anti-Markownikoff addition of hydrogen bromide to alkenes was one of the earliest free-radical reactions to be put on a firm mechanistic basis. In the presence of a suitable initiator, such as peroxides, a radical chain mechanism becomes competitive with the ionic mechanism for addition of hydrogen bromide.

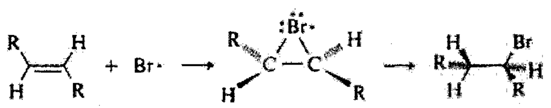
$$\begin{gathered} \mathrm{In}\cdot + \mathrm{HBr} \longrightarrow \mathrm{Br}\cdot + \mathrm{HIn} \\ \mathrm{Br}\cdot + \mathrm{RCH{=}CH_2} \longrightarrow \mathrm{R\underset{\cdot}{C}HCH_2Br} \\ \mathrm{R\underset{\cdot}{C}HCH_2Br} + \mathrm{HBr} \longrightarrow \mathrm{RCH_2CH_2Br} + \mathrm{Br}\cdot \end{gathered}$$

Since the bromine atom adds to the less substituted carbon atom of the double bond, thus generating the more substituted radical intermediate, the regioselectivity of radical chain hydrobromination is opposite to that of ionic addition. The work on the radical mechanism originated in studies of the addition of hydrogen bromide that were undertaken to understand why Markownikoff's rule was violated under certain circumstances. The cause was found to be conditions, such as peroxide impurities or light, which initiated the radical chain process. Some examples of radical chain additions of hydrogen bromide to alkenes are included in Scheme 12.5.

The stereochemistry of radical addition of hydrogen bromide to alkenes has been studied with both acylic and cyclic alkenes.[88] *Anti* addition is favored.[89,90] This is contrary to what would be expected if the sp^2 carbon of the radical were rapidly rotating with respect to the remainder of the molecule:



The stereospecificity of the radical addition can be explained in terms of a bridged structure similar to that involved in discussion of ionic bromination of alkenes[91]:



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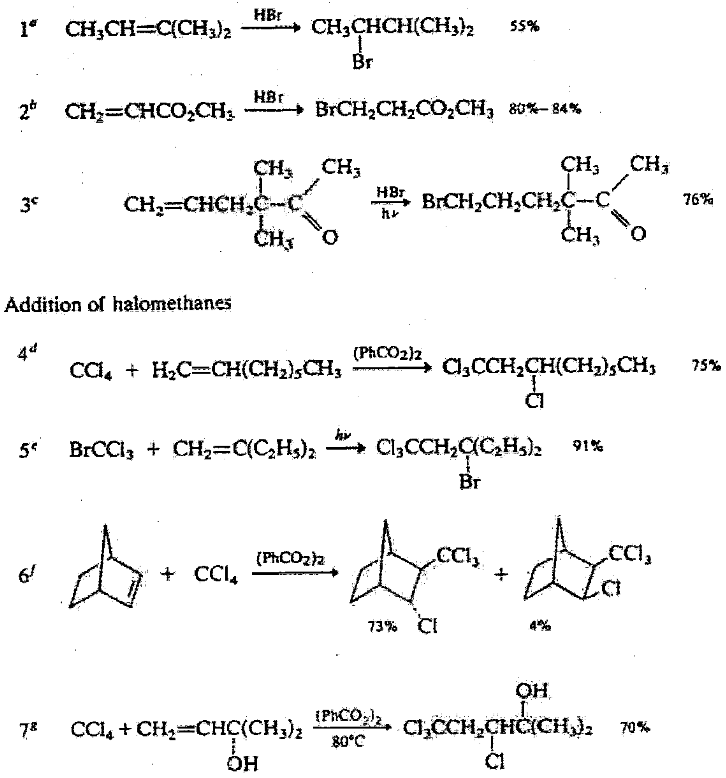
[88] B. A. Bohm and P. I. Abell, *Chem. Rev.* **62**, 599 (1962).

[89] P. S. Skell and P. K. Freeman, *J. Org. Chem.* **29**, 2524 (1964).

[90] H. L. Goering and D. W. Larsen, *J. Am. Chem. Soc.* **81**, 5937 (1959).

[91] P. S. Skell and J. G. Traynham, *Acc. Chem. Res.* **17**, 160 (1984).

Scheme 12.5. Free-Radical Chain



Hydrogen bromide

1^a $\mathrm{CH_3CH{=}C(CH_3)_2 \xrightarrow{HBr} CH_3\underset{Br}{C}HCH(CH_3)_2}$ 55%

2^b $\mathrm{CH_2{=}CHCO_2CH_3 \xrightarrow{HBr} BrCH_2CH_2CO_2CH_3}$ 80%–84%

3^c $\mathrm{CH_2{=}CHCH_2\overset{CH_3}{\underset{CH_3}{C}}{-}C({=}O)CH_3 \xrightarrow[h\nu]{HBr} BrCH_2CH_2CH_2\overset{CH_3}{\underset{CH_3}{C}}{-}C({=}O)CH_3}$ 76%

Addition of halomethanes

4^d $\mathrm{CCl_4 + H_2C{=}CH(CH_2)_5CH_3 \xrightarrow{(PhCO_2)_2} Cl_3CCH_2\underset{Cl}{C}H(CH_2)_5CH_3}$ 75%

5^e $\mathrm{BrCCl_3 + CH_2{=}C(C_2H_5)_2 \xrightarrow{h\nu} Cl_3CCH_2\underset{Br}{C}(C_2H_5)_2}$ 91%

6^f

7^g $\mathrm{CCl_4 + CH_2{=}CH\underset{OH}{C}(CH_3)_2 \xrightarrow[80^\circ C]{(PhCO_2)_2} Cl_3CCH_2\underset{Cl}{C}H\overset{OH}{C}(CH_3)_2}$ 70%

a. W. J. Bailey and S. S. Hirsch, *J. Org. Chem.* **28**, 2894 (1963).
b. R. Mozingo and L. A. Patterson, *Org. Synth.* III, 576 (1955).
c. H. O. House, C.-Y. Chu, W. V. Phillips, T. S. B. Sayer, and C.-C. Yau, *J. Org. Chem.* **42**, 1709 (1977).
d. M. S. Kharasch, E. V. Jensen, and W. H. Urry, *J. Am. Chem. Soc.* **69**, 1100 (1947).
e. M. S. Kharasch and M. Sage, *J. Org. Chem.* **14**, 537 (1949).
f. C. L. Osborn, T. V. Van Auken, and D. J. Trecker, *J. Am. Chem. Soc.* **90**, 5806 (1968).
g. P. D. Klemmensen, H. Kolind-Andersen, H. B. Madsen, and A. Svendsen, *J. Org. Chem.* **44**, 416 (1979).
h. M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.* **14**, 248 (1949).

Further evidence for a bromine-bridged radical comes from radical substitution of optically active 2-bromobutane. Most of the 2,3-dibromobutane that is formed is racemic, indicating that the chiral center has been involved in the reaction. When the 3-deuterated reagent is used, it can be shown that the hydrogen (or deuterium) that is abstracted is replaced by bromine with *retention of stereochemistry.*[92] These results are consistent with a bridged bromine radical.

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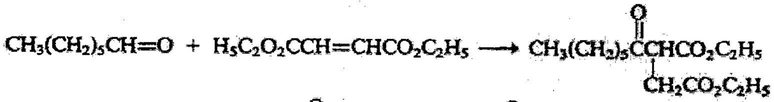
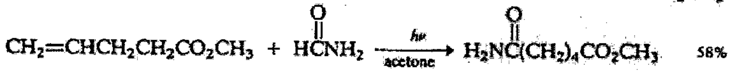
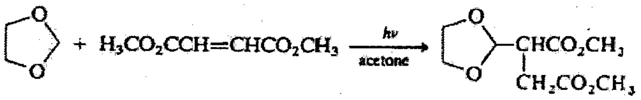
[92] P. S. Skell, R. R. Pavlis, D. C. Lewis, and K. J. Shea, *J. Am. Chem. Soc.* **95**, 6735 (1973).

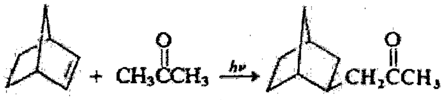
Addition of other carbon radicals

8[h] 
$CH_3CH{=}O + CH_2{=}CH(CH_2)_5CH_3 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}(CH_2)_7CH_3$ 64%

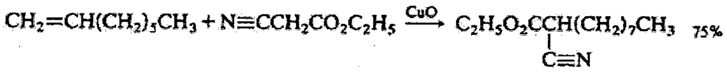
9[i] 
$CH_3(CH_2)_5CH{=}O + H_5C_2O_2CCH{=}CHCO_2C_2H_5 \longrightarrow CH_3(CH_2)_5\overset{O}{\overset{\|}{C}}\underset{CH_2CO_2C_2H_5}{\underset{|}{C}}HCO_2C_2H_5$

10[j] 
$CH_2{=}CHCH_2CH_2CO_2CH_3 + H\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[\text{acetone}]{h\nu} H_2N\overset{O}{\overset{\|}{C}}(CH_2)_4CO_2CH_3$ 58%

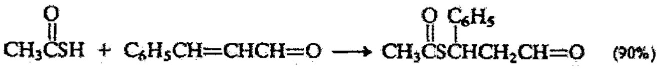
11[k] 

12[l] 

13[m] $CH_2{=}CH(CH_2)_5CH_3 + CH_2(CO_2C_2H_5)_2 \xrightarrow{ROOR} CH_3(CH_2)_7CH(CO_2C_2H_5)_2$ (67–85%)

14[n] 
$CH_2{=}CH(CH_2)_5CH_3 + N{\equiv}CCH_2CO_2C_2H_5 \xrightarrow{CuO} C_2H_5O_2C\underset{C\equiv N}{\underset{|}{C}}H(CH_2)_7CH_3$ 75%

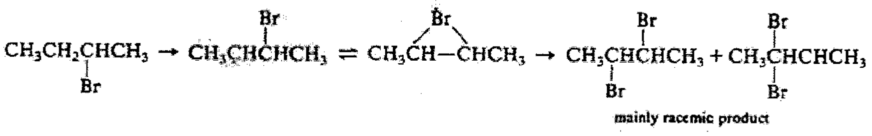
Additions of thiols and thio acids

15[o] 
$CH_3\overset{O}{\overset{\|}{C}}SH + C_6H_5CH{=}CHCH{=}O \longrightarrow CH_3\overset{O}{\overset{\|}{C}}S\overset{C_6H_5}{\overset{|}{C}}HCH_2CH{=}O$ (90%)

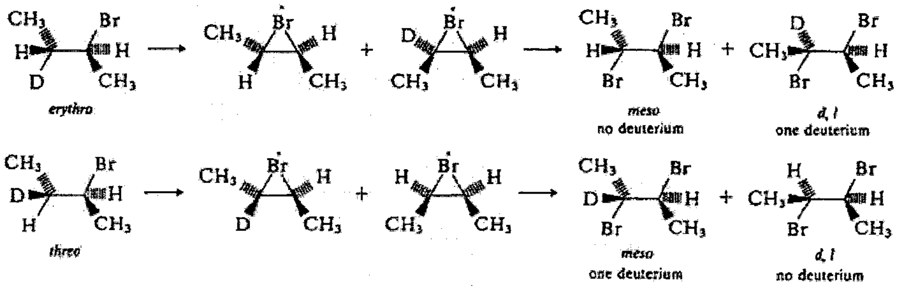
16[p] $CH_3CH_2CH_2CH_2SH + CH_2{=}CH(CH_2)_4CH_3 \xrightarrow{(PhCO_2)_2} CH_3(CH_2)_3S(CH_2)_6CH_3$ 68%

---

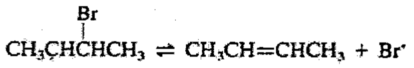
i. T. M. Patrick, Jr., and F. B. Erikson, *Org. Synth.* IV, 430 (1963).
j. D. Elad and J. Rokach, *J. Org. Chem.* 29, 1855 (1964).
k. I. Rosenthal and D. Elad, *J. Org. Chem.* 33, 805 (1968).
l. W. Reusch, *J. Org. Chem.* 27, 1882 (1962).
m. J. C. Allen, J. I. G. Cadogan, B. W. Harris and D. H. Hey, *J. Chem. Soc.*, 4468 (1962).
n. A. Hájek and J. Malek, *Synthesis*, 454 (1977).
o. R. Brown, W. E. Jones, and A. R. Pinder, *J. Chem. Soc.*, 2123 (1951).
p. D. W. Grattan, J. M. Locke, and S. R. Wallis, *J. Chem. Soc. Perkin Trans. 1*, 2264 (1973).


$CH_3CH_2\underset{Br}{\underset{|}{C}}HCH_3 \rightarrow CH_3\dot{C}H\overset{Br}{\overset{|}{C}}HCH_3 \rightleftharpoons CH_3\overset{\overset{Br}{\diagup\diagdown}}{CH{-}CH}CH_3 \rightarrow CH_3\underset{Br}{\underset{|}{C}}H\overset{Br}{\overset{|}{C}}HCH_3 + CH_3\underset{Br}{\underset{|}{C}}H\overset{Br}{\overset{|}{C}}HCH_3$

mainly racemic product



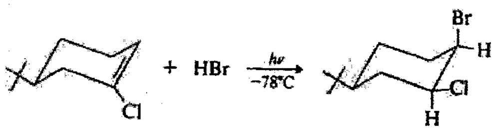
Other mechanisms must also operate, however, to account for the fact that 5–10% of the product is formed with retained configuration at the chiral center. Isotopic labeling studies have also demonstrated that the 3-bromo-2-butyl radical undergoes reversible loss of bromine atom to give 2-butene at a rate that is competitive with that of the bromination reaction.



$$CH_3\dot{C}H\overset{Br}{\overset{|}{C}}HCH_3 \rightleftharpoons CH_3CH{=}CHCH_3 + Br\cdot$$

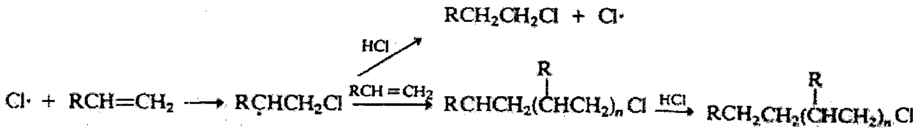
This process can account for some of the observed loss of optical purity by a mechanism which does not involve the bridged intermediate.[93]

trans-Diaxial addition is the preferred stereochemical mode for addition to cyclohexene and its derivatives[94]:



This stereochemistry can be explained in terms of a bromine-bridged intermediate.

Product mixtures from radical chain addition of hydrogen chloride to alkenes are much more complicated than is the case for hydrogen bromide. The problem is that the rate of abstraction of hydrogen from hydrogen chloride is not large relative to addition of the alkyl radical to the alkene. This results in the formation of low-molecular-weight polymers in competition with simple addition.



$$Cl\cdot + RCH{=}CH_2 \longrightarrow R\dot{C}HCH_2Cl \xrightarrow{HCl} RCH_2CH_2Cl + Cl\cdot$$

$$R\dot{C}HCH_2Cl \xrightarrow{RCH=CH_2} RCHCH_2(\overset{R}{\overset{|}{\dot{C}}}HCH_2)_nCl \xrightarrow{HCl} RCH_2CH_2(\overset{R}{\overset{|}{C}}HCH_2)_nCl$$

Radical chain additions of hydrogen fluoride and hydrogen iodide to alkenes are not observed. In the case of hydrogen iodide, the addition of an iodine atom to an alkene is an endothermic process and is too slow to permit a chain reaction, even though the hydrogen abstraction step would be favorable. In the case of hydrogen fluoride, the abstraction of hydrogen from hydrogen fluoride is energetically prohibitive.

12.4.2. Addition of Halomethanes

One of the older preparative free-radical reactions is the addition of polyhalomethanes to alkenes. Examples of addition of carbon tetrabromide, carbon

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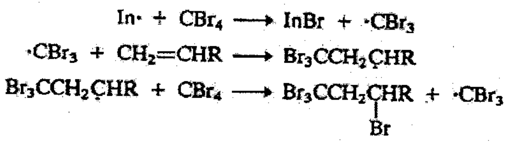
[93] D. D. Tanner, E. V. Blackburn, Y. Kosugi, and T. C. S. Rao, *J. Am. Chem. Soc.* **99**, 2714 (1977).

[94] H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.* **77**, 3465 (1955); N. A. LeBel, R. F. Czaja, and A. DeBoer, *J. Org. Chem.* **34**, 3112 (1969); P. D. Readio and P. S. Skell, *J. Org. Chem.* **31**, 753 (1966); H. L. Goering, P. I. Abell, and B. F. Aycock, *J. Am. Chem. Soc.* **74**, 3588 (1952).

tetrachloride, and bromoform have been recorded.[95] The reactions are chain processes that depend on facile abstraction of halogen or hydrogen from the halomethane.

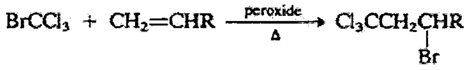


$$\mathrm{In\cdot + CBr_4 \longrightarrow InBr + \cdot CBr_3}$$
$$\mathrm{\cdot CBr_3 + CH_2{=}CHR \longrightarrow Br_3CCH_2\underset{\cdot}{C}HR}$$
$$\mathrm{Br_3CCH_2\underset{\cdot}{C}HR + CBr_4 \longrightarrow Br_3CCH_2\underset{Br}{\underset{|}{C}}HR + \cdot CBr_3}$$

or

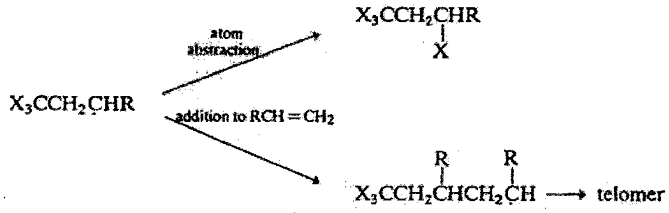
$$\mathrm{In\cdot + HCBr_3 \longrightarrow InH + \cdot CBr_3}$$
$$\mathrm{\cdot CBr_3 + CH_2{=}CHR \longrightarrow Br_3CCH_2\underset{\cdot}{C}HR}$$
$$\mathrm{Br_3CCH_2\underset{\cdot}{C}HR + HCBr_3 \longrightarrow Br_3CCH_2CH_2R + \cdot CBr_3}$$

Bromotrichloromethane can also be used effectively in the addition reaction. Because of the preferential abstraction of bromine, a trichloromethyl unit is added to the less substituted carbon atom of the alkene.



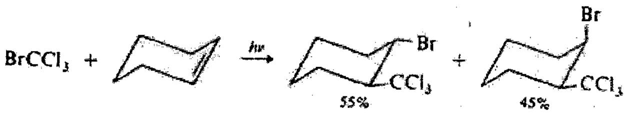
$$\mathrm{BrCCl_3 + CH_2{=}CHR \xrightarrow[\Delta]{peroxide} Cl_3CCH_2\underset{Br}{\underset{|}{C}}HR}$$

The efficiency of the halomethane addition process depends on the relative rate of halogen atom abstraction versus that of addition to the alkene.



For a given alkene, the order of reactivity of the halomethanes is $\mathrm{CBr_4 > CBrCl_3 > CCl_4 > CH_2Cl_2 > CHCl_3}$. The efficiency of 1:1 addition for a given alkene depends on the ease with which it undergoes radical chain polymerization, since rapid polymerization will compete with the halogen atom abstraction step in the chain mechanism. Polymerization is usually most rapid for terminal alkenes bearing stabilizing substituents such as a phenyl or ester group. Several specific examples of additions of polyhaloalkanes are included in Scheme 12.5.

The addition of bromotrichloromethane to cyclohexene gives a nearly 1:1 mixture of the two possible stereoisomers.[96]



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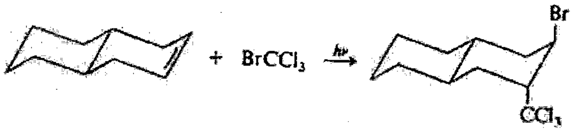
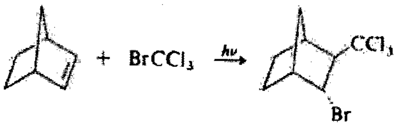
95. E. Sosnovsky, *Free Radical Reactions in Preparative Organic Chemistry*, MacMillan, New York, 1964, Chapter 2.
96. J. G. Traynham, A. G. Lane, and N. S. Bhacca, *J. Org. Chem.* 34, 1302 (1969).

This result shows that the initially added trichloromethyl group has little influence on the stereochemistry of the subsequent bromine atom abstraction. In contrast, in the case of $\Delta^{2,3}$-octahydronaphthalene, the addition is exclusively *trans*-diaxial:



The *trans*-fused decalin system is conformationally rigid, and the stereochemistry of the product indicates that the initial addition of the trichloromethyl radical is from an axial direction. This would be expected on stereoelectronic grounds, because the radical should initially interact with the π^* orbital. The axial trichloromethyl group then shields the adjacent radical position enough to direct the bromine abstraction in the *trans* sense. The results from the addition to cyclohexene indicate that the flexible 2-trichloromethylcyclohexyl radical must undergo conformational relaxation faster than bromine atom abstraction.

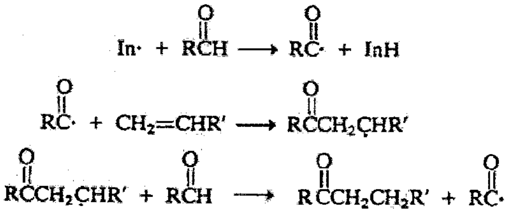
Addition of bromotrichloromethane to norbornene is also *anti*.



This is again the result of steric shielding by the trichloromethyl group, which causes the bromine atom to be abstracted from the *endo* face of the intermediate radical.

12.4.3. Addition of Other Carbon Radicals

Other functional groups can also provide sufficient stabilization of radicals to permit successful chain additions to alkenes. Acyl radicals are formed by abstraction of the formyl hydrogen from aldehydes. As indicated in Table 12.5, the resulting acyl radicals are somewhat stabilized. The chain process results in formation of a ketone by addition of the aldehyde to an alkene.



$$\mathrm{In\cdot + R\overset{O}{\overset{\|}{C}}H \longrightarrow R\overset{O}{\overset{\|}{C}}\cdot + InH}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}\cdot + CH_2{=}CHR' \longrightarrow R\overset{O}{\overset{\|}{C}}CH_2\underset{\cdot}{C}HR'}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}CH_2\underset{\cdot}{C}HR' + R\overset{O}{\overset{\|}{C}}H \longrightarrow R\overset{O}{\overset{\|}{C}}CH_2CH_2R' + R\overset{O}{\overset{\|}{C}}\cdot}$$

Some specific examples are included in Scheme 12.5.

The chain addition of formamide to alkenes is a closely related reaction. It results in the formation of primary amides.[97] The reaction is carried out with irradiation in acetone. The photoexcited acetone initiates the chain reaction by abstracting hydrogen from formamide.

$$\begin{aligned}
\mathrm{CH_3COCH_3} &\xrightarrow{h\nu} \mathrm{CH_3COCH_3^*} \\
\mathrm{CH_3COCH_3^* + HCONH_2} &\longrightarrow \mathrm{\cdot CONH_2 + (CH_3)_2\dot{C}OH} \\
\mathrm{\cdot CONH_2 + RCH{=}CH_2} &\longrightarrow \mathrm{R\underset{\cdot}{C}HCH_2CONH_2} \\
\mathrm{R\underset{\cdot}{C}HCH_2CONH_2 + HCONH_2} &\longrightarrow \mathrm{RCH_2CH_2CONH_2 + \cdot CONH_2}
\end{aligned}$$

12.4.4. Addition of Thiols and Thiocarboxylic Acids

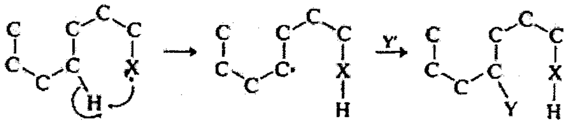
The addition of S—H compounds to alkenes by a radical chain mechanism is a quite general and efficient reaction.[98] The mechanism is analogous to that for hydrogen bromide addition. The energetics of both the hydrogen abstraction and addition steps are favorable. Entries 15 and 16 in Scheme 12.5 are examples.

$$\begin{aligned}
\mathrm{In\cdot + R'SH} &\longrightarrow \mathrm{In{-}H + R'S\cdot} \\
\mathrm{R'S\cdot + CH_2{=}CHR} &\longrightarrow \mathrm{R'SCH_2\underset{\cdot}{C}HR} \\
\mathrm{R'SCH_2\underset{\cdot}{C}HR + R'SH} &\longrightarrow \mathrm{R'SCH_2CH_2R + R'S\cdot}
\end{aligned}$$

The preferred stereochemistry of addition to cyclic alkenes is *anti*.[99] The additions are not as highly stereoselective as hydrogen bromide additions, however.

12.5. Intramolecular Free-Radical Reactions

Both substitution and addition reactions can occur intramolecularly. Intramolecular substitution reactions that involve hydrogen abstraction have some important synthetic applications, since they permit functionalization of carbon atoms relatively remote from the initial reaction site. The preference for a six-membered cyclic transition state in the hydrogen abstraction step imparts considerable position selectivity to the process.



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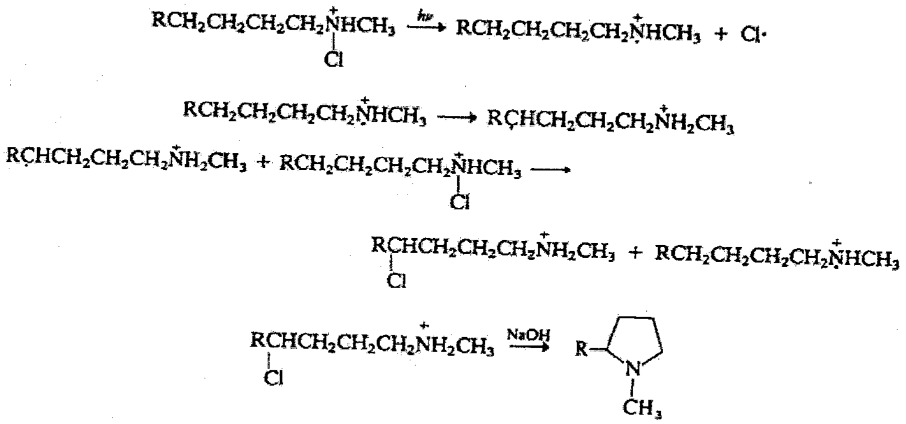
[97] D. Elad and J. Rokach, *J. Org. Chem.* 29, 1855 (1964).
[98] K. Griesbaum, *Angew Chem. Int. Ed. Engl.* 9, 273 (1970).
[99] N. A. LeBel, R. F. Czaja, and A. DeBoer, *J. Org. Chem.* 34, 3112 (1969); P. D. Readio and P. S. Skell, *K. Org. Chem.* 31, 759 (1966); F. G. Bordwell, P. S. Landis, and G. S. Whitney, *J. Org. Chem.* 30, 3764 (1965); E. S. Huyser, H. Benson, and H. J. Sinnige, *J. Org. Chem.* 32, 622 (1967).

There are several reaction sequences which involve such intramolecular hydrogen abstraction steps. One example is the photolytically initiated decomposition of *N*-haloamines in acidic solution, which is known as the *Hofmann–Loeffler reaction*.[100] The reaction leads initially to δ-haloamines, but these are usually converted to pyrrolidines by intramolecular nucleophilic substitution.



$$RCH_2CH_2CH_2CH_2\underset{Cl}{\overset{+}{N}}HCH_3 \xrightarrow{h\nu} RCH_2CH_2CH_2CH_2\overset{+}{\dot{N}}HCH_3 + Cl\cdot$$

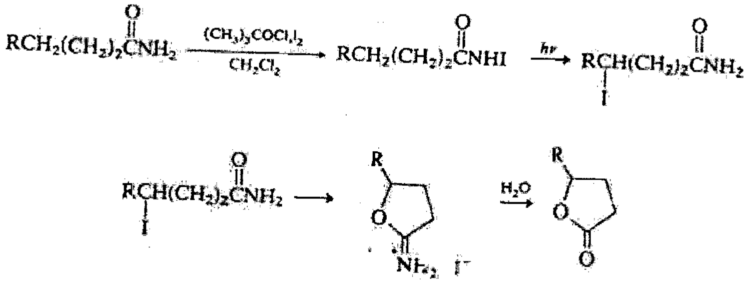
$$RCH_2CH_2CH_2CH_2\overset{+}{\dot{N}}HCH_3 \longrightarrow R\dot{C}HCH_2CH_2CH_2\overset{+}{N}H_2CH_3$$

$$R\dot{C}HCH_2CH_2CH_2\overset{+}{N}H_2CH_3 + RCH_2CH_2CH_2CH_2\underset{Cl}{\overset{+}{N}}HCH_3 \longrightarrow$$

$$R\underset{Cl}{C}HCH_2CH_2CH_2\overset{+}{N}H_2CH_3 + RCH_2CH_2CH_2CH_2\overset{+}{\dot{N}}HCH_3$$

$$R\underset{Cl}{C}HCH_2CH_2CH_2\overset{+}{N}H_2CH_3 \xrightarrow{NaOH}$$

There are related procedures involving *N*-haloamides which lead to lactones via iminolactone intermediates.[101]



$$RCH_2(CH_2)_2\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[CH_2Cl_2]{(CH_3)_3COCl, I_2} RCH_2(CH_2)_2\overset{O}{\overset{\|}{C}}NHI \xrightarrow{h\nu} R\underset{I}{C}H(CH_2)_2\overset{O}{\overset{\|}{C}}NH_2$$

$$R\underset{I}{C}H(CH_2)_2\overset{O}{\overset{\|}{C}}NH_2 \longrightarrow$$

A significant point about the final step in these reaction sequences is that the intramolecular nucleophilic attack by the amide group involves the oxygen, not the nitrogen, as the site of nucleophilic reactivity. Amides are generally more nucleophilic at oxygen than at nitrogen. This reflects both the fact that the oxygen is a site of relatively high electron density and also that the O-alkylated product retains a conjugated four-π-electron system.

A procedure for intramolecular functionalization of alcohols has been developed in studies carried out primarily with steroid derivatives.[102] The alcohol is converted to a nitrite ester by reaction with nitrosyl chloride. Photolysis effects

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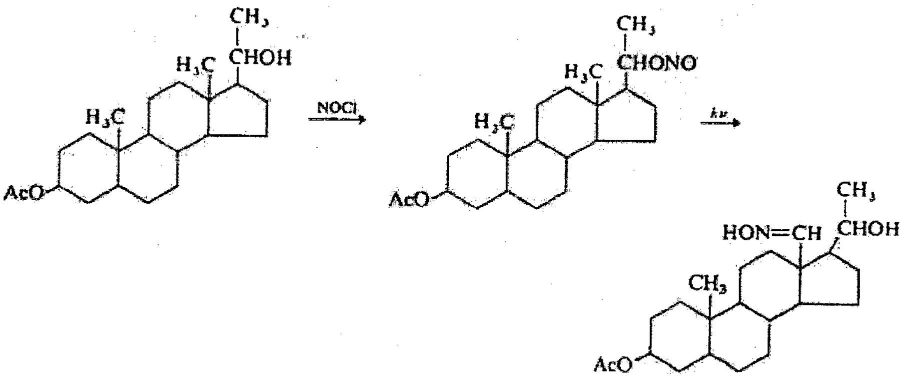
[100] M. E. Wolff, *Chem. Rev.* **63**, 55 (1963).

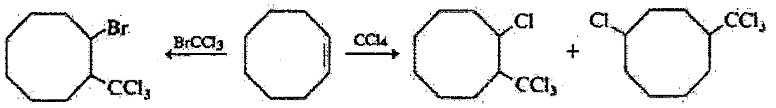
[101] D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 181 (1965); R. S. Neale, N. L. Marcus, and R. G. Schepers, *J. Am. Chem. Soc.* **88**, 3051 (1966).

[102] R. H. Hesse, *Adv. Free Radicals Chem.* **3**, 83 (1969); D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.* **83**, 4076 (1961).

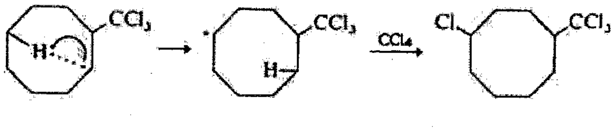
introduction of a nitroso function at an adjacent unsubstituted carbon atom. The nitrosoalkyl group is equivalent to an aldehyde or ketone group, since alkyl nitroso compounds rearrange to oximes. This reaction involves a hydrogen abstraction by photolytically generated alkoxy radicals but is not believed to be a chain process, since the quantum yield is less than unity.[103] Labeling studies using nitrogen-15 have established that the NO group is transferred intermolecularly, rather than in a cage process.[104]



Intramolecular hydrogen abstraction reactions have also been observed in medium-sized rings. The reaction of cyclooctene with carbon tetrachloride and bromotrichloromethane is an interesting case. As shown in the equation below, bromotrichloromethane adds in a completely normal manner, but carbon tetrachloride gives some 4-chloro-1-trichloromethylcyclooctane as well as the expected product.[105]



In the case of carbon tetrachloride, the radical intermediate is undergoing two competing reactions; intramolecular hydrogen abstraction is competitive with abstraction of a chlorine atom from carbon tetrachloride.



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[103] P. Kabasakalian and E. R. Townley, *J. Am. Chem. Soc.* **84**, 2711 (1962).

[104] M. Akhtar and M. M. Pechet, *J. Am. Chem. Soc.* **86**, 265 (1964).

[105] J. G. Traynham, T. M. Couvillon, and N. S. Bhacca, *J. Org. Chem.* **32**, 529 (1967); J. G. Traynham and T. M. Couvillon, *J. Am. Chem. Soc.* **87**, 5806 (1965); J. G. Traynham and T. M. Couvillon, *J. Am. Chem. Soc.* **89**, 3205 (1967).

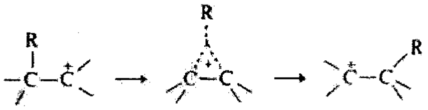
No product derived from the transannular hydrogen abstraction is observed in the addition of bromotrichloromethane because bromine atom abstraction is sufficiently rapid to prevent effective competition by the intramolecular hydrogen abstraction.

Intramolecular addition reactions are quite common when radicals are generated in molecules with unsaturation in a sterically favorable position.[106] Cyclization reactions based on intramolecular addition of radical intermediates have become synthetically useful, and several specific cases will be considered in Part B, Section 10.3.4.

12.6. Rearrangement and Fragmentation Reactions of Free Radicals

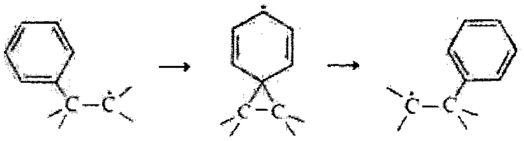
12.6.1. Rearrangement Reactions

Compared with rearrangement of cationic species, rearrangements of radical intermediates are quite rare. However, for specific structural types, free-radical migrations can be expected. The groups that are frequently capable of migration in free-radical intermediates include aryl, vinyl, acyl, and other unsaturated substituents. Migration of saturated groups is very unusual, and there is a simple structural reason for this. In cationic intermediates, migration occurs through a bridged transition state (or intermediate) that involves a three-center two-electron bond:



In a free radical, there is a third electron in the system. It cannot occypy the same orbital as the other two electrons. It must instead be in an antibonding level. As a result, the transition state for migration is less favorable than for the corresponding carbocation.

The more facile migration of aryl and other unsaturated groups is the result of formation of bridged intermediates by an addition process. In the case of aryl migration, the intermediate is a cyclohexadienyl radical.



Aryl migrations are promoted by steric crowding in the initial radical. This trend is illustrated by data from the thermal decomposition of a series of diacyl peroxides.

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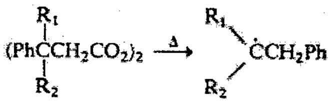
[106] A. L. J. Beckwith, *Tetrahedron* 37, 3073 (1981).

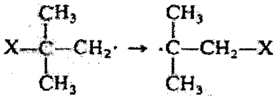
The amount of product derived from rearrangement increases with the size and number of substituents.[107]



$(PhCR_1R_2CH_2CO_2)_2 \xrightarrow{\Delta} R_1R_2\dot{C}CH_2Ph$

R_1	R_2	Rearrangement
CH_3	H	39%
Ph	H	63%
Ph	Ph	100%

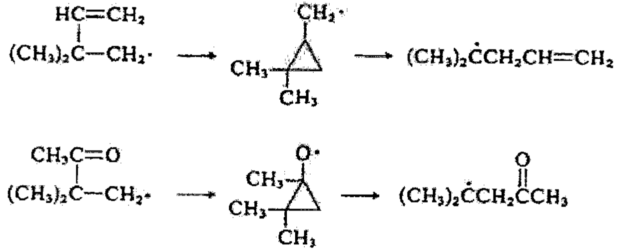
It has been possible to measure absolute rates and activation energies for migration in a series of 2-substituted 2,2-dimethylethyl radicals. The rates at 25°C and the E_a values for several substituents are indicated below.[108]



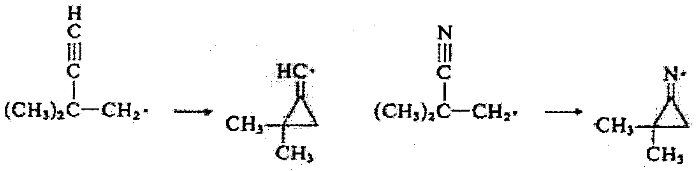
$X{-}C(CH_3)_2{-}CH_2\cdot \rightarrow \cdot C(CH_3)_2{-}CH_2{-}X$

X	k (s^{-1})	E_a (kcal/mol)
Ph	7.6×10^2	11.8
$CH_2{=}CH$	10^7	5.7
$(CH_3)_3CC{\equiv}C$	9.3	12.8
$(CH_3)_3CC{=}O$	1.7×10^5	7.8
$C{\equiv}N$	9.0	16.4

The rapid rearrangement of vinyl and acyl substituents can be explained as proceeding through intermediate cyclopropyl species.



The relatively slower rearrangement of alkynyl and cyano substituents can be attributed to the reduced stability of the intermediate derived from cyclization of the triply bonded substituents.



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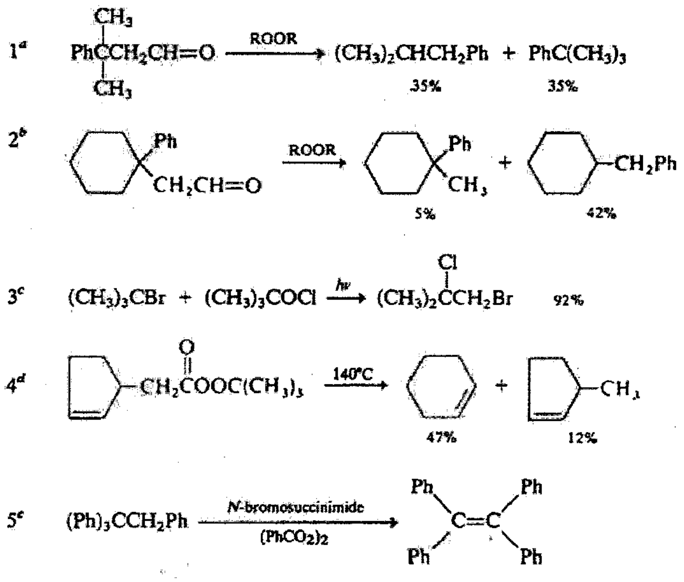
107. W. Rickatson and T. S. Stevens, *J. Chem. Soc.*, 3960 (1963).
108. D. A. Lindsay, J. Lusztyk, and K. U. Ingold, *J. Am. Chem. Soc.* **106**, 7087 (1984).

Scheme 12.6. Free-Radical Rearrangements

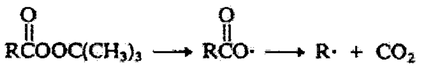


a. S. Winstein and F. H. Seubold, Jr., *J. Am. Chem. Soc.* **69**, 2916 (1947).
b. J. W. Wilt and H. P. Hogan, *J. Org. Chem.* **24**, 441 (1959).
c. P. S. Skell, R. G. Allen, and N. D. Gilmour, *J. Am. Chem. Soc.* **83**, 504 (1961).
d. L. H. Slaugh, *J. Am. Chem. Soc.* **87**, 1522 (1965).
e. H. Meislich, J. Costanza, and J. Strelitz, *J. Org. Chem.* **33**, 3221 (1968).

Scheme 12.6 gives some examples of reactions in which free-radical rearrangements have been observed.

12.6.2. Fragmentation Reactions

In earlier sections, we have already brought forward several examples of radical fragmentation reactions, although the terminology was not explicitly used. The facile decarboxylation of acyloxy radicals was mentioned earlier.



$$\mathrm{R\overset{O}{\overset{\|}{C}}OOC(CH_3)_3} \longrightarrow \mathrm{R\overset{O}{\overset{\|}{C}}O\cdot} \longrightarrow \mathrm{R\cdot} + \mathrm{CO_2}$$

For the acetoxy radical, the E_a for decarboxylation is about 6.5 kcal/mol and the rate is about $10^9\ \mathrm{s}^{-1}$ at 60°C and $10^6\ \mathrm{s}^{-1}$ at −80°C.[109] Thus, only very rapid reactions can compete with decarboxylation. As would be expected because of the lesser stability of aryl radicals, the rates of decarboxylation of aroyloxy radicals are less. The rate for *p*-methoxylbenzoyloxy radical has been determined to be about 3 ×

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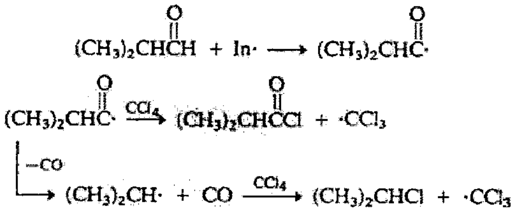
[109] J. Chateauneuf, J. Lusztyk, and K. U. Ingold, *J. Am. Chem. Soc.* **109**, 897 (1987).

$10^5\,s^{-1}$ near room temperature.[109] Hydrogen donation by very reactive hydrogen atom donors such as triethylsilane can compete with decarboxylation at moderate temperatures.

Acyl radicals can fragment with loss of carbon monoxide. Decarbonylation is slower than decarboxylation, but the rate also depends on the stability of the radical that is formed.[110] For example, when reaction of isobutyraldehyde with carbon tetrachloride is initiated by *t*-butyl peroxide, both isopropyl chloride and isobutyryl chloride are formed. Decarbonylation is competitive with the chlorine atom abstraction.



$$(CH_3)_2CH\overset{O}{\overset{\|}{C}}H + In\cdot \longrightarrow (CH_3)_2CH\overset{O}{\overset{\|}{C}}\cdot$$

$$(CH_3)_2CH\overset{O}{\overset{\|}{C}}\cdot \xrightarrow{CCl_4} (CH_3)_2CH\overset{O}{\overset{\|}{C}}Cl + \cdot CCl_3$$

$$\xrightarrow{-CO} (CH_3)_2CH\cdot + CO \xrightarrow{CCl_4} (CH_3)_2CHCl + \cdot CCl_3$$

Another common fragmentation reaction is the cleavage of an alkoxy radical to an alkyl radical and a carbonyl compound.[111]

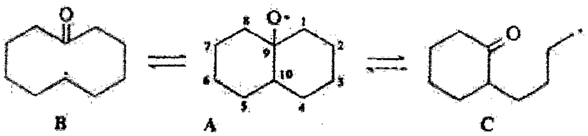
$$(CH_3)_3CO\cdot \longrightarrow CH_3\cdot + (CH_3)_2C{=}O$$

This type of fragmentation is involved in the chain decomposition of alkyl hypochlorites.[112]

$$RCH_2OCl \longrightarrow RCH_2O\cdot + Cl\cdot$$
$$RCH_2O\cdot \longrightarrow R\cdot + CH_2{=}O$$
$$R\cdot + RCH_2OCl \longrightarrow RCl + RCH_2O\cdot$$

In this reaction, too, the stability of the radical being eliminated is the major factor in determining the rate of fragmentation.

In cyclic systems, the fragmentation of alkoxy radicals can be a reversible process. The 10-decalyloxy radical can undergo fragmentation of either the 1-9 or the 9-10 bond:



B A C

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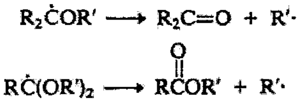
[110] D. E. Applequist and L. Kaplan, *J. Am. Chem. Soc.* **87**, 2194 (1965); W. H. Urry, D. J. Tecker, and H. D. Hartzler, *J. Org. Chem.* **29**, 1663 (1964); H. Fischer and H. Paul, *Acc. Chem. Res.* **20**, 200 (1987).

[111] P. Gray and A. Williams, *Chem. Rev.* **59**, 239 (1959).

[112] F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith, and P. M. Zanet, *J. Org. Chem.* **28**, 55 (1963); C. Walling and A. Padwa, *J. Am. Chem. Soc.* **85**, 1593, 1597 (1963).

By using various trapping reagents, it has been deduced that the transannular fragmentation is rapidly reversible. The cyclization of the fragmented radical **C** is less favorable, and it is trapped at rates which exceed that for recyclization under most circumstances.[113]

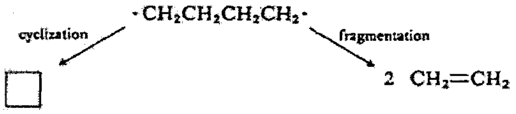
Radicals derived from ethers and acetals by hydrogen abstraction are subject to fragmentation, with formation of a ketone or an ester, respectively.



$$R_2\dot{C}OR' \longrightarrow R_2C{=}O + R'\cdot$$
$$R\dot{C}(OR')_2 \longrightarrow R\overset{\overset{\displaystyle O}{\|}}{C}OR' + R'\cdot$$

These fragmentations are sufficiently slow, however, that the initial radicals can undergo reactions, addition to alkenes being one example, at rates that are competitive with that of fragmentation.

A special case of fragmentation is that of 1,4-diradicals where fragmentation can lead to two stable molecules. In the case of 1,4-diradicals without functional group stabilization, reclosure to cyclobutanes is normally competitive with fragmentation to two molecules of alkene.



Theoretical calculations on the simplest such radical, 1,4-butadiyl, indicate that both processes are exothermic and can proceed with little if any barrier.[114]

A study of the biradicals **A**, **B**, and **C**, which were generated from the corresponding azo compounds, found that the lifetimes decreased in the order **A** > **B** > **C**. The lifetime of **A** is on the order of 1×10^{-6} s.[115]


A


B


C

The major factor identified in controlling the lifetimes of these radicals is the orientation of the singly occupied orbitals with respect to one another. In **A**, they are essentially parallel. This is a poor orientation for interaction. Diradical **B** is more flexible and rapidly reacts to give the coupling and fragmentation products. The geometry of the bicyclic ring system in radical C directs the half-filled orbitals

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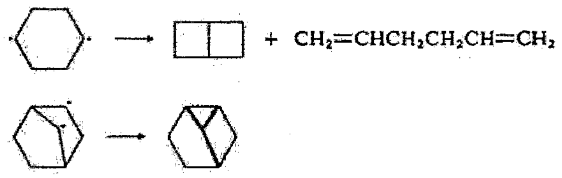
[113] A. L. J. Beckwith, P. Kazlauskas, and M. R. Syner-Lyons, *J. Org. Chem.* **48**, 4718 (1983).

[114] C. Doubleday, Jr., R. N. Camp, H. F. King, J. W. McIver, Jr., D. Mullaly, and M. Page, *J. Am. Chem. Soc.* **106**, 447 (1984).

[115] W. Adam, K. Hanneman, and R. M. Wilson, *J. Am. Chem. Soc.* **106**, 7646 (1984); W. Adam, K. Hanneman, and R. M. Wilson, *Angew. Chem. Int. Ed. Engl.* **24**, 1071 (1985).

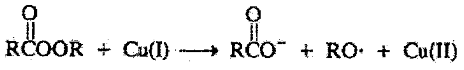
towards one another and its lifetime is less than 1 × 10^{-10} sec.



12.7. Electron Transfer Reactions Involving Transition Metal Ions

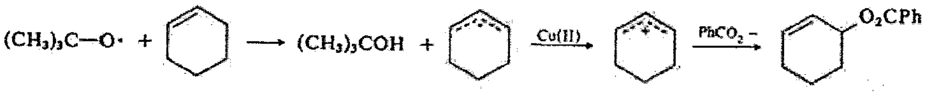
Most of the free-radical mechanisms discussed thus far have involved some combination of homolytic bond dissociation, atom abstraction, and addition steps. In this section, we will discuss reactions that include discrete electron transfer steps. Addition to or removal of one electron from a diamagnetic organic molecule generates a radical. Many organic reactions that involve electron transfer steps are mediated by transition metal ions. Many transition metal ions have two or more relatively stable oxidation states differing by one electron. Transition metal ions therefore frequently participate in electron transfer processes.

The decomposition of peroxy esters has been shown to be strongly catalyzed by Cu(I). The process is believed to involve oxidation of the copper to Cu(II):



$$R\overset{O}{\overset{\|}{C}}OOR + Cu(I) \longrightarrow R\overset{O}{\overset{\|}{C}}O^- + RO\cdot + Cu(II)$$

An example of this reaction is the reaction of cyclohexene with *t*-butyl perbenzoate, which is mediated by Cu(I).[116] The initial step is the reductive cleavage of the peroxy ester. The *t*-butoxy radical then abstracts hydrogen from cyclohexene to give an allylic radical. The radical is oxidized by Cu(II) to the carbocation, which captures benzoate ion.



The reactions of copper salts with diacyl peroxides have been investigated quite thoroughly, and the mechanistic studies indicate that both radicals and carbocations are involved as intermediates. The radicals are oxidized to carbocations by Cu(II), and the final products can be recognized as having arisen from carbocations because characteristic patterns of substitution, elimination, and rearrangement can be

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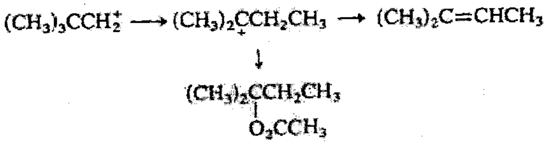
[116] K. Pedersen, P. Jakobsen, and S.-O. Lawesson, *Org. Synth.* V, 71 (1973).

discerned.[117]

$$[(CH_3)_3CCH_2CO_2]_2 + Cu(I) \longrightarrow (CH_3)_3CCH_2CO_2^- + (CH_3)_3CCH_2\cdot + CO_2 + Cu(II)$$

$$(CH_3)_3CCH_2\cdot + Cu(II) \longrightarrow (CH_3)_3CCH_2^+ + Cu(I)$$



$$(CH_3)_3CCH_2^+ \longrightarrow (CH_3)_2\underset{+}{C}CH_2CH_3 \longrightarrow (CH_3)_2C{=}CHCH_3$$

$$\downarrow$$

$$(CH_3)_2\underset{O_2CCH_3}{\underset{|}{C}}CH_2CH_3$$

When the radicals have β hydrogens, alkenes are formed by a process in which carbocations are probably bypassed. Instead, the oxidation and elimination of a proton probably occur in a single step through an alkylcopper species. The oxidation state of copper in such an intermediate is Cu(III).

$$R_2CHCH_2\cdot + Cu(II) \rightarrow R_2CHCH_2Cu(III) \rightarrow R_2C{=}CH_2 + Cu(I) + H^+$$

When halide ions or anions such as thiocyanate or azide are present, these anions are incorporated into the organic radical generated by decomposition of the peroxide. This anion transfer presumably occurs in the same step as the redox interaction with Cu(II), and such reactions have been called *ligand transfer reactions.*[118]

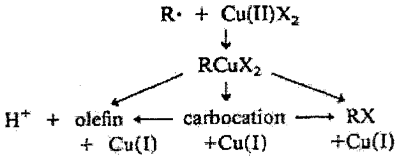
$$(RCO_2)_2 + Cu(I)X \rightarrow RCO_2^- + R\cdot + CO_2 + Cu(II)X$$

$$R\cdot + Cu(II)X \rightarrow R{-}Cu(III)X$$

$$R{-}Cu(III)X \rightarrow R{-}X + Cu(I)$$

These reactions do not appear to involve free carbocations, because they proceed effectively in nucleophilic solvents that would successfully compete with halide or similar anions for free carbocations. Also, rearrangements are unusual under these conditions, although they have been observed in special cases.

A unified concept of these reactions is provided by the proposal that alkylcopper intermediates are involved in each of these reactions at the stage of the oxidation of the radical.[119]



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[117] J. K. Kochi, *J. Am. Chem. Soc.* **85**, 1958 (1963); J. K. Kochi and A. Bemis, *J. Am. Chem. Soc.* **90**, 4038 (1968).

[118] C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.* **94**, 856 (1972).

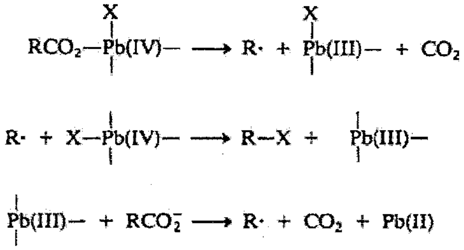
[119] C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.* **94**, 843 (1972).

The organocopper intermediate has three possible fates, and the preferred path is determined by the structure of the group R and the identity of the copper ligand X. If R is potentially a very stable carbocation, the intermediate breaks down to generate the carbocation and the products are derived from it. When X is halide or a pseudohalide such as ^{-}CN, ^{-}SCN, or $^{-}N_3$, the preferred pathway is ligand transfer leading to the alkyl halide or pseudohalide. If the R group is not capable of sustaining formation of a carbocation and no easily transferred anion is present, the organocopper intermediate is converted primarily to alkene by elimination of a proton.

One-electron oxidation of carboxylate ions generates acyloxy radicals, which can undergo the usual decarboxylation. Such electron transfer reactions can be effected by strong one-electron oxidants, such as Mn(III), Ag(II), Ce(IV), and Ph(IV).[120] These metal ions are also capable of oxidizing the radical intermediate, so the products are those expected from carbocations. The oxidative decarboxylation by Pb(IV) in the presence of halide salts leads to alkyl halides.[121] For example, oxidation of pentanoic acid with lead tetraacetate in the presence of lithium chloride gives 1-chlorobutane in 71% yield.

$$CH_3(CH_2)_3CO_2H \xrightarrow[\text{LiCl}]{\text{Pb(OAc)}_4} CH_3(CH_2)_3Cl + CO_2$$

A chain mechanism is proposed. The first step is oxidation of a carboxylate ion coordinated to Pb(IV), with formation of alkyl radical, carbon dioxide, and Pb(III). The alkyl radical then abstracts halogen from a Pb(IV) complex, generating a Pb(III) species that decomposes to Pb(II) with release of an alkyl radical. This alkyl radical can continue the chain process. The step involving abstraction of halide from a complex with a change in metal ion oxidation state is a ligand transfer type reaction.



$$RCO_2{-}\overset{X}{\underset{|}{\overset{|}{Pb}}}(IV){-} \longrightarrow R\cdot + \overset{X}{\underset{|}{\overset{|}{Pb}}}(III){-} + CO_2$$

$$R\cdot + X{-}\underset{|}{\overset{|}{Pb}}(IV){-} \longrightarrow R{-}X + \underset{|}{\overset{|}{Pb}}(III){-}$$

$$\underset{|}{\overset{|}{Pb}}(III){-} + RCO_2^{-} \longrightarrow R\cdot + CO_2 + Pb(II)$$

In the absence of halide salts, the principal products may be alkanes, alkenes, or acetate esters.

A classic reaction involving electron transfer and decarboxylation of acyloxy radicals is the Kolbe electrolysis, in which an electron is abstracted from a carboxy-

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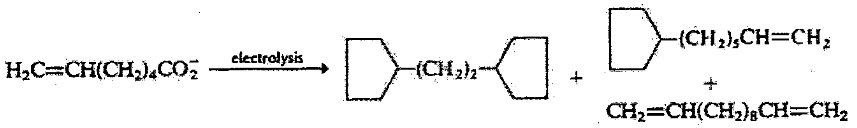
[120] J. M. Anderson and J. K. Kochi, *J. Am. Chem. Soc.* **92**, 2450 (1970); J. M. Anderson and J. K. Kochi, *J. Am. Chem. Soc.* **92**, 1651 (1970); R. A. Sheldon and J. K. Kochi, *J. Am. Chem. Soc.* **90**, 6688 (1968); W. A. Mosher and C. L. Kehr, *J. Am. Chem. Soc.* **75**, 3172 (1953); J. K. Kochi, *J. Am. Chem. Soc.* **87**, 1811 (1965).

[121] J. K. Kochi, *J. Org. Chem.* **30**, 3265 (1965); R. A. Sheldon and J. K. Kochi, *Org. React.* **19**, 279 (1972).

late ion at the anode of an electrolysis system. This reaction gives products derived from coupling of the decarboxylated radicals:

$$\begin{aligned} RCO_2^- &\longrightarrow RCO_2\cdot + e^- \\ RCO_2\cdot &\longrightarrow R\cdot + CO_2 \\ 2\,R\cdot &\longrightarrow RR \end{aligned}$$

Other transformations of the radicals are also possible. For example, the 5-hexenyl radical partially cyclizes in competition with coupling[122]:



Carbocations can also be generated during the electrolysis, and they give rise to alcohols and alkenes. The carbocations are presumably formed by an oxidation of the radical at the electrode before it reacts or diffuses into solution. For example, an investigation of the electrolysis of phenylacetic acid in methanol has led to the identification of benzyl methyl ether (30%), toluene (1%), benzaldehyde dimethylacetal (1%), methyl phenylacetate (6%), and benzyl alcohol (5%), in addition to the coupling product bibenzyl (26%).[123]

12.8. $S_{RN}1$ Substitution Processes

Electron transfer processes are also crucially involved in a group of reactions which are designated by the mechanistic description $S_{RN}1$. This refers to a nucleophilic substitution via a radical intermediate which proceeds by unimolecular decomposition of a radical anion derived from the substrate. There are two families of such reactions that have been developed to a stage of solid mechanistic understanding and also synthetic utility. The common mechanistic pattern involves electron transfer to the substrate, generating a radical anion which then expels the leaving group. This becomes a chain process if the radical generated by expulsion of the leaving group then reacts with the nucleophile to give a radical anion capable of sustaining a chain reaction.

$$\begin{array}{ll} \text{initiation} & R{-}X + e^- \rightarrow R{-}X^{\overset{.}{-}} \rightarrow R\cdot + X^- \\ \text{propagation} & R\cdot + Nu^- \rightarrow R{-}Nu^{\overset{.}{-}} \\ & R{-}Nu^{\overset{.}{-}} + R{-}X \rightarrow R{-}Nu + R{-}X^{\overset{.}{-}} \\ & R{-}X^{\overset{.}{-}} \rightarrow R\cdot + X^- \end{array}$$

A mechanism of this type permits substitution of certain aromatic and aliphatic nitro compounds by a variety of nucleophiles. These reactions were discovered as the result of efforts to explain the mechanistic basis for high-yield carbon alkylation

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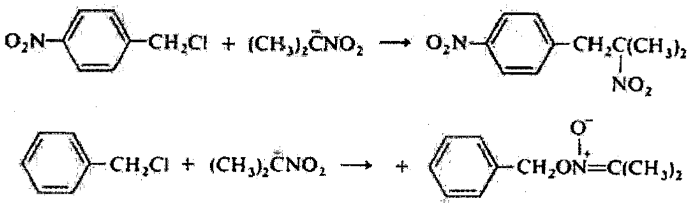
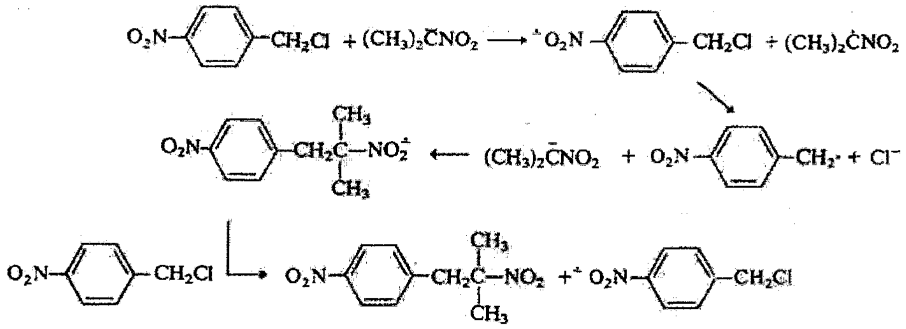
[122] R. F. Garwood, C. J. Scott, and B. C. L. Weedon, *J. Chem. Soc., Chem. Commun.*, 14 (1965).
[123] S. D. Ross and M. Finkelstein, *J. Org. Chem.* **34**, 2923 (1969).

of the 2-nitropropane anion by *p*-nitrobenzyl chloride. The corresponding bromide and iodide and benzyl halides that do not contain a nitro substituent give mainly the unstable oxygen alkylation product with this ambident anion.[124]



The mixture of carbon and oxygen alkylation is what would be expected for an S_N2 substitution process. The high preference for carbon alkylation suggested that a new mechanism operates with *p*-nitrobenzyl chloride. This conclusion was further strengthened by the fact that the chloride is more reactive than would be predicted on the basis of the usual I > Br > Cl reactivity trend for leaving groups in S_N2 reactions. The involvement of a free-radical process was indicated by EPR studies and by the observation that typical free-radical inhibitors decrease the rate of the carbon alkylation process. The mechanism proposed is a free-radical chain process initiated by electron transfer from the nitronate anion to the nitroaromatic compound.[125] This process is the principal reaction only for the chloride, because with the better leaving groups bromide and iodide, a direct S_N2 process is more rapid.



The absolute rate of dissociation of the radical anion of *p*-nitrobenzyl chloride has been measured as $4 \times 10^3\ s^{-1}$. The *m*-nitro isomer does not undergo a corresponding reaction.[126]

The synthetic value of the reaction has been developed from this mechanistic understanding. The reaction has been shown to be capable of providing highly substituted carbon skeletons that would be inaccesible by normal S_N2 processes.

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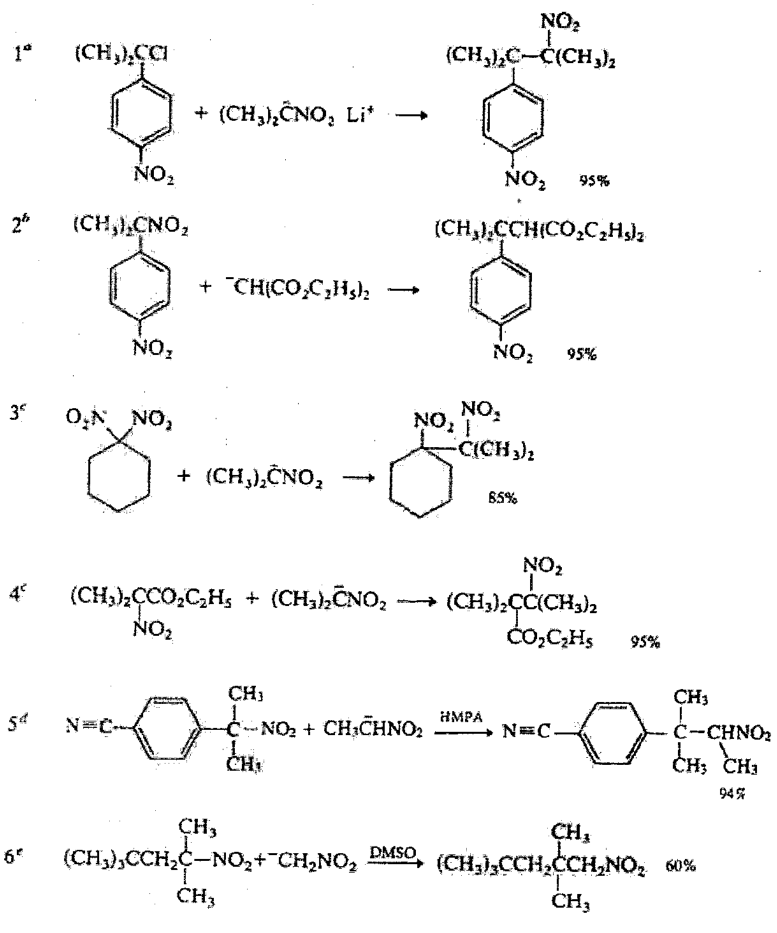
[124] N. Kornblum, *Angew Chem. Int. Ed. Engl.* **14**, 734 (1975); N. Korblum, in *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*, S. Patai (ed.), Wiley Interscience, New York, 1982, Chapter 10.

[125] N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Am. Chem. Soc.* **88**, 5662 (1966); G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.* **88**, 5663 (1966).

[126] R. K. Norris, S. D. Baker, and P. Neta, *J. Am. Chem. Soc.* **106**, 3140 (1984).

Scheme 12.7. Carbon Alkylation via Nitroalkane Radical Anions Generated by Electron Transfer



a. N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.* **89**, 725 (1967).
b. N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.* **89**, 5714 (1967).
c. N. Kornblum, S. D. Boyd, and F. W. Stuchal, *J. Am. Chem. Soc.* **92**, 5783 (1970).
d. N. Kornblum, S. C. Carlson, J. Widmer, M. Fifolt, B. N. Newton, and R. G. Smith, *J. Org. Chem.* **43**, 1394 (1978).
e. N. Kornblum and A. S. Erickson, *J. Org. Chem.* **46**, 1037 (1981).

For example, tertiary *p*-nitrocumyl halides can act as alkylating agents in high yield. The nucleophile need not be a nitroalkane anion, but can be such anions as thiolate, phenolate, or a carbanion such as those derived from malonate esters.[127] The same

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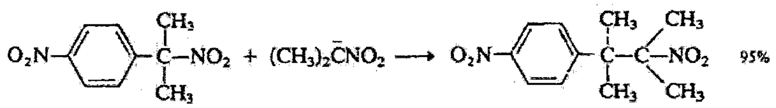
[127] N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.* **89**, 725 (1967); N. Kornblum, L. Cheng, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. M. Kestner, J. W. Manthey, M. T. Musser, H. W. Pinnick, D. H. Snow, F. W. Stuchal, and R. T. Swiger, *J. Org. Chem.* **52**, 196 (1987).

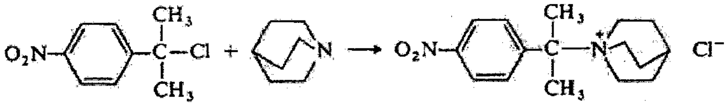
mechanism operates as for the nitronate anion. Furthermore, the leaving group need not be a halide. Displacement of nitrite ion from α,p-nitrocumene occurs with good efficiency.[128]



Azido, sulfonyl, and quaternary nitrogen groups can also be displaced by this mechanism.[129]

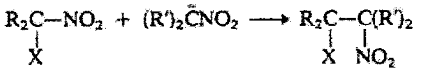
The $S_{RN}1$ reaction also proceeds with tertiary benzyl nitro compounds lacking a p-nitro substituent. The nitro group at the benzyl position acts as the electron acceptor, and decomposes to the benzyl radical and nitrite anion. The nitronate anion nucleophiles are then alkylated.[130] Entry 5 in Scheme 12.7 provides a specific example.

A similar mechanism has been proposed for the alkylation of amines by p-nitrocumyl chloride[131]:



Clearly, the tertiary nature of the chloride would make any proposal of an S_N2 mechanism highly suspect. Furthermore, the nitro substituent is essential to the success of these reactions. Cumyl chloride itself undergoes elimination of HCl on reaction with amines.

A related process constitutes a method of carrying out alkylation reactions to give highly branched alkyl chains that could not easily be formed by S_N2 mechanisms. The alkylating agent must contain a nitro group and a second electron-attracting group. These compounds react with nitronate anions to effect displacement of the nitro group.[132]



$$\underset{X}{R_2C}-NO_2 + (R')_2\bar{C}NO_2 \longrightarrow \underset{X}{R_2C}-\underset{NO_2}{C}(R')_2$$

$$X = C{\equiv}N, CO_2C_2H_5, \overset{O}{\overset{\|}{C}}R, NO_2$$

Experiments in which radical scavengers are added indicate that a chain reaction is involved, because the reaction is greatly retarded in the presence of the scavengers.

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[128] N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.* **89**, 5714 (1967).

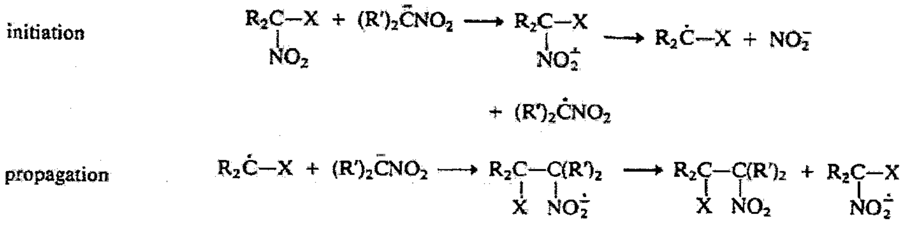
[129] N. Kornblum, P. Ackerman, J. W. Manthey, M. T. Musser, H. W. Pinnick, S. Singaram, and P. A. Wade, *J. Org. Chem.* **53**, 1475 (1988).

[130] N. Kornblum, S. G. Carlson, J. Widmer, M. J. Fifolt, B. N. Newton, and R. G. Smith, *J. Org. Chem.* **43**, 1394 (1978).

[131] N. Kornblum and F. W. Stuchal, *J. Am. Chem. Soc.* **92**, 1804 (1970).

[132] N. Kornblum and S. D. Boyd, *J. Am. Chem. Soc.* **92**, 5784 (1970).

The mechanism shown below indicates that one of the steps in the chain process is an electron transfer and that none of the steps involves atom abstraction. The elimination of nitrite occurs as a unimolecular decomposition of the radical anion intermediate, and the $S_{RN}1$ mechanistic designation would apply.



$$\text{initiation}\quad \underset{NO_2}{R_2C}{-}X + (R')_2\bar{C}NO_2 \longrightarrow \underset{NO_2^{\dot{-}}}{R_2C}{-}X \longrightarrow R_2\dot{C}{-}X + NO_2^- \quad + (R')_2\dot{C}NO_2$$

$$\text{propagation}\quad R_2\dot{C}{-}X + (R')_2\bar{C}NO_2 \longrightarrow \underset{X}{R_2C}{-}\underset{NO_2^{\dot{-}}}{C(R')_2} \longrightarrow \underset{X}{R_2C}{-}\underset{NO_2}{C(R')_2} + \underset{NO_2^{\dot{-}}}{R_2C}{-}X$$

This reaction can also be applied to tertiary nitroalkanes lacking any additional functional group. The reactions with nitro compounds lacking additional anion-stabilizing groups are carried out in dimethyl sulfoxide solution.[133]

$$R_3CNO_2 + {}^-CH_2NO_2 \xrightarrow{DMSO} R_3CCH_2NO_2$$

These reactions also appear to be chain reactions that proceed through the $S_{RN}1$ mechanism. Dimethyl sulfoxide is a particularly favorable solvent for this reaction, probably because its conjugate base acts as an efficient chain initiator by transferring an electron to the nitroalkane.

Although the nitro group plays a crucial role in most of these $S_{RN}1$ reactions, they have synthetic application beyond the area of nitro compounds. The nitromethyl groups can be converted to other functional groups, including aldehydes and carboxylic acids.[134] Nitro groups at tertiary positions can be reductively removed by reaction with the methanethiolate anion.[135] This reaction also appears to be of the electron transfer type, with the methanethiolate anion acting as the electron donor.

$$R_3C{-}NO_2 + CH_3S^- \rightarrow R_3C{-}NO_2^{\dot{-}} + CH_3S\cdot$$
$$R_3C{-}NO_2^{\dot{-}} \rightarrow R_3C\cdot + NO_2^-$$
$$R_3C\cdot + CH_3S^- \rightarrow R_3C{-}H + H_2\dot{C}S^-$$
$$H_2\dot{C}S^- + R_3C{-}NO_2 \rightarrow H_2C{=}S + R_3C{-}NO_2^{\dot{-}}$$

The unique feature of the $S_{RN}1$ reactions of substituted alkyl nitro compounds is the facility with which carbon-carbon bonds between highly branched centers can be formed. This point is illustrated by several of the examples in Scheme 12.7.

A second general reaction which proceeds by an $S_{RN}1$ mechanistic pattern involves aryl halides. Aryl halides undergo substitution be certain nucleophiles by

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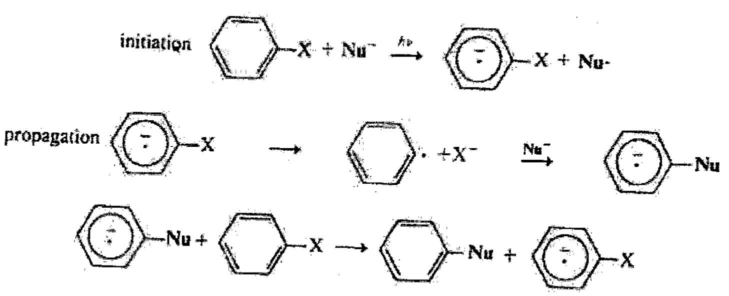
[133] N. Kornblum and A. S. Erickson, *J. Org. Chem.* 46, 1037 (1981).
[134] N. Kornblum, A. S. Erickson, W. J. Kelly, and B. Henggeler, *J. Org. Chem.* 47, 4534 (1982).
[135] N. Kornblum, S. C. Carlson, and R. G. Smith, *J. Am. Chem. Soc.* 101, 647 (1979).

a chain mechanism of the $S_{RN}1$ class.[136] Many of the reactions are initiated photochemically, and most have been conducted in liquid-ammonia solution.



The reactions can also be initiated by a strong chemical reductant or electrochemically.[137] There are several lines of evidence which support the operation of a chain mechanism, one of the most general observations being that the reactions are stopped or greatly retarded by radical traps. The reaction is not particularly sensitive to the aromatic ring substituents. Both electron-releasing groups such as methoxy and electron-attracting groups such as benzoyl can be present.[138] Groups which easily undergo one-electron reduction, especially the nitro group, cause the reaction to fail. The nucleophiles which have been used successfully include sulfide and phosphide anions, dialkyl phosphite anions, and certain enolates. Scheme 12.8 illustrates some typical reactions.

Kinetic studies have shown that the enolate and phosphorus nucleophiles all react at about the same rate. This suggests that the only step directly involving the nucleophile (step 2 of the propagation sequence) occurs at essentially the diffusion-controlled rate so that there is little selectivity among the individual nucleophiles.[139] The synthetic potential of the reaction lies in the fact that other substituents which activate the halide to substitution are not required, in contrast to aromatic nucleophilic substitution which proceeds by an addition–elimination mechanism (Section 10.5).

Instances of substitution of hindered alkyl halides by the $S_{RN}1$ mechanism have also been documented.[140] Some examples are shown below.

$$(CH_3)_3CCH_2Br + PhS^- \xrightarrow[NH_3]{h\nu} (CH_3)_3CCH_2SPh \quad 60\% \qquad \text{Ref. 141}$$

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[136] J. F. Bunnett, *Acc. Chem. Res.* **11**, 413 (1978); R. A. Rossi and R. H. deRossi, *Aromatic Substitution by the $S_{RN}1$ Mechanism*, American Chemical Society Monograph No. 178, Washington, D.C., 1983.

[137] C. Amatore, J. Chaussard, J. Pinson, J.-M. Saveant, and A. Thiebault, *J. Am. Chem. Soc.* **101**, 6012 (1979).

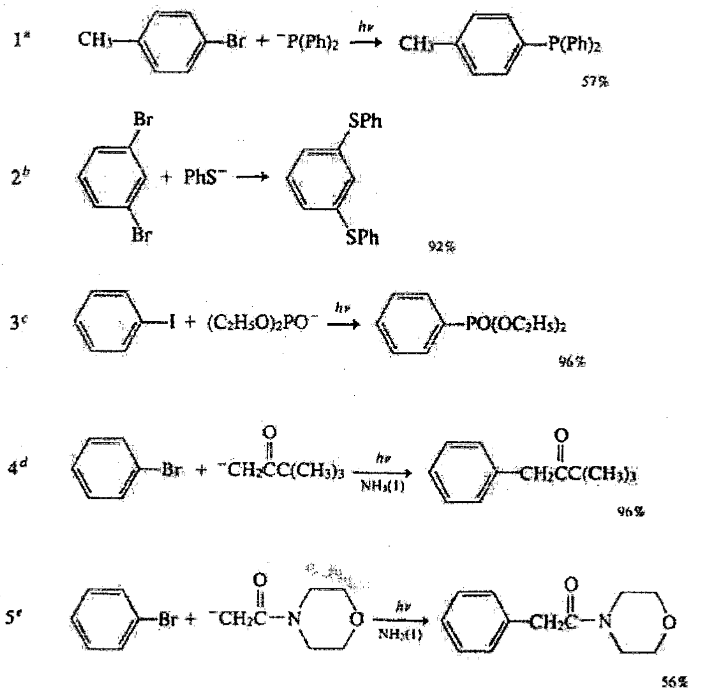
[138] J. F. Bunnett and J. E. Sundberg, *Chem. Pharm. Bull.* **23**, 2620 (1975); R. A. Rossi, R. H. deRossi, and A. F. Lopez, *J. Org. Chem.* **41**, 3371 (1976).

[139] C. Galli and J. F. Bunnett, *J. Am. Chem. Soc.* **103**, 7140 (1981); R. G. Scamehorn, J. M. Hardacre, J. M. Lukanich, and L. R. Sharpe, *J. Org. Chem.* **49**, 4881 (1984).

[140] S. M. Palacios, A. N. Santiago, and R. A. Rossi, *J. Org. Chem.* **49**, 4609 (1984).

[141] A. B. Pierini, A. B. Penenory, and R. A. Rossi, *J. Org. Chem.* **50**, 2739 (1985).

Scheme 12.8. Aromatic Substitution by the $S_{RN}1$ Mechanism



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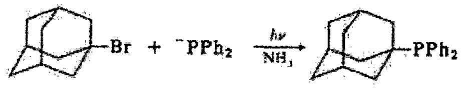
a. J. E. Swartz and J. F. Bunnett, *J. Org. Chem.* 44, 340 (1979).
b. J. F. Bunnett and X. Creary, *J. Org. Chem.* 39, 3611 (1974).
c. J. F. Bunnett and X. Creary, *J. Org. Chem.* 39, 3612 (1974).
d. M. F. Semmelhack and T. Bargar, *J. Am. Chem. Soc.* 102, 7765 (1980).
e. R. A. Rossi and R. A. Alonso, *J. Org. Chem.* 45, 1239 (1980).



Ref. 142

Ref. 143

The mechanism is the same as for aryl halides:

$$
\begin{array}{ll}
\text{initiation} & e^- + R{-}X \rightarrow R{-}X^{\dot{-}} \rightarrow R\cdot + X^- \\
\text{propagation} & R^\cdot + Nu{:} \rightarrow R{-}Nu^{\dot{-}} \\
 & R{-}Nu^{\dot{-}} + R{-}X \rightarrow R{-}Nu + R{-}X^{\dot{-}} \\
 & R{-}X^{\dot{-}} \rightarrow R^\cdot + X^-
\end{array}
$$

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142. R. A. Rossi, S. M. Palacios, and A. N. Santiago, *J. Org. Chem.* 47, 4654 (1982).
143. R. A. Rossi, A. N. Santiago, and S. M. Palacios, *J. Org. Chem.* 49, 3387 (1984).

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A. G. Lawler and H. R. Ward, in *Determination of Organic Structures by Physical Methods*, Vol. 5, F. C. Nachod and J. J. Zuckerman (eds.), Academic Press, New York, 1973, Chapter 3.

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E. T. Kaiser and L. Kevan (eds.), *Radical Ions*, Wiley-Interscience, New York, 1968.

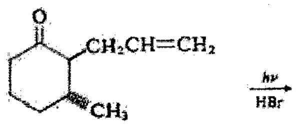
143

Problems

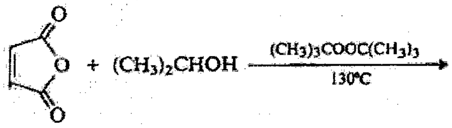
(*References for these problems will be found on page* 784.)

1. Predict the products of the following reactions.

(a)



(b)

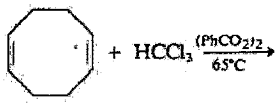


(c) $CH_3(CH_2)_6CH_2OCl \xrightarrow[1\,M \text{ in } CCl_4]{h\nu}$

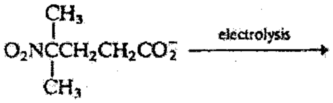
(d) $CH_3CH{=}O + H_2C{=}CHCH(OCH_3)_2 \xrightarrow[(PhCO_2)_2]{\Delta}$

(e)

(f)

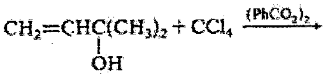


(g)



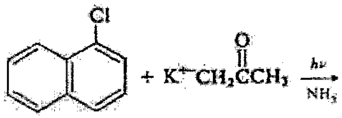
$O_2N\overset{CH_3}{\underset{CH_3}{C}}CH_2CH_2CO_2^- \xrightarrow{\text{electrolysis}}$

(h)



$CH_2{=}CH\underset{OH}{C}(CH_3)_2 + CCl_4 \xrightarrow{(PhCO_2)_2}$

(i)

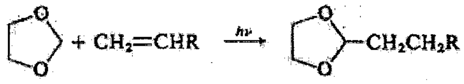


(j) $C_4H_9SH + CH_3(CH_2)_4CH{=}CH_2 \xrightarrow{(PhCO_2)_2}$

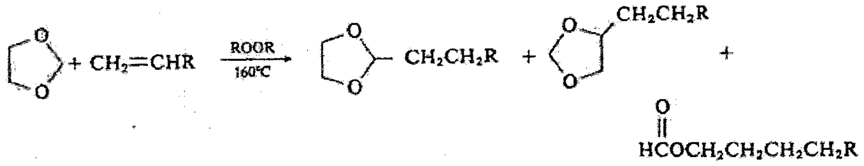
2. Using Table III in Ref. 58 (p. 679), calculate the expected product composition from the gas phase photochemical chlorination and bromination of 3-methylpentane under conditions (excess hydrocarbon) in which only monohalogenation would occur.

3. A careful study of the photoinitiated addition of HBr to 1-hexene established the following facts: (1) The quantum yield is 400; (2) the products are 1-bromohexane, 2-bromohexane, and 3-bromohexane. The amounts of 2- and 3-bromohexane formed are always nearly identical and increase from about 8% each at 4°C to about 22% at 63°C; (3) during the course of the reaction, small amounts of 2-hexene can be detected. Write a mechanism that could accommodate all these facts.

4. The irradiation of 1,3-dioxolane in the presence of alkenes and a photochemically activated initiator at 30°C leads to 2-alkyldioxolanes:



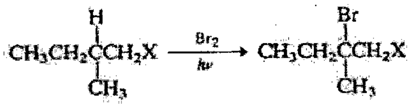
The reaction is particularly effective with alkenes with electron-attracting substituents such as diethyl maleate. When the reaction is conducted thermally with a peroxide initiator at 160°C, the product mixture is much more complex:



(a) Provide a mechanism for the formation of the observed products.
(b) Why is diethyl maleate an especially good reactant?
(c) Why does the photochemical method lead to a different product distribution than the peroxide-catalyzed reaction?

5. Provide a detailed mechanistic explanation of the following results.

(a) Photochemical bromination of **1**, $\alpha_D + 4.21°$, affords **2**, which is optically active, $\alpha_D - 3.23°$, but **3** under the same conditions gives **4**, which is optically inactive.



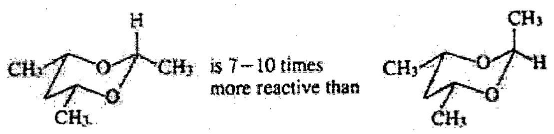
$$CH_3CH_2\overset{H}{\underset{CH_3}{C}}CH_2X \xrightarrow[h\nu]{Br_2} CH_3CH_2\overset{Br}{\underset{CH_3}{C}}CH_2X$$

1: X = Br
3: X = F

2: X = Br
4: X = F

(b) The stereoisomerization shown below proceeds efficiently, with no other chemical change occurring at a comparable rate, when the compound is warmed with *N*-bromosuccinimide and a radical chain initiator.

(c) There is a substantial difference in the reactivity of the two stereoisomeric compounds shown below toward abstraction of a hydrogen atom by the *t*-butoxy radical.



(d) Free-radical chlorination of optically active 1-chloro-2-methylbutane yields six dichloro derivatives of which four are optically active and two are not. Identify the optically active and optically inactive products and provide an explanation for the origin of each product.

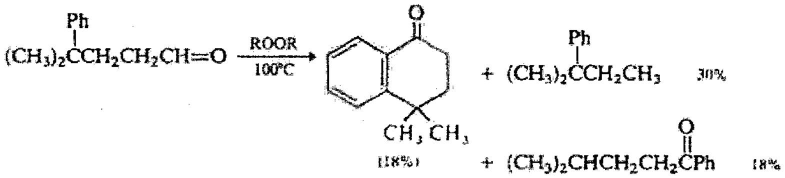
(e) Irradiation of a mixture of the hydrocarbon **B** and di-*t*-butyl peroxide generates a free radical which can be identified as the 2-phenylethyl radical by its EPR spectrum. This is the only spectrum which can be observed, even when the photolysis is carried out at low temperature (−173°C).

B

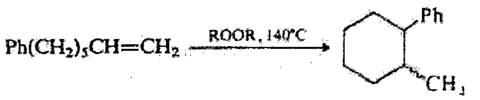
(f) Among the products from heating 1,5-heptadiene with 1-iodoperfluoropropane in the presence of azobis(isobutyronitrile) are two saturated 1:1 adducts. Both adducts gave the same olefin on dehydrohalogenation, and this olefin was shown by spectroscopic means to contain a $CH_2{=}C$ unit. Give the structures of the two adducts and propose a mechanism for their formation.

6. Write mechanisms which satisfactorily account for the following reactions.

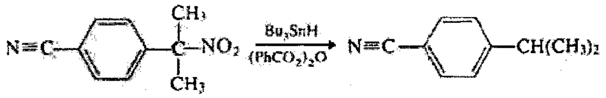
(a)



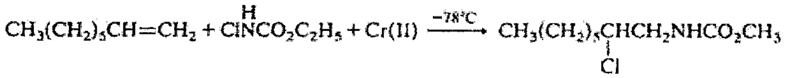
(b)



(c)

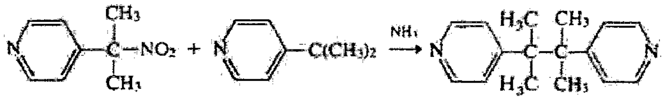


(d)

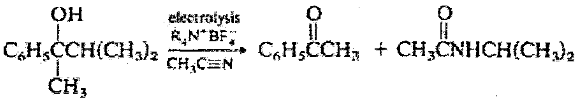


$$CH_3(CH_2)_5CH{=}CH_2 + Cl\overset{H}{N}CO_2C_2H_5 + Cr(II) \xrightarrow{-78^\circ C} CH_3(CH_2)_5\underset{Cl}{C}HCH_2NHCO_2CH_3$$

(e)

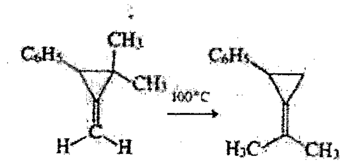


(f)

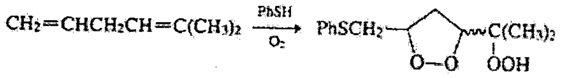


$$C_6H_5\overset{OH}{\underset{CH_3}{C}}CH(CH_3)_2 \xrightarrow[CH_3C\equiv N]{\text{electrolysis}\ R_4N^+BF_4^-} C_6H_5\overset{O}{\overset{\|}{C}}CH_3 + CH_3\overset{O}{\overset{\|}{C}}NHCH(CH_3)_2$$

(g)



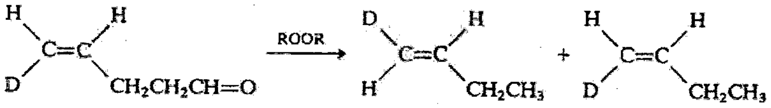
(h)



7. The decarbonylation of the two labeled pentenals shown below has been studied. Write a mechanism that could explain the distribution of deuterium label found in the two products.

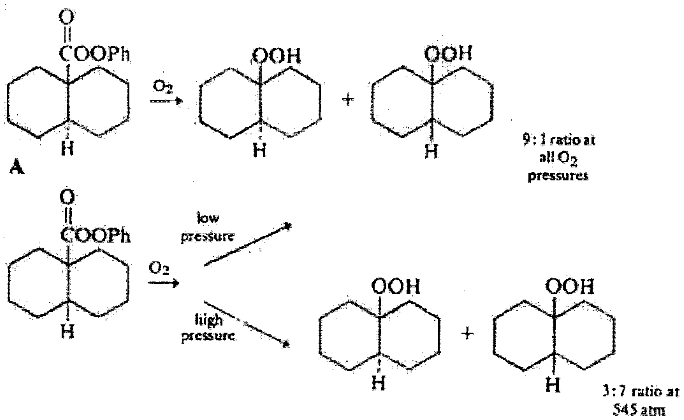
$$CH_2{=}CHCH_2CD_2CH{=}O \xrightarrow{ROOR} CH_2{=}CHCD_2CH_3 + CH_2{=}CHCH_2CHD_2$$

1 : 1 ratio in dilute solution, increasing to 1 : 1.5 in concentrated solution

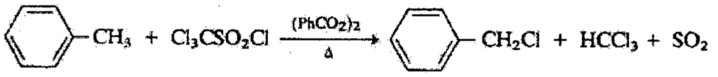


1 : 1 ratio in dilute solution, increasing to 1 : 1.4 in concentrated solution

8. Decomposition of the *trans*-decalyl perester **A** gives a 9 : 1 ratio of *trans* : *cis* hydroperoxide product at all oxygen pressures studied. The product ratio from the *cis* isomer is dependent on the oxygen pressure. At 1 atm O_2, it is 9 : 1 *trans* : *cis*, as with the *trans* substrate, but this ratio decreases and eventually inverts with increasing O_2 pressure. It is 7 : 3 *cis* : *trans* at 545 atm oxygen pressure. What deduction about the stereochemistry of the decalyl free radical can be made from these data?



9. (a) Trichloromethanesulfonyl chloride, Cl_3CSO_2Cl, can chlorinate hydrocarbons as described in the stoichiometric equation below. The reaction is a chain process. Write at least two possible sequences for chain propagation. Suggest some likely termination steps.



(b) Given the following additional information, choose between the chain propagation sequences you have postulated in part (a).

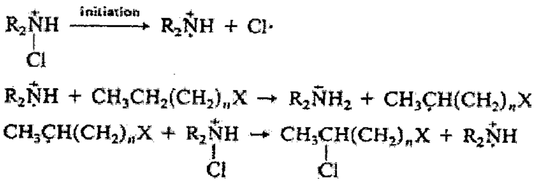
(1) In the reaction

$$R{-}H + BrCCl_3 \xrightarrow{h\nu} RBr + HCCl_3$$

the reactivity of cyclohexane is about one-fifth of toluene.

(2) In the chlorination by trichloromethanesulfonyl chloride, cyclohexane is about three times as reactive as toluene.

10. A highly selective photochemical chlorination of esters, amides, and alcohols can be effected in 70%–90% H_2SO_4 using *N*-chlorodialkylamines as chlorinating agents. Mechanistic studies indicate that a chain reaction is involved:



$$R_2\underset{\mathrm{Cl}}{\overset{+}{N}}H \xrightarrow{\text{initiation}} R_2\overset{+}{\dot{N}}H + Cl\cdot$$

$$R_2\overset{+}{\dot{N}}H + CH_3CH_2(CH_2)_nX \rightarrow R_2\overset{+}{N}H_2 + CH_3\dot{C}H(CH_2)_nX$$

$$CH_3\dot{C}H(CH_2)_nX + R_2\underset{\mathrm{Cl}}{\overset{+}{N}}H \rightarrow CH_3\underset{\mathrm{Cl}}{C}H(CH_2)_nX + R_2\overset{+}{\dot{N}}H$$

where $X = CO_2CH_3$, CH_2OH, or $CONH_2$. A very interesting feature of the reaction is that the chlorine atom is introduced on the next to terminal carbon atom for reactant molecules with $n = 4$ or 6. In contrast, chlorination of these same compounds with chlorine in nonpolar solvents shows little position selectivity. Rationalize the observed selectivity.

11. Analyze the hyperfine coupling in the spectrum of the butadiene radical anion given in Fig. 12.P11. What is the spin density at each carbon atom according to the McConnell equation?

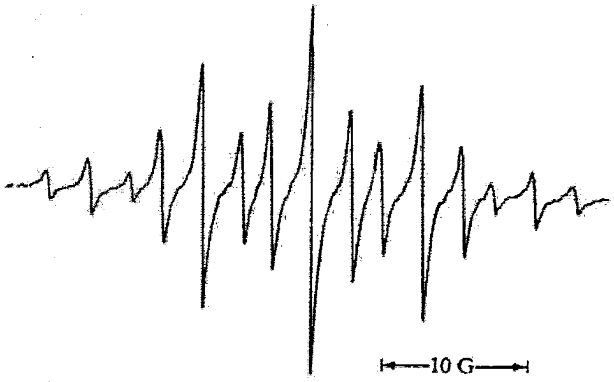
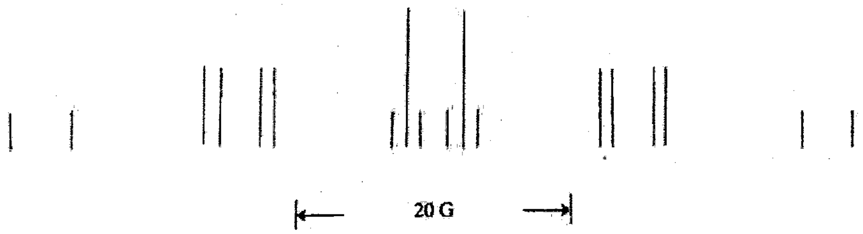


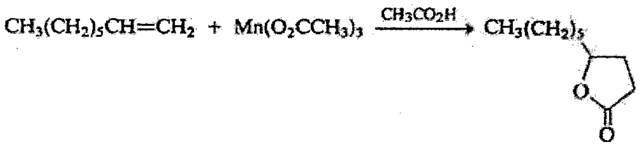
Fig. 12.P11. Spectrum of the butadiene radical anion. [From D. H. Levy and R. J. Meyers, *J. Chem. Phys.* 41, 1062 (1964).]

(b) A representation of the EPR spectrum of allyl radical is presented below. Interpret the splitting pattern and determine the values of the hyperfine splitting constants.

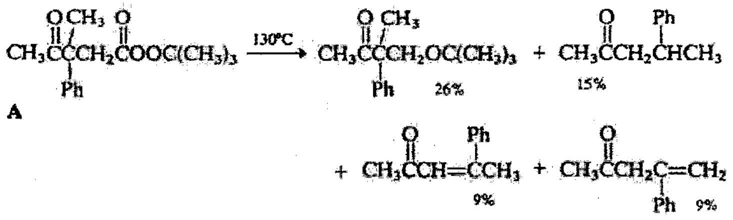


12. The oxidation of norbornadiene by *t*-butyl perbenzoate and Cu(I) leads to 7-*t*-butoxynorbornadiene. Similarly, oxidation with dibenzoyl peroxide and CuBr leads to 7-benzyloxynorbornadiene. In both cases, when a 2-monodeuterated sample of norbornadiene is used, the deuterium is found distributed at all seven carbons in the product. Provide a mechanism which could account for this result. In what ways does this mechanism differ from the general mechanism discussed on pp. 709–710?

13. A very direct synthesis of certain lactones can be achieved by heating an alkene, a carboxylic acid, and the Mn(III) salt of the acid. Suggest a mechanism by which this reaction might proceed.



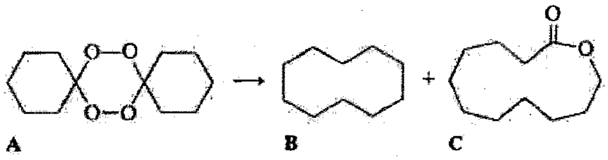
14. Indicate mechanisms that would account for each of the products observed in the thermal decomposition of compound **A**:



$$\underset{\mathbf{A}}{CH_3\overset{O}{\overset{\|}{C}}\overset{CH_3}{\underset{Ph}{C}}CH_2\overset{O}{\overset{\|}{C}}OOC(CH_3)_3} \xrightarrow{130°C} \underset{26\%}{CH_3\overset{O}{\overset{\|}{C}}\overset{CH_3}{\underset{Ph}{C}}CH_2OC(CH_3)_3} + \underset{15\%}{CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{Ph}{CH}CH_3}$$

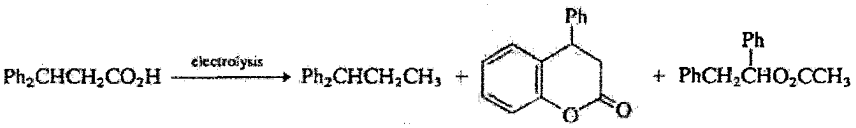
$$+ \underset{9\%}{CH_3\overset{O}{\overset{\|}{C}}CH{=}\overset{Ph}{C}CH_3} + CH_3\overset{O}{\overset{\|}{C}}CH_2\underset{Ph}{C}{=}CH_2 \; 9\%$$

15. The *spiro* peroxide **A**, which is readily prepared from cyclohexanone and hydrogen peroxide, decomposes thermally to give substantial amounts of cyclodecane and 11-undecanolactone (**C**). Account for the efficient formation of these macrocyclic compounds.



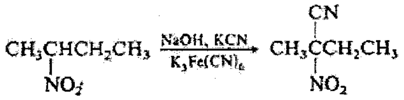
16. Methylcyclopropane shows strikingly different reactivity toward chlorination and bromination under radical chain conditions. With chlorine, cyclopropyl chloride (56%) is the major product, along with small amounts of 1,3-dichlorobutane (7%). Bromine gives a quantitative yield of 1,3-dibromobutane. Offer an explanation for the difference.

17. Electrolysis of 3,3-diphenylpropanoic acid in acetic acid-acetate solution gives the products shown below. Propose mechanisms for the formation of each of the major products.



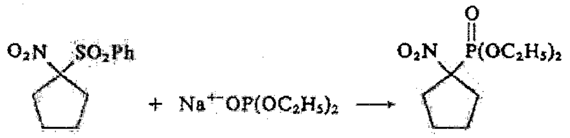
18. Write a mechanism to account for the formation of the observed product of each of the following reactions.

(a)

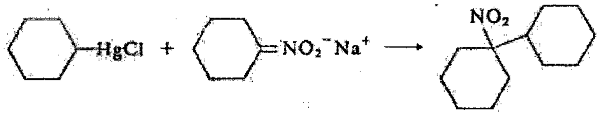


$$CH_3\underset{NO_2}{C}HCH_2CH_3 \xrightarrow[K_3Fe(CN)_6]{NaOH,\ KCN} CH_3\overset{CN}{\underset{NO_2}{C}}CH_2CH_3$$

(b)



(c)



19. The *N*-benzoyl methyl esters of the amino acids valine, alanine, and glycine have been shown to react with *N*-bromosuccinimide to give monobromination products containing bromine at the α carbon of the amino acid structure. The order of reactivity is glycine > alanine > valine (23:8:1). Account for the observed trend in reactivity.

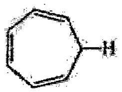
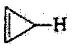
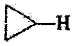
20. By measurements in an ion cyclotron resonance spectrometer, the proton affinity (PA) of free radicals can be measured.

$$RH^+ \rightarrow R^\cdot + H^+, \qquad \Delta H_{298} = PA$$

These data can be combined with ionization potential (IP) data according to the scheme below to determine bond dissociation energies (BDE).

$$\begin{array}{ll} RH^+ \rightarrow R^\cdot + H^+ & \Delta H_{298} = PA \\ RH \rightarrow RH^+ + e^- & \Delta H_{298} = IP \\ e^- + H^+ \rightarrow H^\cdot & \Delta H_{298} = -313.6\ \text{kcal/mol} \\ \hline RH \rightarrow R^\cdot + H^\cdot & \Delta H_{298} = BDE \end{array}$$

Data for PA and IP are given for several hydrocarbons of interest.

	IP	PA
$PhCH_2$—H	203	198
	190	200
	198	199
	224	180
CH_2=$CHCH_2$—H	224	180
	232	187
CH_2=CH—H	242	183

According to these data, which structural features provide stabilization of radical centers? Determine the level of agreement between these data and the "radical stabilization energies" given in Table 12.5 if the standard C—H bond dissociation energy is taken to be 98.8 kcal/mol. (Compare the calculated and observed bond dissociation energies for the benzyl, allyl, and vinyl systems.)