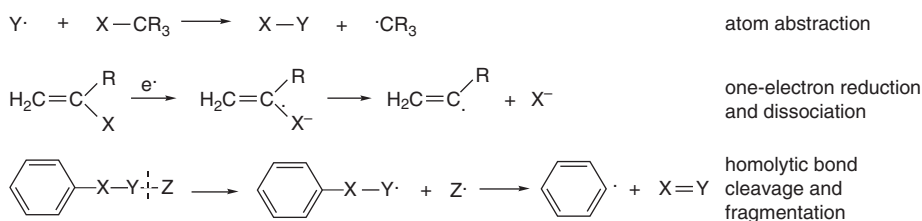


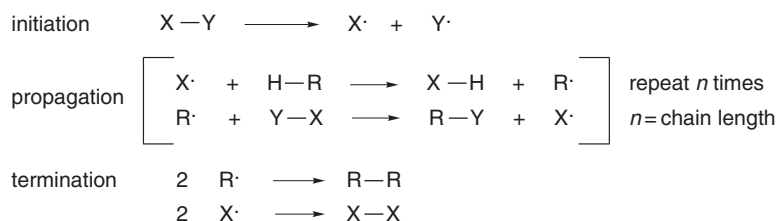
Free Radical Reactions

Introduction

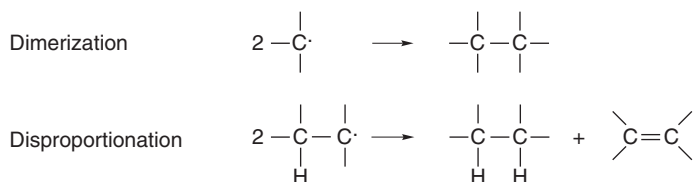
A free radical reaction involves molecules having unpaired electrons. The radical can be a starting compound or a product, but radicals are usually intermediates in reactions. Most of the reactions discussed to this point have been *heterolytic processes* involving polar intermediates and/or transition structures *in which all electrons remained paired throughout the course of the reaction*. In radical reactions, *homolytic bond cleavages* occur, with each fragment retaining one of the bonding electrons. The generalized reactions below illustrate the formation of alkyl, vinyl, and aryl free radicals by homolytic processes.



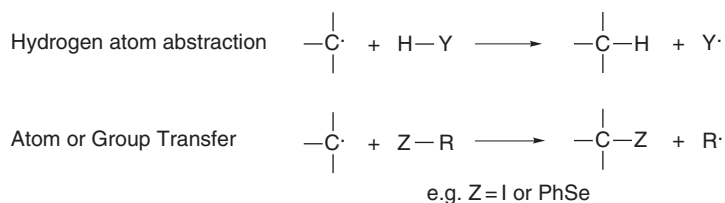
Free radicals are often involved in *chain reactions*. The overall mechanism consists of a series of reactions that regenerates a radical that can begin a new cycle of reactions. This sequence of reactions is called the *propagation phase*. Free radicals are usually highly reactive and the individual steps in a chain reaction typically have high absolute rate constants. However, the concentrations of the intermediates are low. The overall rates of reaction depend on the balance between the *initiation* and *termination* phases of the reaction, which start and end the chain sequence. The *chain length* is an important characteristic of free radical reactions. It specifies the average number of propagation sequences that occur per initiation step.



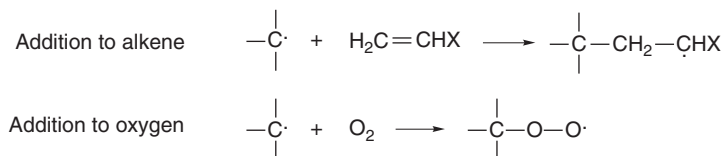
The effect of substituents on radical stability was introduced in Section 3.4.3. Most organic free radicals have very short lifetimes and dimerize or disproportionate at a diffusion-controlled rate. The usual disproportionation process for alkyl radicals involves transfer of a hydrogen from the β -carbon to the radical site, leading to formation of an alkane and an alkene. Disproportionation is facilitated by the weak β -C-H bond (see p. 311)



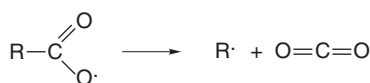
There are several fundamental types of radical reactions. Radicals can abstract hydrogen or other atoms from many types of solvents and reagents. This is a particularly important example of an *atom or group transfer reaction*.



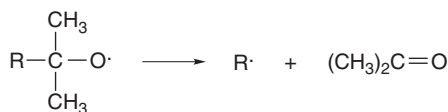
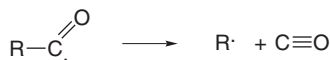
Radicals are also capable of addition reactions. For synthetic purposes, additions to alkenes are particularly important. Most radicals are highly reactive toward O_2 .



Radicals also undergo fragmentation reactions. Most of these are β -scission reactions, such as illustrated by decarboxylation and fragmentation of alkoxy radicals, but decarbonylation, an α -cleavage, is also facile.



decarboxylation

 β -fragmentation of alkoxy radical

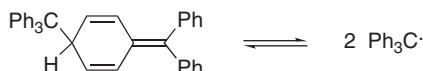
decarbonylation

As we discuss specific reaction mechanisms, we will see that they are combinations of a relatively small number of reaction types that are applicable to a number of different reactants and reaction sequences.

11.1. Generation and Characterization of Free Radicals

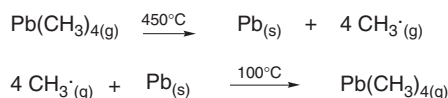
11.1.1. Background

Two early 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 $\text{Ph}_3\text{C}\cdot$ in equilibrium with a less reactive molecule. Eventually it was shown that the dimeric product is a cyclohexadiene derivative.¹



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

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



Since these early experiments, a great deal of additional information about the structure and properties of free radical intermediates has been developed. In this chapter, we discuss the structure of free radicals and some of the special features associated with free radical reactions. We also consider some of the key chemical reactions that involve free radical intermediates.

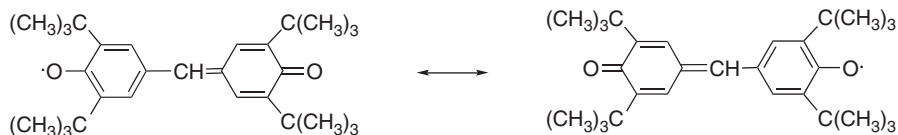
¹. H. Lankamp, W. Th. Nauta, and C. MacLean, *Tetrahedron Lett.*, 249 (1968); J. M. McBride, *Tetrahedron*, **30**, 2009 (1974); K. J. Skinner, H. S. Hochster, and J. M. McBride, *J. Am. Chem. Soc.*, **96**, 4301 (1974).

11.1.2. Long-Lived Free Radicals

Radicals that have long lifetimes and are resistant to dimerization, disproportionation, and other routes to self-annihilation are called *persistent free radicals*. Scheme 11.1 gives some examples of long-lived free radicals. A few free radicals are indefinitely stable, such as Entries 1, 3, and 6, and are just as stable to ordinary conditions of temperature and atmosphere as typical closed-shell molecules. Entry 2 is somewhat less stable to oxygen, although it can exist indefinitely in the absence of oxygen. The structures shown in Entries 1, 2, and 3 all permit extensive delocalization of the unpaired electron into aromatic rings. These highly delocalized radicals show little tendency toward dimerization or disproportionation. The radical shown in Entry 3 is unreactive under ordinary conditions and is thermally stable even at 300°C.²

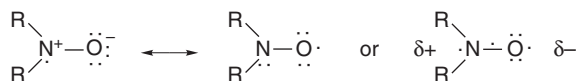
The *bis*-(*t*-butyl)methyl radical shown in Entry 4 has only alkyl substituents and yet has a significant lifetime in the absence of oxygen. The *tris*-(*t*-butyl)methyl radical has an even longer lifetime with a half-life of about 20 min at 25°C.³ The steric hindrance provided by the *t*-butyl substituents greatly retards the rates of dimerization of these radicals. Moreover, they lack β -hydrogens, precluding the normal disproportionation reaction. They remain highly reactive toward oxygen, however. The extended lifetimes have more to do with kinetic factors than with inherent stability.⁴ Entry 5 is a sterically hindered perfluorinated radical that is even more long-lived than similar alkyl radicals.

Certain radicals are stabilized by synergistic conjugation involving two or more functional groups. Entries 6 and 7 are examples. Galvinoxyl, the compound shown in Entry 6 benefits not only from delocalization over the two aromatic rings, but also from the equivalence of the two oxygens, which is illustrated by the resonance structures. The hindered nature of the oxygens also contributes to persistence.



Entry 7 also benefits from interaction between the ester and amino groups, as is discussed in Section 11.1.6.

There are only a few functional groups that contain an unpaired electron and yet are stable in a wide range of structural environments. The best example is the nitroxide group illustrated in Entry 8. There are numerous specific nitroxide radicals that have been prepared and characterized. The unpaired electron is delocalized between nitrogen and oxygen in a structure with a N–O bond order of 1.5.

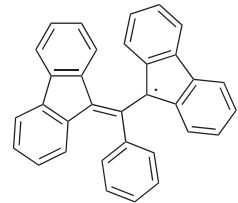
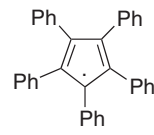
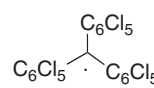
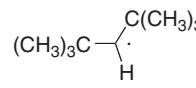
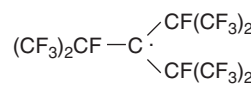
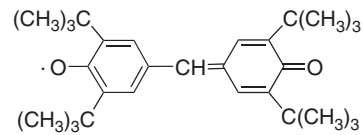
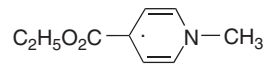
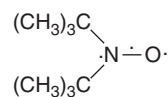


Many nitroxides are stable under normal conditions, and heterolytic reactions can be carried out on other functional groups in the molecule without affecting the nitroxide

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).

Structure	Stability
<p>1^a</p> 	<p>Indefinitely stable as a solid, even in the presence of air</p>
<p>2^b</p> 	<p>Crystalline substance is not rapidly attacked by oxygen, although solutions are air-sensitive. The compound is stable to high temperature in the absence of air.</p>
<p>3^c</p> 	<p>Stable in solution for days, even in the presence of air. Indefinitely stable in the solid state. Thermally stable up to 300°C.</p>
<p>4^d</p> 	<p>Persistent in dilute solution ($<10^{-5} M$) below -30°C in the absence of oxygen; $t_{1/2}$ of 50 s at 25°C.</p>
<p>5^e</p> 	<p>Thermally stable to 70°C; stable to O_2.</p>
<p>6^f</p> 	<p>Stable to oxygen; stable to extended storage as a solid. Slowly decomposes in solution.</p>
<p>7^g</p> 	<p>Stable distillable liquid that is only moderately sensitive to O_2.</p>
<p>8^h</p> 	<p>Stable to oxygen, even above 100°C</p>

- a. C. F. Koelsch, *J. Am. Chem. Soc.*, **79**, 4439 (1957).
 b. K. Ziegler and B. Schnell, *Liebigs Ann. Chem.*, **445**, 266 (1925).
 c. M. Ballester, J. Riera, J. Castaner, C. Badia, and J. M. Monso, *J. Am. Chem. Soc.*, **93**, 2215 (1971).
 d. G. D. Mendenhall, D. Griller, D. Lindsay, T. T. Tidwell, and K. U. Ingold, *J. Am. Chem. Soc.*, **96**, 2441 (1974).
 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. J. Hermolin, M. Levin, and E. M. Kosower, *J. Am. Chem. Soc.*, **103**, 4808 (1981).
 h. A. K. Hoffmann and A. T. Henderson, *J. Am. Chem. Soc.*, **83**, 4671 (1961).

group.⁵ Nitroxides are very useful in biochemical studies by being easily detected paramagnetic probes.⁶

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

11.1.3. Direct Detection of Radical Intermediates

The distinguishing characteristic of free radicals is the presence of an unpaired electron. Species with an unpaired electron are *paramagnetic*, that is, they have a nonzero electronic spin. The most useful method for detecting and characterizing unstable radical intermediates is *electron spin resonance* (ESR) spectroscopy,⁷ also known as *electron paramagnetic resonance* (EPR) spectroscopy. ESR 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 ESR 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. ESR spectroscopy is a highly specific tool for detecting radical species because only molecules with unpaired electrons give rise to ESR spectra. As with other spectroscopic methods, detailed analysis of the absorption spectrum can provide 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:

$$h\nu = E = g\mu_B H \quad (11.1)$$

where μ_B is the Bohr magneton (a constant equal to 9.273 ergs/gauss) 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 position in NMR spectra is characteristic of the absorbing nucleus.

More detailed structural information can be deduced from the *hyperfine splitting* in ESR spectra. The origin of this splitting is closely related to the factors that cause spin-spin splitting in ¹H-NMR spectra. Certain nuclei have a magnetic moment, and among those of greatest interest in organic chemistry are ¹H, ¹³C, ¹⁴N, ¹⁹F, and ³¹P. Interaction of the electron with one or more of these nuclei splits the signal arising from the unpaired electron. The number of lines is given by the equation

$$\text{Number of lines} = 2nI + 1 \quad (11.2)$$

where *I* is the nuclear spin quantum number and *n* is the number of equivalent interacting nuclei. For ¹H, ¹³C, ¹⁹F, and ³¹P, *I* = 1/2. so a single hydrogen splits a

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-Labeling*, Vol. 2, Academic Press, New York, 1979; S. Banerjee and G. K. Trivedi, *J. Sci. Ind. Res.*, **54**, 623 (1995); L. B. Volodarsky, V. A. Reznikov, and V. I. Ovcharenko, *Synthetic Chemistry of Stable Nitroxides*, CRC Press, Boca Raton, FL, 1994.

⁶. G. L. Millhauser, W. R. Fiori, and S. M. Miick, *Methods Enzymol.*, **246**, 589 (1995).

⁷. B. Mile, *Current Org. Chem.*, **4**, 55 (2000); F. Gerson and W. Huber, *Electron Spin Resonance of Organic Radicals*, Wiley-VCH, Weinheim, 2003.

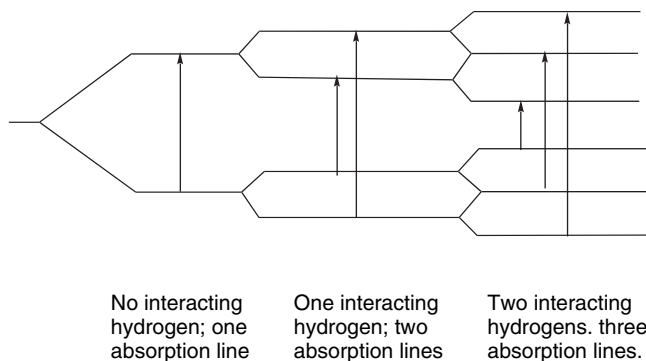


Fig. 11.1. Hyperfine splitting in ESR spectra.

signal into a doublet. Interaction with three equivalent hydrogens, as in a methyl group, gives splitting into four lines. This splitting is illustrated in Figure 11.1. Nitrogen (^{14}N) with $I = 1$ splits each energy level into three lines. Neither ^{12}C nor ^{16}O has a nuclear magnetic moment, and just as they cause no signal splitting in NMR spectra, they have no effect on the multiplicity in ESR 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 conjugated 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 equation⁸:

$$a = \rho Q \quad (11.3)$$

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 $Q = 23.0\text{ G}$, the hyperfine splitting in the benzene radical anion can be readily calculated by taking $\rho = 1/6$, because 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 (Figure 11.2a) consists of seven lines separated by a coupling constant of 3.75 G .⁹ Note that EPR spectra, unlike NMR and IR spectra, are displayed as the derivative of absorption rather than as absorption.

The ESR spectrum of the ethyl radical shown in Figure 11.2b is readily interpreted, and the results are of interest with respect to the distribution of unpaired electron density in the molecule.¹⁰ The 12-line spectrum is a triplet of quartets resulting from unequal coupling of the electron spin to the α - and β -hydrogens. The two coupling constants, $a_\alpha = 22.4\text{ G}$ and $a_\beta = 26.9\text{ G}$, imply extensive delocalization of spin density through the σ bonds.

⁸. H. M. McConnell, *J. Chem. Phys.*, **24**, 764 (1956).

⁹. J. R. Bolton, *Mol. Phys.*, **6**, 219 (1963).

¹⁰. R. W. Fessenden and R. M. Shuler, *J. Chem. Phys.*, **33**, 935 (1960); *J. Phys. Chem.*, **39**, 2147 (1963).

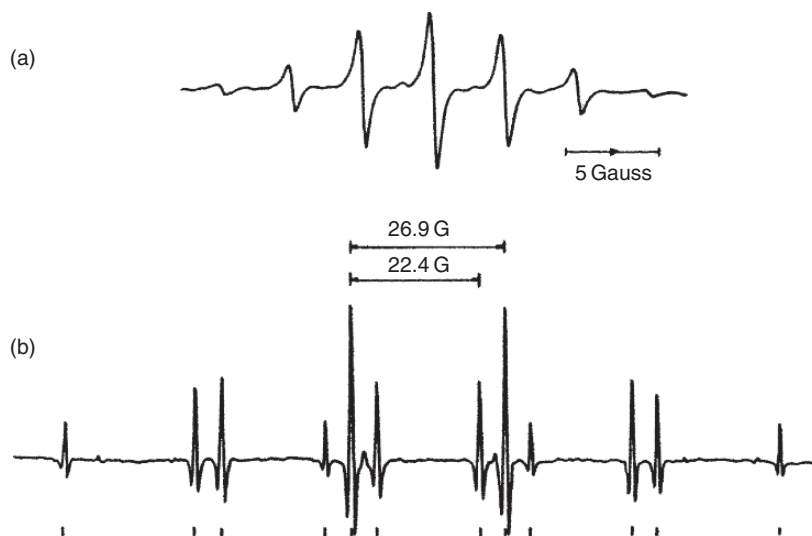
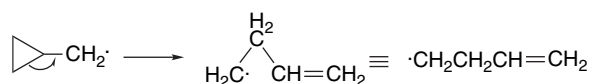
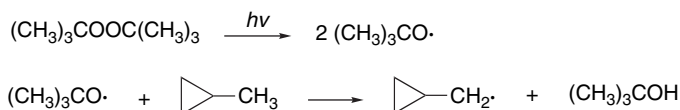


Fig. 11.2. Some EPR spectra of small radicals: (a) Spectrum of the benzene radical anion. From *Mol. Phys.*, **6**, 219 (1963); (b) Spectrum of the ethyl radical. From *J. Chem. Phys.*, **33**, 935 (1960); *J. Phys. Chem.* **39**, 2147 (1963). Reproduced by permission of Taylor and Francis, Ltd, and the American Institute of Physics, respectively.

ESR spectra have been widely used in the study of reactions to detect free radical intermediates. An important example involves the cyclopropylmethyl radical. Much chemical experience has indicated that this radical is unstable, rapidly giving rise to the 3-butenyl radical after being generated.



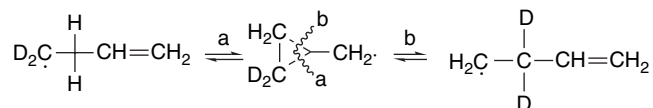
The radical was generated by photolytic decomposition of di-*t*-butyl peroxide in methylcyclopropane, a process that leads to selective abstraction of a methyl hydrogen.



Below -140°C , the ESR 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 second spectrum was shown to be that of the 3-butenyl radical.¹¹ This study also established that the 3-butenyl radical does not revert to the cyclopropylmethyl radical on being cooled back to -140°C . The conclusion is that the ring opening of the cyclopropyl radical is a very facile process and its lifetime above -100°C is very short. Even

¹¹ J. K. Kochi, P. J. Krusic, and D. R. Eaton, *J. Am. Chem. Soc.*, **91**, 1877 (1969).

though the equilibrium favors the 3-butenyl radical, the reversible ring closure can be detected by an isotopic-labeling experiment that reveals the occurrence of deuterium exchange.

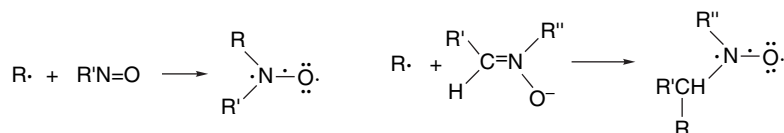


The rate of both the ring opening ($k = 1 \times 10^8 \text{ s}^{-1}$ at 25°C) and the ring closure ($k = 3 \times 10^3 \text{ s}^{-1}$) have been measured and confirm that only a very small amount of the cyclopropylmethyl radical is present at equilibrium, in agreement with the ESR results.¹²

Several MO and DFT computations on the energetics of the ring opening of the cyclopropylmethyl radical have been carried out. The computed energy profile shown in Figure 11.3 is derived from CCSD(T)/cc-pvTZ-level calculations.¹³ A barrier of 8.5 kcal/mol is calculated for the ring opening, along with smaller barriers associated with rotations in the reactant and product. A value of 7.2 kcal/mol has been obtained from CBS-RAD calculations.¹⁴ The experimental barrier is about 7.5 kcal/mol. It is worth noting that the rotational process is analogous to the interconversion of the perpendicular and bisected conformations of the cyclopropylmethyl cation. The radical rotamers differ by less than 3 kcal/mol, whereas the difference is nearly 30 kcal/mol in the cation (see Section 4.4.1).

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 leads to rapid disappearance of the ESR spectrum because the radicals react rapidly and are not replaced by continuing radical formation. Under many conditions, the steady state concentration of a radical intermediate may be too low to permit direct detection. Therefore, failure to observe an ESR signal cannot be taken as conclusive evidence against a radical intermediate.

A technique called *spin trapping* can also be used to study radicals. A diamagnetic molecule that reacts 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 radicals that are detectable. The most useful spin traps are nitrones and nitroso compounds, which react rapidly with radicals to give stable nitroxides.¹⁵ Analysis of the ESR spectrum of the nitroxide can provide information about the structure of the original radical.



12. A. Effio, 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); M. Newcomb and A. G. Glenn, *J. Am. Chem. Soc.*, **111**, 275 (1989); A. L. J. Beckwith and V. W. Bowry, *J. Org. Chem.*, **54**, 2681 (1989); D. C. Nonhebel, *Chem. Soc. Rev.*, **22**, 347 (1993).

13. A. L. Cooksy, H. F. King, and W. H. Richardson, *J. Org. Chem.*, **68**, 9441 (2003).

14. D. M. Smith, A. Nicolaides, B. T. Golding, and L. Radom, *J. Am. Chem. Soc.*, **120**, 10223 (1998).

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

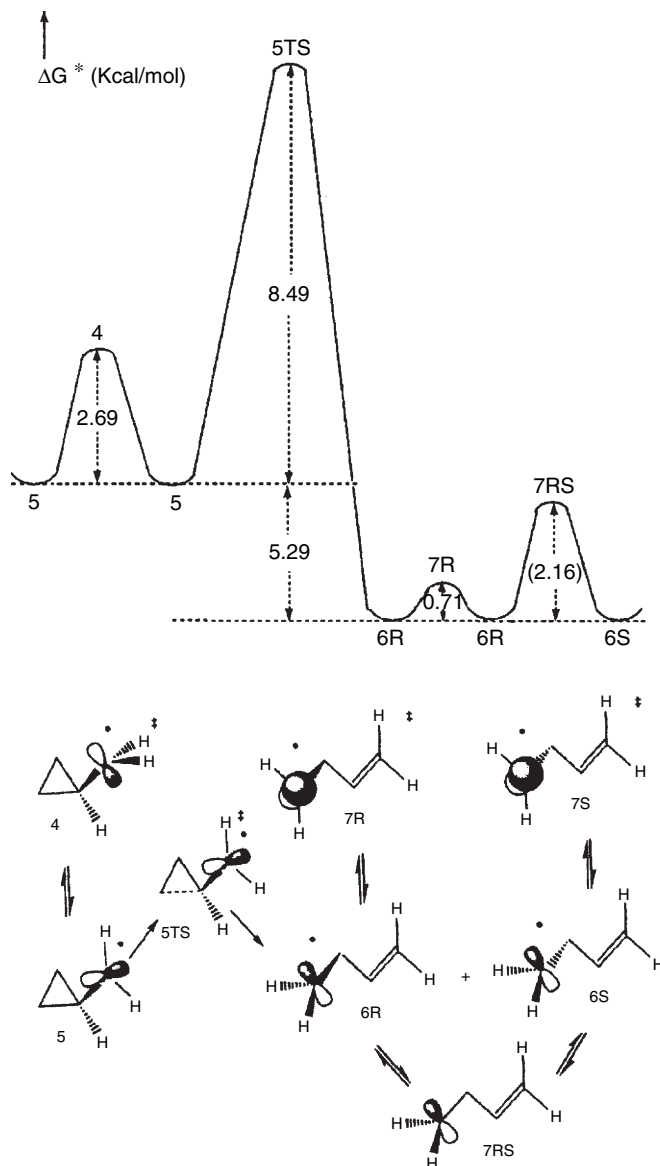


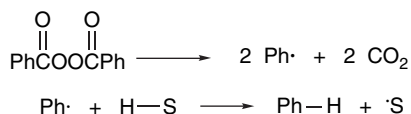
Fig. 11.3. Energy profile for rotation and ring opening of the cyclopropyl methyl radical derived from CCSD(T)/cc-pvTZ computations. Reproduced from *J. Org. Chem.*, **68**, 9441 (2003), by permission of the American Chemical Society.

Another technique that is specific for radical processes is known as CIDNP, an abbreviation for *chemically induced dynamic nuclear polarization*.¹⁶ The instrumentation required for such studies is an NMR spectrometer. CIDNP is observed as a strong perturbation of the intensity of NMR signals in products formed in certain types of free radical reactions. The variation in intensity results when the normal population of

¹⁶ H. R. Ward, *Acc. Chem. Res.*, **5**, 18 (1972); R. G. Lawler, *Acc. Chem. Res.*, **5**, 25 (1972).

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. Molecules 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.¹⁷

Figure 11.4 shows the observation of CIDNP during the decomposition of benzoyl peroxide in cyclohexanone.



The emission signal corresponding to benzene confirms that it is formed by a free radical process. As in steady state ESR experiments, the enhanced emission and absorption are observed only as long as the reaction is proceeding. When the reaction is complete or is stopped in some way, the signals return to their normal intensity because equilibrium population of the two spins states is rapidly reached.

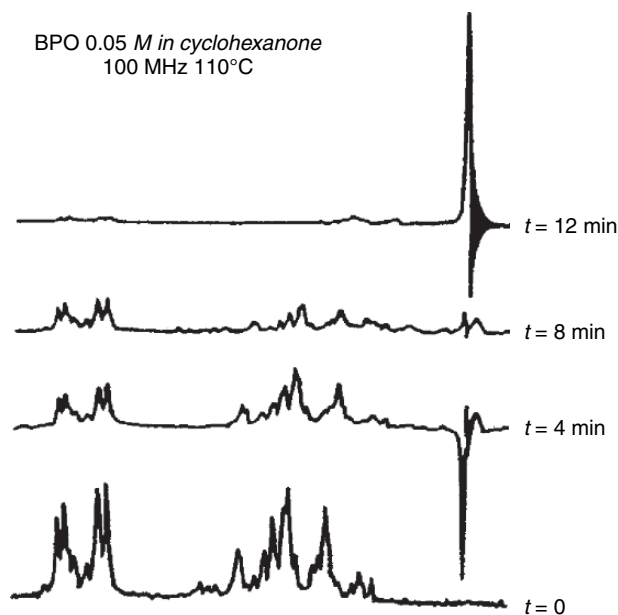
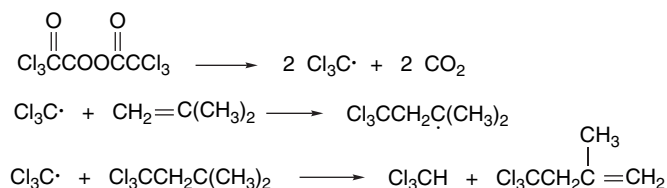


Fig. 11.4. NMR spectra recorded during decomposition of dibenzoyl peroxide. The upfield signal is due to benzene; the other signals are due to dibenzoyl peroxide. Reproduced from *Acc. Chem. Res.*, **2**, 110 (1969), by permission of the American Chemical Society.

¹⁷. For a discussion of the theory of CIDNP and the conditions under which spin polarization occurs, see G. L. Closs, *Adv. Mag. Res.*, **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).

One aspect of both EPR and CIDNP studies that should be kept in mind is that either is capable of detecting very small amounts of radical intermediates. Although this sensitivity makes both techniques very useful, it can also present a pitfall. The most prominent features of either ESR or CIDNP spectra may actually be due to radicals that account for only minor amounts of the total reaction process. An example of this was found in a study of the decomposition of trichloroacetyl peroxide in alkenes.

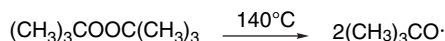


In addition to the emission signals of CHCl_3 and $\text{Cl}_3\text{CCH}_2\text{C}(\text{CH}_3)=\text{CH}_2$, which are the major products, a strong emission signal for $\text{Cl}_3\text{CCHCl}_2$ was identified. However, this compound is a very minor product of the reaction and when the signals have returned to their normal intensity, $\text{Cl}_3\text{CCHCl}_2$ is present in such a small amount that it cannot be detected.¹⁸

11.1.4. Generation of Free Radicals

There are several reactions that are used frequently to generate free radicals, both to study radical structure and reactivity and in synthetic processes. Some of the most general methods are outlined here. These methods will be encountered again when we discuss specific examples of free radical reactions. For the most part, we defer discussion of the reactions of the radicals until that point.

Peroxides are a common source of radical intermediates. Commonly used initiators include benzoyl peroxide, *t*-butyl peroxybenzoate, di-*t*-butyl peroxide, and *t*-butyl hydroperoxide. Reaction generally occurs at relatively low temperature ($80^\circ - 100^\circ\text{C}$). The oxygen-oxygen bond in peroxides is weak ($\sim 30 \text{ kcal/mol}$) and activation energies for radical formation are low. Dialkyl peroxides decompose thermally to give two alkoxy radicals.¹⁹



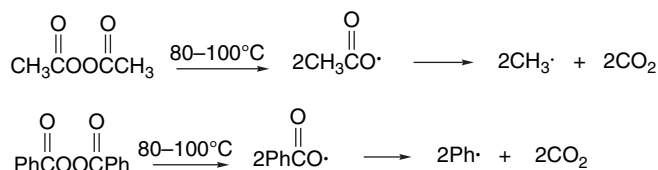
Diacyl peroxides are sources of alkyl radicals because the carboxyl radicals that are initially formed lose CO_2 very rapidly.²⁰ In the case of aroyl peroxides, products can be derived from either the carboxyl radical or the radical formed by decarboxylation.²¹ The decomposition of peroxides can also be accomplished by photochemical excitation.

¹⁸. H. Y. Loken, R. G. Lawler, and H. R. Ward, *J. Org. Chem.*, **38**, 106 (1973).

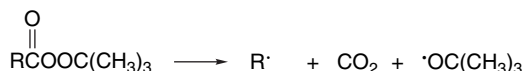
¹⁹. W. A. Pryor, D. M. Huston, T. R. Fiske, T. L. Pickering, and E. Ciuffarin, *J. Am. Chem. Soc.*, **86**, 4237 (1964).

²⁰. 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).

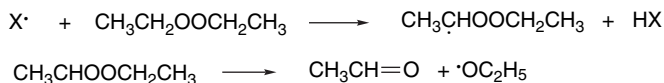
²¹. D. F. DeTar, R. A. J. Long, J. Rendleman, J. Bradley, and P. Duncan, *J. Am. Chem. Soc.*, **89**, 4051 (1967).



Peroxyesters are also sources of radicals. The acyloxy portion normally loses carbon dioxide, so peroxyesters yield an alkyl (or aryl) and alkoxy radical.²²

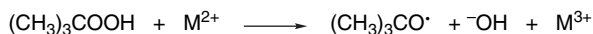


The thermal decompositions described above are unimolecular reactions that should exhibit first-order kinetics. Peroxides often decompose at rates faster than expected for unimolecular thermal decomposition and with more complicated kinetics. This behavior is known as *induced decomposition* and occurs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



The amount of induced decomposition that occurs depends on the concentration and reactivity of the radical intermediates and the susceptibility of the reactant to radical attack. The radical $\text{X}\cdot$ may be formed from the peroxide, but it can also be derived from subsequent reactions with the solvent. For this reason, both the structure of the peroxide and the nature of the reaction medium are important in determining the extent of induced decomposition relative to unimolecular homolysis. All of the peroxides are used in relatively dilute solution. Many peroxides are explosive, and due precautions must be taken.

Alkyl hydroperoxides give alkoxy radicals and the hydroxyl radical. *t*-Butyl hydroperoxide is often used as a radical source. Detailed studies on the mechanism of the decomposition indicate that it is a more complicated process than simple unimolecular decomposition.²³ The alkyl hydroperoxides are sometimes used in conjunction with a transition metal salt. Under these conditions, an alkoxy radical is produced, but the hydroxyl portion appears as hydroxide ion as the result of one-electron reduction by the metal ion.²⁴



A technique that provides a convenient source of radicals for study by ESR involves photolysis of a mixture of di-*t*-butyl peroxide, triethylsilane, and the alkyl bromide corresponding to the radical to be studied.²⁵ Photolysis of the peroxide gives

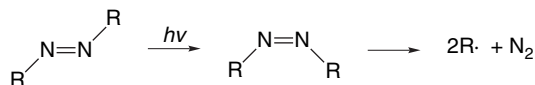
²². P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.*, **80**, 1398 (1958).

²³. R. Hiatt, T. Mill, and F. R. Mayo, *J. Org. Chem.*, **33**, 1416 (1968), and accompanying papers.

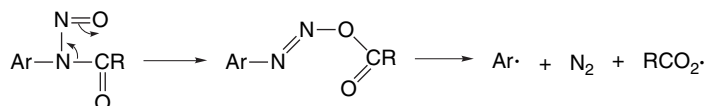
²⁴. W. H. Richardson, *J. Am. Chem. Soc.*, **87**, 247 (1965).

²⁵. A. Hudson and R. A. Jackson, *Chem. Commun.*, 1323 (1969); D. J. Edge and J. K. Kochi, *J. Am. Chem. Soc.*, **94**, 7695 (1972).

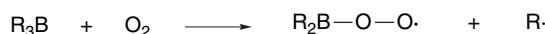
Many azo compounds also generate radicals when photolyzed. This occurs by a thermal decomposition of the *cis*-azo compounds that are formed in the photochemical step.²⁹ The *cis* isomers are thermally much more labile than the *trans* isomers.



N-Nitrosoanilides are a convenient source of aryl radicals. There is a close mechanistic relationship to the decomposition of azo compounds. The *N*-nitrosoanilides rearrange to intermediates having a nitrogen-nitrogen double bond. The intermediate then decomposes to generate aryl and acyloxy radicals.³⁰

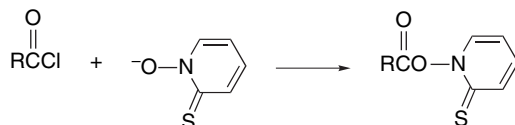


Triethylboron³¹ and 9-borabicyclo[3.3.1]nonane³² (9-BBN) are good radical sources for certain synthetic procedures. The reactions involve oxidation of the borane.



These initiators can be used in conjunction with stannanes and halides, as well as other reagents that undergo facile chain reactions. The reaction can be initiated at temperatures as low as -78°C .³³

The acyl derivatives of *N*-hydroxypyridine-2-thione are a versatile source of free radicals.³⁴ These compounds are readily prepared from reactive acylating agents, such as acyl chlorides, and a salt of the *N*-hydroxypyridine-2-thione.



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

²⁹ M. Schmittel and C. Rüchardt, *J. Am. Chem. Soc.*, **109**, 2750 (1987).

³⁰ C. Rüchardt and B. Freudenberg, *Tetrahedron Lett.*, 3623 (1964); J. I. G. Cadogan, *Acc. Chem. Res.*, **4**, 186 (1971).

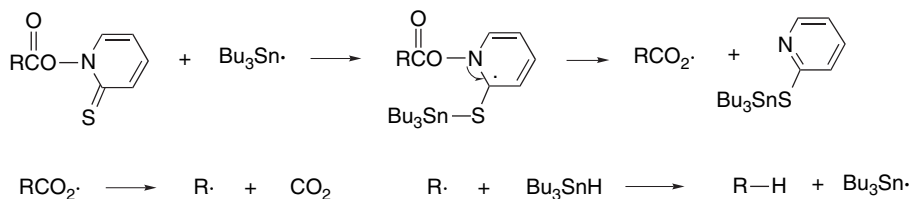
³¹ K. Nozaki, K. Oshima, and K. Utimoto, *J. Am. Chem. Soc.*, **109**, 2547 (1987).

³² V. T. Perchyonok and C. H. Schiesser, *Tetrahedron Lett.*, **39**, 5437 (1998).

³³ K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, **62**, 143 (1989).

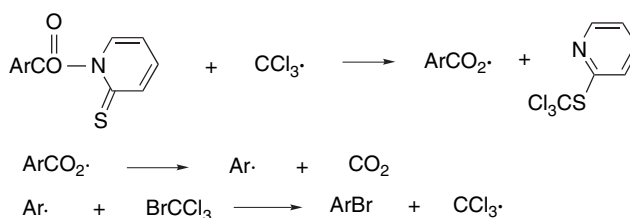
³⁴ D. H. R. Barton, D. Crich, and W. B. Motherwell, *Tetrahedron*, **41**, 3901 (1985).

a. Reductive decarboxylation by reaction with tri-*n*-butylstannane.



Ref. 35

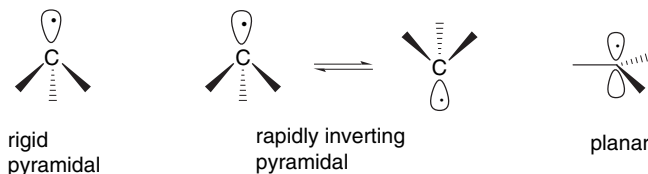
b. Conversion of arenecarboxylic acid to aryl bromide by reaction with bromotrichloromethane.



Ref. 36

11.1.5. Structural and Stereochemical Properties of Free Radicals

ESR studies and other physical methods have provided insight into the geometry of free radicals.³⁷ Deductions about structure can also be drawn from the study of the stereochemistry of reactions involving radical intermediates. Several structural possibilities can be considered. If discussion is limited to alkyl radicals, the possibilities include a rigid pyramidal structure, rapidly inverting pyramidal structures, or a planar structure.



Precise description of the pyramidal structures also requires that the bond angles be specified. The ESR spectrum of the methyl radical leads to the conclusion that its structure could be either planar or a shallow pyramid with a very low barrier to inversion.³⁸ The IR spectrum of methyl radical at very low temperature in frozen argon puts a maximum of about 5° on the deviation from planarity.³⁹ A microwave study has also indicated the methyl radical is planar.⁴⁰ Various MO calculations indicate a planar structure.⁴¹

³⁵ D. H. R. Barton, D. Crich, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 939 (1983).

³⁶ D. H. R. Barton, B. Lacher, and S. Z. Zard, *Tetrahedron Lett.*, **26**, 5939 (1985).

³⁷ For a review, see J. K. Kochi, *Adv. Free Radicals*, **5**, 189 (1975).

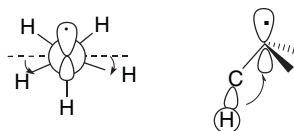
³⁸ M. Karplus and G. K. Fraenkel, *J. Chem. Phys.*, **35**, 1312 (1961).

³⁹ L. Andrews and G. C. Pimentel, *J. Chem. Phys.*, **47**, 3637 (1967).

⁴⁰ E. Hirota, *J. Phys. Chem.*, **87**, 3375 (1983).

⁴¹ F. M. Bickelhaupt, T. Ziegler, and P. v. R. Schleyer, *Organometallics*, **15**, 1477 (1996).

Simple alkyl radicals are generally pyramidal, although the barrier to inversion is very small. According to MP2/6-311G** and MM computations, substituted alkyl radicals become successively more pyramidal in the order ethyl < *i*-propyl < *t*-butyl.⁴² The *t*-butyl radical has been studied extensively, and both experimental and theoretical calculations indicate a pyramidal structure.⁴³ The pyramidal geometry results from interaction of the SOMO and alkyl group hydrogens. There is a hyperconjugative interaction between the half-filled orbital and the hydrogen that is aligned with it. The pyramidalization also leads to a staggered conformation. The hyperconjugation is stronger in the conformation in which the pyramidalization is in the same direction as to minimize eclipsing.^{42a,44} The C—H bonds *anti* to the unpaired electron are longer than those that are *gauche*. The *anti* hydrogens have maximum hyperconjugation with the orbital containing the unpaired electron and make a higher contribution to the SOMO orbital. There is also a shortening of the C—C bond, which is consistent with hyperconjugation.⁴⁵ Note that this hyperconjugative interaction accounts for the substantial hyperfine coupling with the β -H that was discussed in Section 11.1.3. The β -C—H bond is also greatly weakened by the hyperconjugation. MP4/6-311G(*d,p*) calculations assign a bond energy of only about 36 kcal/mol.⁴⁶



hyperconjugation in pyramidal radicals

Radical geometry is also significantly affected by substituent groups that can act as π donors. Addition of a fluorine or oxygen substituent favors a pyramidal structure. Analysis of the ESR spectra of the mono-, di-, and trifluoromethyl radicals indicate a progressive distortion from planarity.^{43d,47} Both ESR and IR studies of the trifluoromethyl radical show it to be pyramidal.⁴⁸ The basis of this structural effect has been probed by MO calculations and is considered to result from interactions of both the σ and π type. There is a repulsive interaction between the singly occupied p orbital and the filled orbitals occupied by unshared electrons on the fluorine or oxygen substituents. This repulsive interaction is reduced by adoption of a pyramidal geometry.

^{42.} (a) J. Pacansky, W. Koch, and M. D. Miller, *J. Am. Chem. Soc.*, **113**, 317 (1991); (b) R. Liu and N. L. Allinger, *J. Comput. Chem.*, **15**, 283 (1994).

^{43.} (a) D. E. Wood, C. F. Williams, R. F. Sprecher, and W. A. Lathan, *J. Am. Chem. Soc.*, **94**, 6241 (1972); (b) T. Koenig, T. Balle, and W. Snell, *J. Am. Chem. Soc.*, **97**, 662 (1975); (c) P. J. Krusic and P. Meakin, *J. Am. Chem. Soc.*, **98**, 228 (1976); (d) P. J. Krusic and R. C. Bingham, *J. Am. Chem. Soc.*, **98**, 230 (1976); (e) L. Bonazzola, N. Leray, and J. Roncin, *J. Am. Chem. Soc.*, **99**, 8348 (1977); (f) D. Griller, K. U. Ingold, P. J. Krusic, and H. Fischer, *J. Am. Chem. Soc.*, **100**, 6750 (1978); (g) J. Pacansky and J. S. Chang, *J. Phys. Chem.*, **74**, 5539 (1978); (g) B. Schrader, J. Pacansky, and U. Pfeiffer, *J. Phys. Chem.*, **88**, 4069 (1984).

^{44.} M. N. Paddon-Row and K. N. Houk, *J. Am. Chem. Soc.*, **103**, 5046 (1981).

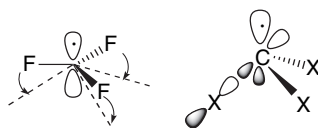
^{45.} M. N. Paddon-Row and K. N. Houk, *J. Phys. Chem.*, **89**, 3771 (1985).

^{46.} J. A. Seetula, *J. Chem. Soc., Faraday Trans.*, **94**, 1933 (1998).

^{47.} F. Bernardi, W. Cherry, S. Shaik, and N. D. Epitotis, *J. Am. Chem. Soc.*, **100**, 1352 (1978).

^{48.} 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).

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 interaction increases electron density on the more electronegative fluorine or oxygen atom. This stabilizing p – σ^* interaction is increased by pyramidal geometry.



pyramidalization reduces electron-electron repulsion and enhances p – σ^* interaction

Computations on the $\text{FCH}_2\cdot$, $\text{F}_2\text{CH}\cdot$, and $\text{F}_3\text{C}\cdot$ radicals indicate successively greater pyramidalization.⁴⁹ Chlorinated methyl radicals and mixed chlorofluoro radicals show the same trend toward increasing pyramidalization,⁵⁰ as illustrated in Figure 11.5.

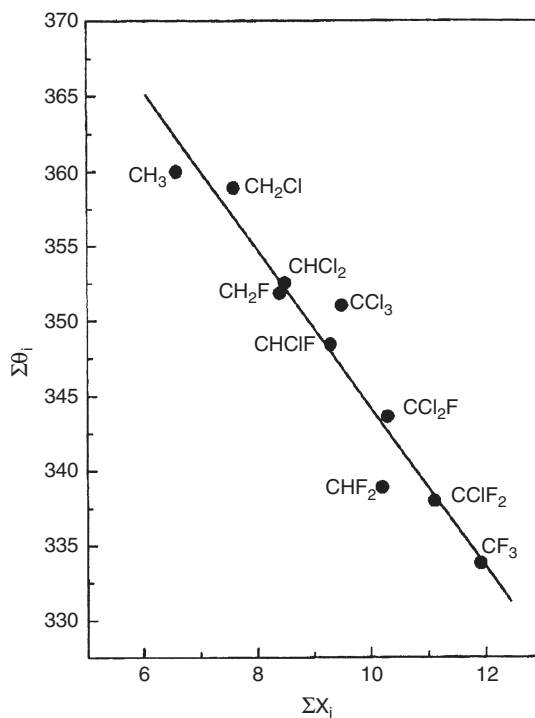


Fig. 11.5. Degree of pyramidalization of halogenated methyl radicals. The sum of the bond angles $\Sigma\theta$ is plotted against the sum of the electronegativity ($\Sigma\chi_i$) of the substituents. $\Sigma\theta = 360^\circ$ for planar and 323.7° for tetrahedral geometry. Reproduced from *J. Chem. Phys.*, **118**, 557 (2003), by permission of the American Institute of Physics.

⁴⁹ Q.-S. Li, J.-F. Zhao, Y. Xie, and H. F. Schaefer, III, *Mol. Phys.*, **100**, 3615 (2002).

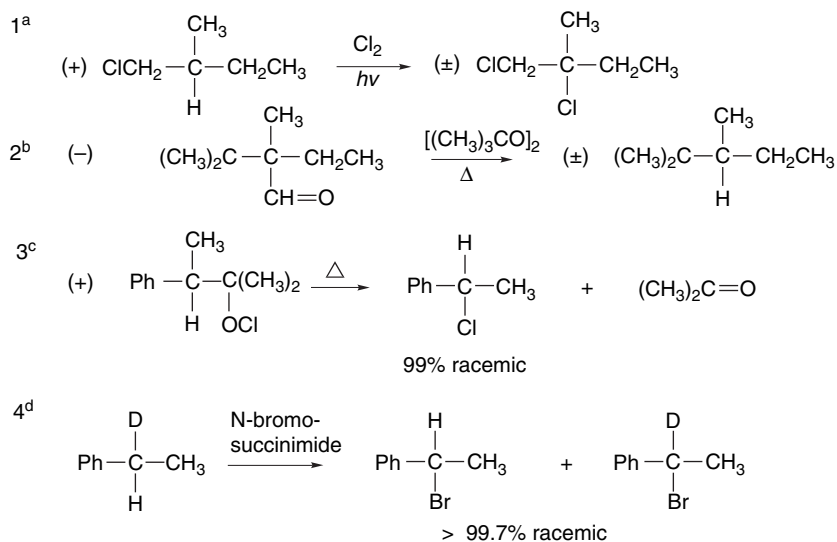
⁵⁰ M. Schwartz, L. R. Peebles, R. J. Berry, and P. Marshall, *J. Chem. Phys.*, **118**, 557 (2003).

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 stereogenic center. A planar or rapidly inverting radical leads to racemization, whereas a rigid pyramidal structure would lead to product of retained configuration. Some examples of reactions that have been subjected to this kind of study are shown in Scheme 11.2. In each case racemic product is formed, indicating that alkyl radicals do not retain the tetrahedral geometry of their precursors.

Entry 1 is a chlorination at a stereogenic tertiary center and proceeds with complete racemization. In Entry 2, a tertiary radical is generated by loss of $\text{C}\equiv\text{O}$, again with complete racemization. In Entry 3, an α -methylbenzyl radical is generated by a fragmentation and the product is again racemic. Entry 4 involves a benzylic bromination by NBS. The chirality of the reactant results from enantiospecific isotopic labeling of ethylbenzene. The product, which is formed via an α -methylbenzyl radical intermediate, is racemic.

Cyclic molecules 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.⁵¹ 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 *t*-butylcyclohexyl radicals are usually not very stereoselective, but some show a preference for formation of the *cis* product. This has been explained in terms of a torsional effect. The pyramidalization of the radical is

Scheme 11.2. Stereochemistry of Radical Reactions at Stereogenic Carbon Centers



a. H. C. Brown, M. S. Kharasch, and T. H. Chao, *J. Am. Chem. Soc.*, **62**, 3435 (1940).

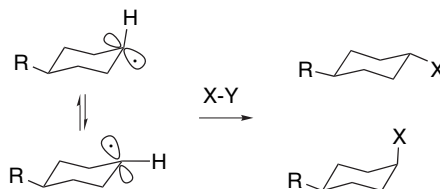
b. W. v. E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *J. Am. Chem. Soc.*, **74**, 3000 (1952).

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).

⁵¹ F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Am. Chem. Soc.*, **90**, 5793 (1968).

expected to be in the direction favoring axial attack.⁵² Structural evidence suggests that the cyclohexyl radical is somewhat pyramidal with an equatorial hydrogen.⁵³ Equatorial attack leading to *trans* product causes the hydrogen at the radical site to become eclipsed with the two neighboring equatorial hydrogens. Axial attack does not suffer from this strain, since the hydrogen at the radical site moves away from the equatorial hydrogens toward the staggered conformation that is present in the chair conformation of the ring.

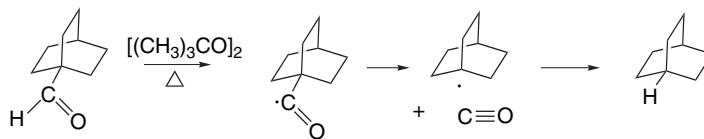


The inversion of the cyclohexyl radical can occur by a conformational process. This is expected to have a higher barrier than the radical inversion, since it involves bond rotations very similar to the ring inversion in cyclohexane. An E_a of 5.6 kcal/mol has been measured for the cyclohexyl radical.⁵⁴ A measurement of the rate of inversion of a tetrahydropyranyl radical ($k = 5.7 \times 10^8 \text{ s}^{-1}$ at 22°C) has been reported.⁵⁵



It can be concluded from these data that radical inversion is also fast in cyclic systems.

Another approach to obtaining information about the geometric requirements of free radicals has been to examine bridgehead systems. Recall that small bicyclic rings strongly resist formation of carbocations at bridgehead centers because the skeletal rigidity prevents attainment of the preferred planar geometry. There is significant rate retardation for reactions in which the norbornyl radical is generated in a rate-determining step.⁵⁶ 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 the 10^{-14} found in S_N1 solvolysis (see p. 435). Rate retardation is still smaller for less strained bicyclic systems. The decarbonylation of less strained bridgehead aldehydes was found to proceed without special difficulty.⁵⁷



⁵² W. Damm, B. Giese, J. Hartung, T. Hasskerl, K. N. Houk, O. Huter, and H. Zipse, *J. Am. Chem. Soc.*, **114**, 4067 (1992).

⁵³ J. E. Freitas, H. J. Wang, A. B. Ticknor, and M. A. El-Sayed, *Chem. Phys. Lett.*, **183**, 165 (1991); A. Hudson, H. A. Hussain, and J. N. Murrell, *J. Chem. Soc., A*, 2336 (1968).

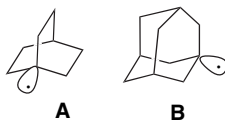
⁵⁴ B. P. Roberts and A. J. Steel, *J. Chem. Soc., Perkin Trans. 2*, 2025 (1992).

⁵⁵ A. J. Buckmelter, A. I. Kim, and S. D. Rychnovsky, *J. Am. Chem. Soc.*, **122**, 9386 (2000).

⁵⁶ 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).

⁵⁷ W. v. E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *J. Am. Chem. Soc.*, **74**, 3000 (1952).

Conclusions about radical structure can also be drawn from analysis of ESR spectra. The ESR spectra of the bridgehead radicals **A** and **B** are consistent with pyramidal geometry at the bridgehead carbon atoms.⁵⁸



The ESR spectra of a number of bridgehead radicals have been determined and the hyperfine couplings measured (see Section 11.1.3). Both the H_α and $^{13}\text{C}_\beta$ couplings are sensitive to the pyramidal geometry of the radical.⁵⁹ The reactivity of bridgehead radicals increases with increased pyramidal character.⁶⁰

Radical	H_α	$^{13}\text{C}_\beta$	Φ^a
Adamantyl	6.58	132	113.6
Bicyclo[2.2.2]octyl	6.64	143	113.2
Bicyclo[2.2.1]heptyl	2.35	151	112.9
Bicyclo[2.1.1]hexyl	0	174	111.9
Bicyclo[1.1.1]pentyl	-1.2	223	110.3

a. Φ = the C—C—C bond angle at the bridgedhead radical.

The broad conclusion of all these studies is that alkyl radicals except methyl are pyramidal, but the barrier to inversion 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 π delocalization. Structure parameters have been obtained from ESR, IR, and electron diffraction measurements and confirm that the radical is planar.⁶¹ The vinyl radical, $\text{CH}_2 = \text{CH}\cdot$, is found by both experiment and theory to be bent with a C—C—H bond angle of about 137° .⁶² Substituents affect the preferred geometry of vinyl radicals. Conjugation with π -acceptor substituents favors a linear geometry, whereas σ -donor substituents favor a bent geometry.⁶³ For σ -donors the barriers for isomerization are in the order $\text{CH}_3(3.1) < \text{OH}(13.3) < \text{F}(19.5)$ kcal/mol, according to BLYP/6-311G(2d,2p) calculations. Although these barriers have not been measured experimentally, reaction stereoselectivity is in agreement with the results. For the π -acceptor substituents, the preferred geometry is one in which the substituent is aligned with the singly occupied p orbital, not the π bond.

⁵⁸. P. J. Krusic, T. A. Rettig, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **94**, 995 (1972).

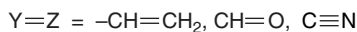
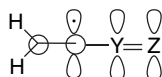
⁵⁹. C. J. Rhodes, J. C. Walton, and E. W. Della, *J. Chem. Soc., Perkin Trans. 2*, 2125 (1993); G. T. Binmore, J. C. Walton, W. Adcock, C. I. Clark, and A. R. Krstic, *Magn. Resonance Chem.*, **33**, Supplement S53 (1995).

⁶⁰. F. Recupero, A. Bravo, H. R. Bjorsvik, F. Fontana, F. Minisci, and M. Piredda, *J. Chem. Soc., Perkin Trans. 2*, 2399 (1997); K. P. Dockery and W. G. Bentrude, *J. Am. Chem. Soc.*, **119**, 1388 (1997).

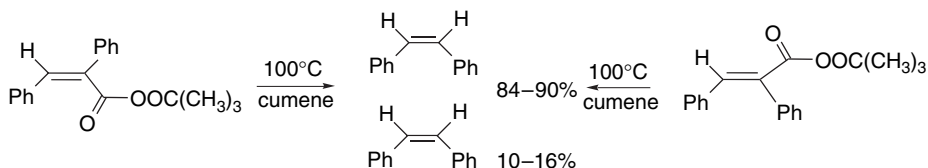
⁶¹. R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963); A. K. Maltsev, V. A. Korolev, and O. M. Nefedov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 555 (1984); E. Vajda, J. Tremmel, B. Rozandai, I. Hargittai, A. K. Maltsev, N. D. Kagramanov, and O. M. Nefedov, *J. Am. Chem. Soc.*, **108**, 4352 (1986).

⁶². J. H. Wang, H.-C. Chang, and Y.-T. Chen, *Chem. Phys.*, **206**, 43 (1996).

⁶³. C. Galli, A. Guarnieri, H. Koch, P. Mencarelli, and Z. Rappoport, *J. Org. Chem.*, **62**, 4072 (1997).

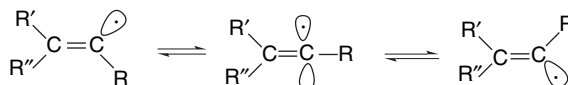


The stereochemistry of reactions involving substituted alkenyl free radicals indicates that radicals formed at trigonal centers rapidly undergo interconversion with the geometric isomer.⁶⁴ Reactions proceeding through alkenyl radical intermediates usually give rise to the same mixture from both the *E*- and *Z*-precursor. In the example given below, more *cis*- than *trans*-stilbene is formed, which is attributed to the steric effects of the β -phenyl group causing the H-abstraction to occur *anti* to the substituent.



Ref. 65

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.⁶⁶ The barrier to inversion is very low (0~2 kcal), so that the lifetime of the individual isomers is very short ($\sim 10^{-9}$ s). The TS for inversion approximates *sp* hybridization.⁶⁷



11.1.6. Substituent Effects on Radical Stability

The basic concepts of radical substituent effects were introduced in Section 3.4.1, where we noted that both donor and acceptor substituents can stabilize radicals. The extent of stabilization can be expressed in terms of the radical stabilization energy (RSE). The stabilization resulting from conjugation with unsaturated groups, such as in allyl and benzyl radicals, was also discussed. These substituent effects can sometimes cause synergistic stabilization. Allylic and benzylic radicals are also stabilized by both acceptor and donor substituents. Calculations at the AUMP2/6-31G* level indicate that substituents at the 2-position are only slightly less effective than 1-substituents in the stabilization of allylic radicals (Table 11.1). This is somewhat surprising in that the SOMO has a node at the 2-position. However, ψ_1 is also stabilized by interaction with the 2-substituent. Calculations have also been done on the stabilizing effect of *p*

⁶⁴. 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).

⁶⁵. 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).

⁶⁶. R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).

⁶⁷. P. R. Jenkins, M. C. R. Symons, S. E. Booth, and C. J. Swain, *Tetrahedron Lett.*, **33**, 3543 (1992).

Table 11.1. Substituent Effects on the Stability of Allylic and Benzylic Radical from Calculation of Radical Stabilization Energy

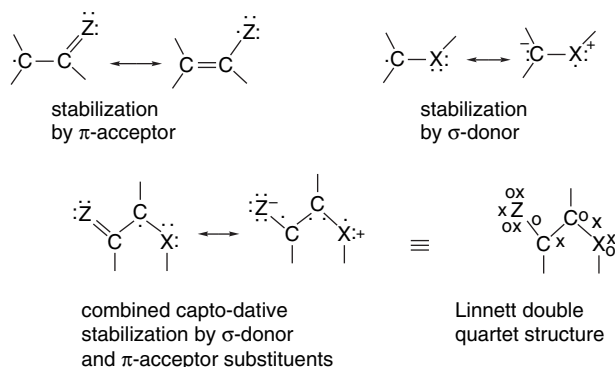
Substituent	Relative Stabilization in kcal/mol		
	Allylic ^a	Benzylic ^b	
	1-position	2-position	<i>p</i> -position
H	0	0	0
CH ₃	5.6	4.3	0.3
CN	9.9	3.0	1.4
CH=O	11.7	11.6	
F	8.3	11.0	-0.1
HO	12.8	12.6	
CH ₃ O			0.7
H ₂ N	13.7	9.4	
(CH ₃) ₂ N			1.8

a. AUMP2/6-31G* calculation from M. Lehd and F. Jensen, *J. Org. Chem.*, **56**, 884 (1991).

b. BLYP/6-31G* calculations from Y.-D. Wu, C.-L. Wong, K. W. K. Chan, G.-Z. Ji, and X.-K. Jang, *J. Org. Chem.*, **61**, 746 (1996).

substituents on benzylic radicals, and the results indicate that both donor and acceptor substituents are stabilizing. The effects are greatly attenuated in the case of the benzyl substituents, owing to the leveling effect of the delocalization in the ring.

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*”⁶⁸ or “*capto-dative stabilization*,”⁶⁹ and results from mutual reinforcement of the two substituent effects.⁷⁰ The bonding in capto-dative radicals can be represented by resonance or Linnett-type structures (see p. 8).

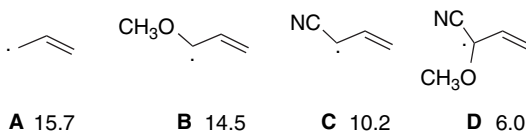


A comparison of the rotational barriers in allylic radicals **A** to **D** provides evidence for the stabilizing effect of the capto-dative combination.

⁶⁸. R. W. Baldock, P. Hudson, A. R. Katritzky, and F. Soti, *J. Chem. Soc., Perkin Trans. 1*, 1422 (1974).

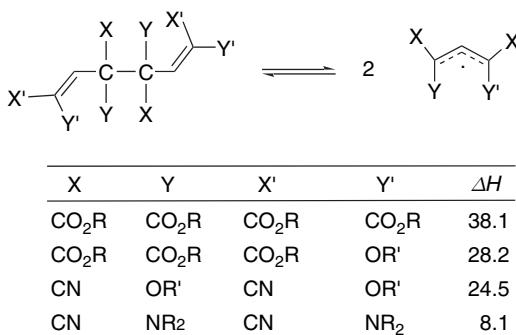
⁶⁹. H. G. Viehe, R. Merenyi, L. Stella, and Z. Janousek, *Angew. Chem. Int. Ed. Engl.*, **18**, 917 (1979).

⁷⁰. R. Sustmann and H.-G. Korth, *Adv. Phys. Org. Chem.*, **26**, 131 (1990).



The decreasing barrier at the formal single bond along the series **A** to **D** implies decreasing π -allyl character in 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** \rightarrow **D** is greater than for **A** \rightarrow **B** indicates a synergistic effect, as implied by the capto-dative formulation. The methoxy group is more stabilizing when it can interact with the cyano group than as an isolated substituent.⁷¹

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).



When the combinations X,Y and X',Y' are of the capto-dative type, as is the case for an alkoxy and ester group, the enthalpy of bond dissociation is 10–15 kcal lower than when all four groups are electron attracting. When the capto-dative combination CN/NR₂ 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.⁷² Scheme 11.3 gives some information on the stability of other examples of this type of radical.

11.1.7. Charged Radicals

Unpaired electrons can be present in ions as well as in the neutral systems that have been considered up to this point. There are many such *radical cations* and *radical anions*, and we consider some representative examples in this section. Various aromatic and conjugated polyunsaturated hydrocarbons undergo one-electron reduction by alkali metals.⁷³ Benzene and naphthalene are examples. The ESR spectrum of the benzene radical anion was shown earlier in Figure 11.2a. These reductions must be carried out in aprotic solvents, and ethers are usually used for that purpose. The ease of formation of the radical anion increases as the number of fused rings increases. The electrochemical reduction potentials of some representative compounds are given in

⁷¹ H.-G. Korth, P. Lommes, and R. Sustmann, *J. Am. Chem. Soc.*, **106**, 663 (1984).

⁷² M. Van Hoecke, A. Borghese, J. Penelle, R. Merenyi, and H. G. Viehe, *Tetrahedron Lett.*, **27**, 4569 (1986).

⁷³ 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).

1 ^a		Wurster's salts. Generated by one-electron oxidation of the corresponding diamine. Indefinitely stable to normal conditions.
2 ^b		Generated by one-electron reduction of the corresponding pyridinium salt. Thermally stable to distillation and only moderately reactive toward oxygen.
3 ^c		Stable to distillation. A small amount of the dimer is present in equilibrium with the radical.
4 ^d		In equilibrium with the dimer Sensitive to oxygen.
5 ^e		Generated by spontaneous dissociation of the dimer. Stable for several days at room temperature, but sensitive to oxygen.
6 ^f		Generated spontaneously from dimethylamino-malonitrile at room temperature. Observed to be persistent over many hours by ESR.
7 ^g		Radical stabilization energy of 19.6 kcal/mol implies about 10 kcal/mol of excess stabilization relative to the combined substituents. The CH-N(CH3)2 rotational barrier is >17 kcal/mol, indicating a strong resonance interaction.
8 ^h		Synergistic stabilization of about 6.3 kcal/mol, based on thermodynamics of dimerization.

- 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).
 g. F. M. Welle, H.-D. Beckhaus, and C. Rüchardt, *J. Org. Chem.*, **62**, 552 (1997).
 h. F. M. Welle, S. P. Verevkin, H.-D. Beckhaus and C. Rüchardt, *Liebigs Ann. Chem.*, 115 (1997).

Table 11.2. The potentials correlate with the energy of the LUMO as calculated by simple Hückel MO theory.⁷⁴ Note that polycyclic aromatics are easier both to reduce and to oxidize than benzene. This is because the HOMO-LUMO gap decreases with

⁷⁴ E. S. Pysh and 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).

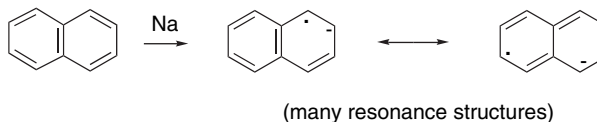
Table 11.2. Oxidation and Reduction Potentials for Some Aromatic Hydrocarbons^a

Hydrocarbon	$\text{Ar-H} \rightarrow [\text{Ar-H}]^{\cdot-}$	$\text{Ar-H} \rightarrow [\text{Ar-H}]^{\cdot+}$
Benzene	-3.42 ^b	+2.06
Naphthalene	-2.95	+1.33
Phenanthrene	-2.87	+1.34
Anthracene	-2.36	+0.89
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).

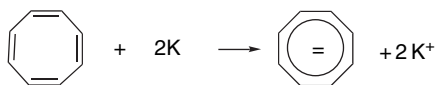
b. J. Mortensen and J. Heinze, *Angew. Chem. Int. Ed. Engl.* **13**, 84 (1984).

the size of the molecule, with the HOMO being higher in energy and the LUMO lower than in benzene. A correlation that includes a more extensive series of compounds can be observed using somewhat more sophisticated MO methods.⁷⁵



In the presence of a proton source, the radical anion is protonated and further reduction occurs (Birch reduction; Part B, Section 5.6.2). 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 preference of aromatic hydrocarbons for one-electron reduction. It is converted to a diamagnetic dianion by addition of two electrons.⁷⁶ It is easy to understand the ease with which the cyclooctatetraene radical accepts a second electron because of the aromaticity of the ten π -electron aromatic system that results (see Section 8.3).



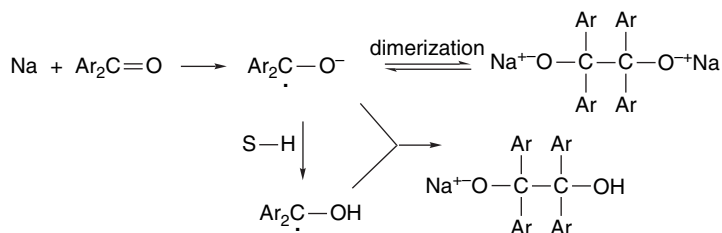
Radical cations can be derived from aromatic hydrocarbons or alkenes by one-electron oxidation. Antimony trichloride and pentachloride are among the chemical oxidants that have been used.⁷⁷ Photodissociation or γ -radiation can generate radical cations from aromatic hydrocarbons.⁷⁸ Most radical cations derived from hydrocarbons

⁷⁵. C. F. Wilcox, Jr., K. A. Weber, H. D. Abruna, and C. R. Cabrera, *J. Electroanal. Chem. Interfacial Electrochem.*, **198**, 99 (1986).

⁷⁶. T. J. Katz, *J. Am. Chem. Soc.*, **82**, 3784 (1960).

⁷⁷. I. C. Lewis and L. S. Singer, *J. Chem. Phys.*, **43**, 2712 (1965); R. M. Dessau, *J. Am. Chem. Soc.*, **92**, 6356 (1970).

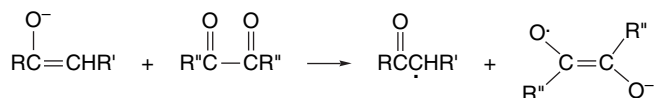
⁷⁸. R. Gschwind and E. Haselbach, *Helv. Chim. Acta*, **62**, 941 (1979); T. Shida, E. Haselbach, and T. Bally, *Acc. Chem. Res.*, **17**, 180 (1984); M. C. R. Symons, *Chem. Soc. Rev.*, **13**, 393 (1984).



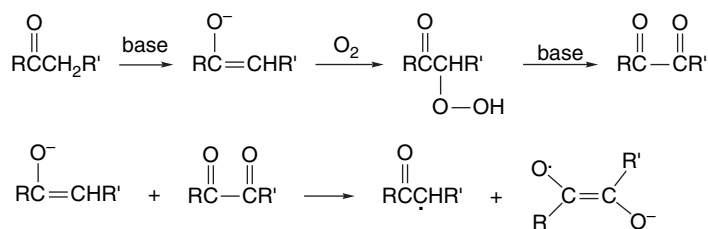
The diagram illustrates the reduction of a 1,2-dicarbonyl compound (R-C(=O)-C(=O)-R) by an electron (e^-) to form a neutral semidione radical. This radical exists in resonance with several structures, including $\text{R}-\text{C}(\text{O}^-)=\text{C}(\text{O}^-)-\text{R}$ and $\text{R}-\text{C}(\text{O})=\text{C}(\text{O}^-)-\text{R}$. Protonation (H^+) of the semidione radical yields a semiquinone radical anion, which is shown in resonance with $\text{HO}-\text{C}_6\text{H}_4-\text{C}(=\text{O})\cdot$ and $\cdot\text{C}_6\text{H}_4-\text{C}(=\text{O})-\text{O}^-$.

⁸¹ G. A. Russell, in *Radical Ions*, E. T. Kaiser and L. Kevan, eds., Interscience, New York, 1968, pp. 87-150.

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



The radicals that are formed from the enolate are rapidly destroyed so only the stable semidione radical remains detectable for ESR study. Semidiones can also be generated oxidatively from ketones by reaction with oxygen in the presence of base.⁸²



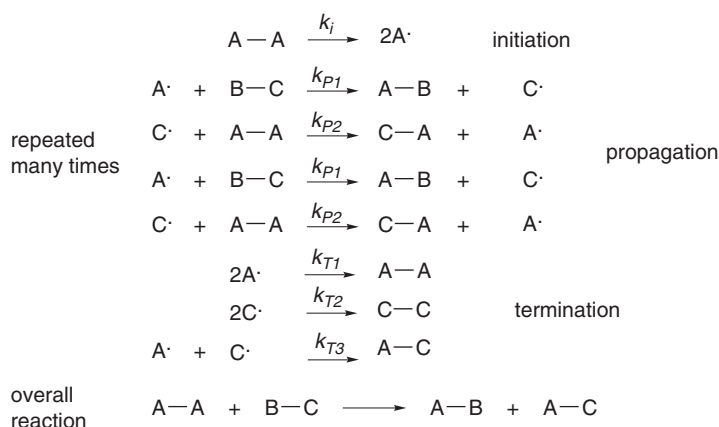
The diketone is presumably generated oxidatively and then reduced to the semidione via reduction by the enolate derived from the original ketone. The ESR spectra of semidione radical anions can provide information on the spin density at the individual atoms. The semidione derived from butane-2,3-dione, 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.

11.2. Characteristics of Reactions Involving Radical Intermediates

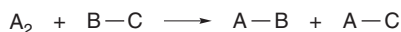
11.2.1. Kinetic Characteristics of Chain Reactions

Certain kinetic 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. The reaction mechanism consists of a cycle of repetitive steps that form many product molecules for each initiation event. The hypothetical mechanism below illustrates a chain reaction.

⁸² G. A. Russell and E. T. Strom, *J. Am. Chem. Soc.*, **86**, 744 (1964).



The step in which the radical intermediate, in this case $A\cdot$, is generated is called the *initiation step*. In the next four equations of 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*, which include all reactions that destroy one of the reactive intermediates necessary for the propagation of the chain. Clearly, the greater the frequency of termination steps, the smaller the chain length will be. The stoichiometry of a free radical chain reaction is independent of the initiating and termination steps because the reactants are consumed and products are formed almost entirely in the propagation steps.



The 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 (see Section 3.2.3) to the radical intermediates. Such intermediates are highly reactive, and their concentrations are low and nearly constant through the course of the reaction. A 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 reaction rate is given by

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

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

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

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

Termination reactions involving coupling or disproportionation of two radicals ordinarily occurs at diffusion-controlled rates. Since the concentration of the reactive

intermediates is very low and these steps involve the reactants, which are present at much higher concentrations, the overall rate of termination is low enough that the propagation steps can compete. The rate of the overall reaction is that of either propagation step:

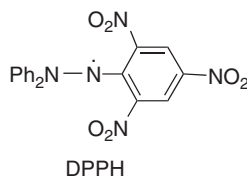
$$\text{Rate} = k_{p2}[\text{C}\cdot][\text{A}_2] = k_{p1}[\text{A}\cdot][\text{B} - \text{C}]$$

After the steady state approximation, both propagation steps must proceed at the same rate or the concentration of $\text{A}\cdot$ or $\text{C}\cdot$ would build up. By substituting for the concentration of the intermediate $\text{C}\cdot$, we obtain

$$\text{Rate} = k_{p2} \left(\frac{k_i}{2k_{t2}} \right)^{1/2} [\text{A}_2]^{3/2} = k_{\text{obs}} [\text{A}_2]^{3/2}$$

The observed rate law is then three-halves order in the reagent A_2 . In most real systems, the situation is somewhat more complicated because more than one termination reaction makes a contribution to the total termination rate. A more complete discussion of the effect of termination steps on the form of the rate law is given by Huyser.⁸³

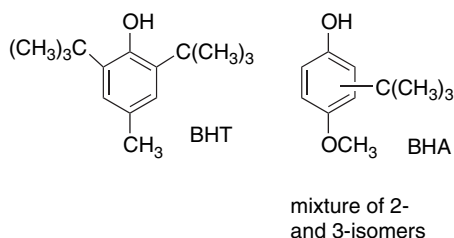
The overall rates of chain reactions can be greatly modified by changing the rate at which initiation or termination steps occur. The idea of initiation was touched on in Section 11.1.4, where sources of free radicals were discussed. Many radical reactions of interest in organic chemistry depend on the presence of an *initiator*, which serves as 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 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. Certain stable free radicals, for example, galvinoxyl (Scheme 11.1, Entry 6) and the hydrazinyl radical diphenylpicrylhydrazyl (DPPH) are used in this way. As they contain an unpaired electron, they are usually very reactive toward radical intermediates. 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.



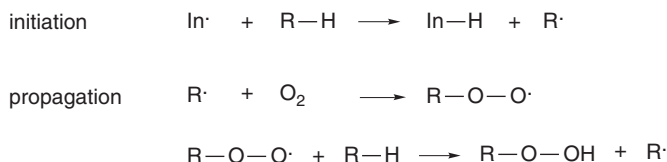
Free radical chain inhibitors are of considerable economic importance. The term *antioxidant* is commonly applied to inhibitors that retard the free radical chain oxidations that can cause deterioration of many commercial materials derived from organic molecules, including foodstuffs, petroleum products,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

⁸³ E. S. Huyser, *Free Radical Chain Reactions*, Wiley-Interscience, New York, 1970, pp. 39–54.

phenols BHT, “butylated hydroxytoluene,” and BHA, “butylated hydroxyanisole,” are used in many commercial foodstuffs.



The chain mechanism for autoxidation of hydrocarbons is:



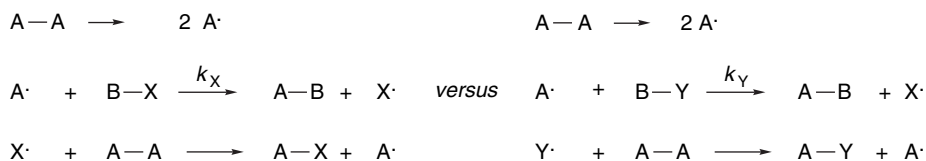
The function of an antioxidant is to divert the peroxy radicals and thus prevent a chain process. The hydroperoxides generated by autoxidation are themselves potential chain initiators, so autoxidations have the potential of being autocatalytic. Some antioxidants function by reducing hydroperoxides and thereby preventing their accumulation. Other antioxidants function by reacting with potential initiators, and retard oxidative degradation by preventing the initiation of autoxidation chains.

The presence of oxygen can modify the course of a free radical chain reaction if a radical intermediate is diverted by reaction with molecular oxygen. The oxygen molecule, with its two unpaired electrons, is extremely reactive to most free radical intermediates. The product that is formed is a reactive peroxy radical that can propagate a chain reaction leading to oxygen-containing products:



11.2.2. Determination of Reaction Rates

Structure-reactivity relationships can be probed by measurements of rates and equilibria, as was discussed in Chapter 3. Direct comparison of reaction rates is used relatively less often in the study of radical reactions than for heterolytic reactions. Instead, *competition methods* have frequently been used. The basis of a competition method lies in the rate expression for a reaction, and the results can be just as valid a comparison of relative reactivity as directly measured rates, *provided the two competing processes are of the same kinetic order*. Suppose we want to compare the reactivity of two related compounds, B-X and B-Y, in a hypothetical sequence:



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.

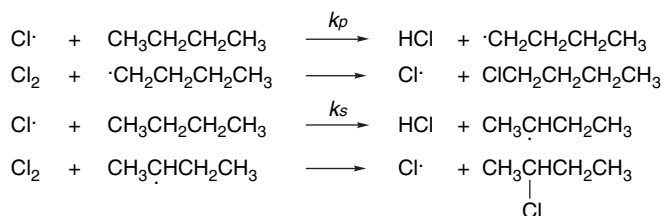
$$\begin{aligned}\frac{-d[B-X]}{dt} &= k_X[A\cdot][B-X] \\ \frac{-d[B-Y]}{dt} &= k_Y[A\cdot][B-Y] \\ \frac{k_X}{k_Y} &= \frac{d[B-X]/[B-X]}{d[B-Y]/[B-Y]}\end{aligned}$$

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 reacted completely. Determination of $[B-X]_t$ and $[B-Y]_t$ then provides the information needed to calculate k_X/k_Y . It is clear that the reactions being compared must be of the same kinetic order. If they are not, division of the two rate expressions would leave uncanceled concentration terms.

Another experiment 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.



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:

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

Techniques for measuring the rates of very fast reactions have permitted absolute rates to be measured for fundamental types of free radical reactions.⁸⁴ Some examples

⁸⁴ M. Newcomb, *Tetrahedron*, **49**, 1151 (1993).




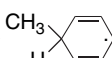

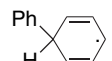




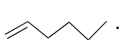

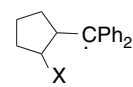
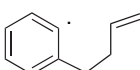
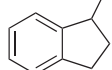
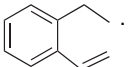
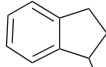
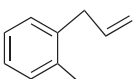
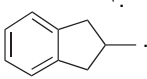
of absolute rates and E_a are given in Table 11.3. The examples include hydrogen abstraction (Section A), addition (Section B), ring closure and opening (Section C), and other types of reactions such as fragmentation and halogen atom abstraction (Section D). In the sections that follow, we discuss some of the reactivity relationships revealed by these data.

Table 11.3. Absolute Rates for Some Free Radical Reactions^a

	Reaction	Rate/ E_a	Reference
A. Hydrogen abstraction reactions			
1	$\text{Ph}\cdot + \text{Cyclopentanol} \longrightarrow \text{Ph-H} + \cdot\text{Cyclopentanol}$	$4.8 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$	b
2	$(\text{CH}_3)_3\text{CO}\cdot + (\text{CH}_3)_2\underset{\text{H}}{\text{CPh}} \longrightarrow (\text{CH}_3)_3\text{COH} + (\text{CH}_3)_2\dot{\text{CPh}}$	$8.7 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	c
3	$(\text{CH}_3)_3\text{CO}\cdot + \text{Cyclopentanol} \longrightarrow (\text{CH}_3)_3\text{COH} + \cdot\text{Cyclopentanol}$	$8.3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$	c
4	$\text{Cl}\cdot + \text{Cyclopentane} \longrightarrow \text{H-Cl} + \cdot\text{Cyclopentane}$ (free)	$4.7 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$	d
5	$\text{Cl}\cdot + \text{Cyclopentane} \longrightarrow \text{H-Cl} + \cdot\text{Cyclopentane}$ (benzene complex)	$4.3 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$	d
6	$\text{CH}_3\cdot + \text{Bu}_3\text{SnH} \longrightarrow \text{CH}_4 + \text{Bu}_3\text{Sn}\cdot$	$1.0 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ $E_a = 3.2 \text{ kcal/mol}$	e
7	$(\text{CH}_3)_3\text{C}\cdot + \text{Bu}_3\text{SnH} \longrightarrow (\text{CH}_3)_3\text{CH} + \text{Bu}_3\text{Sn}\cdot$	$1.8 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ $E_a = 2.95 \text{ kcal/mol}$	e
8	$\text{Ph}\cdot + \text{Bu}_3\text{SnH} \longrightarrow \text{C}_6\text{H}_6 + \text{Bu}_3\text{Sn}\cdot$	$7.8 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$	f
9	$\text{CF}_3\text{CF}_2\text{CF}_2\cdot + \text{Bu}_3\text{SnH} \longrightarrow \text{CF}_3\text{CF}_2\text{CF}_2\text{H} + \text{Bu}_3\text{Sn}\cdot$	$2.0 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$	g
10	$\text{PhCH}_2\cdot + \text{PhSH} \longrightarrow \text{PhCH}_3 + \text{PhS}\cdot$	$3.1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	h
11	$\text{RCH}_2\cdot + (\text{CH}_3)_3\text{CSH} \longrightarrow \text{RCH}_3 + (\text{CH}_3)_3\text{CS}\cdot$	$8 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$	i
12	$\text{Cyclopropyl-CH}_2\cdot + \text{PhSeH} \longrightarrow \text{Cyclopropyl-CH}_3 + \text{PhSe}\cdot$	$2.1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$	j
13	$(\text{CH}_3)_3\text{CC}=\text{O} + \text{Bu}_3\text{SnH} \longrightarrow (\text{CH}_3)_3\text{CCH}=\text{O} + \text{Bu}_3\text{Sn}\cdot$	$3.0 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	k
14	$\text{RC}=\text{O} + \text{Bu}_3\text{SnH} \longrightarrow \text{RCH}=\text{O} + \text{Bu}_3\text{Sn}\cdot$	$1.3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$	l
15	$\text{Ph}_2\text{C}=\text{CPh} + \text{Bu}_3\text{SnH} \longrightarrow \text{Ph}_2\text{C=CHPh} + \text{Bu}_3\text{Sn}\cdot$	$7.5 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$	m
16	$\text{RCH}_2\cdot + [(\text{CH}_3)_3\text{Si}]_3\text{SiH} \longrightarrow \text{RCH}_3 + [(\text{CH}_3)_3\text{Si}]_3\text{Si}\cdot$	$1.0 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	n
17	$\text{Ph}_2\text{C}=\text{CPh} + [(\text{CH}_3)_3\text{Si}]_3\text{SiH} \longrightarrow \text{Ph}_2\text{C=CHPh} + [(\text{CH}_3)_3\text{Si}]_3\text{Si}\cdot$	$1.6 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$	m
18	$\text{RC}=\text{O} + [(\text{CH}_3)_3\text{Si}]_3\text{SiH} \longrightarrow \text{RCH}=\text{O} + [(\text{CH}_3)_3\text{Si}]_3\text{Si}\cdot$	$1.0 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	l

(Continued)

Table 11.3. (Continued)

B. Additions to Alkenes and Aromatic Rings				
19	$\text{CH}_3\cdot + \text{H}_2\text{C}=\text{CHPh} \longrightarrow \text{CH}_3\text{CH}_2\dot{\text{C}}\text{HPh}$	$2.6 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ $E_a = 4.9 \text{ kcal/mol}$		o
20	$\text{CH}_3\cdot + \text{H}_2\text{C}=\text{CHCN} \longrightarrow \text{CH}_3\text{CH}_2\dot{\text{C}}\text{HCN}$	$6.1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$		o
21	$\text{CF}_3\cdot + \text{H}_2\text{C}=\text{CHPh} \longrightarrow \text{CF}_3\text{CH}_2\dot{\text{C}}\text{HPh}$	$5.3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$		p
22	$\text{Ph}\cdot + \text{CH}_2=\text{CHPh} \longrightarrow \text{PhCH}_2\dot{\text{C}}\text{HPh}$	$1.1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$		b
23	$\text{Ph}\cdot + $  $\longrightarrow \text{Ph}-$ 	$2.1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$		q
24	$\text{PhCH}_2\cdot + \text{H}_2\text{C}=\text{C}(\text{CH}_3)_2 \longrightarrow \text{PhCH}_2\text{CH}_2\dot{\text{C}}(\text{CH}_3)_2$	$18 \text{ M}^{-1}\text{s}^{-1}$		r
25	$(\text{CH}_3)_2\dot{\text{C}}\text{CN} + \text{CH}_2=\text{CHPh} \longrightarrow (\text{CH}_3)_2\text{CCH}_2\dot{\text{C}}\text{HPh}$ <div style="margin-left: 100px;">CN</div>	$7.0 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ $E_a = 6.4 \text{ kcal/mol}$		s
26	$\text{CH}_3\cdot + $  $\longrightarrow $ 	$46 \text{ M}^{-1}\text{s}^{-1}$ $E_a = 8.9 \text{ kcal/mol}$		t
27	$\text{Ph}\cdot + $  $\longrightarrow $ 	$4.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$		b
28	$(\text{CH}_3)_3\text{CO}\cdot + \text{H}_2\text{C}=\text{CH}(\text{CH}_2)_5\text{CH}_3 \longrightarrow (\text{CH}_3)_3\text{COCH}_2\dot{\text{C}}\text{H}(\text{CH}_2)_5\text{CH}_3$	$1.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$		c
29	$\text{PhS}\cdot + \text{CH}_2=\text{CHPh} \longrightarrow \text{PhSCH}_2\dot{\text{C}}\text{HPh}$	$2.0 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$		u
C. Cyclization and Ring-Opening				
30	 $\longrightarrow $ 	$9.4 \times 10^7 \text{ s}^{-1}$ $E_a = 7-7.5 \text{ kcal/mol}$		v
31	 $\longrightarrow $ 	$1.8 \times 10^7 \text{ s}^{-1}$		w
32	$\text{Ph}-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2\cdot \xrightleftharpoons{K=80} \text{Ph}-\text{CH}_2-\text{CH}_2-\dot{\text{C}}\text{H}-\text{CH}_2\text{Ph}$	$5.4 \times 10^6 \text{ s}^{-1}$		x
33	 $\longrightarrow $ 	$2.4 \times 10^5 \text{ s}^{-1}$ $E_a = 6.2 \text{ kcal/mol}$		e, y
34	$\text{X}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{Ph})-\dot{\text{C}}\text{HPh} \longrightarrow $ 	$\text{X} = \text{H} \quad 4 \times 10^7 \text{ s}^{-1}(20^\circ \text{C})$ $\text{X} = \text{CH}_3 \quad 2 \times 10^7 \text{ s}^{-1}(20^\circ \text{C})$ $\text{X} = \text{OCH}_3 \quad 4 \times 10^7 \text{ s}^{-1}(20^\circ \text{C})$ $\text{X} = \text{CO}_2\text{C}_2\text{H}_5 \quad 5.4 \times 10^7 \text{ s}^{-1}(20^\circ \text{C})$	z	
35	 $\longrightarrow $ 	$4 \times 10^8 \text{ s}^{-1}$ $E_a = 3.6 \text{ kcal/mol}$		aa
36	 $\longrightarrow $ 	$1.5 \times 10^5 \text{ s}^{-1}$ $E_a = 7.3 \text{ kcal/mol}$		bb
37	 $\longrightarrow $ 	$2 \times 10^{-1} \text{ s}^{-1}$ $E_a = 16.3 \text{ kcal/mol}$		cc

(Continued)

Table 11.3. (Continued)

38		$2.8 \times 10^4 \text{ s}^{-1}$ $E_a = 8.3 \text{ kcal/mol}$	dd
39		$4.2 \times 10^8 \text{ s}^{-1}$	ee
40		$1.4 \times 10^5 \text{ s}^{-1}$ $9.1 \times 10^7 \text{ s}^{-1}$ $E_a = 6.8 \text{ kcal/mol}$	ff
41		$2.5 \times 10^5 \text{ s}^{-1}$ $E_a = 5.4 \text{ kcal/mol}$	gg
D. Other Reactions			
42	$(\text{CH}_3)_3\text{C}\cdot + \text{O}_2 \longrightarrow (\text{CH}_3)_3\text{C}-\text{O}-\text{O}\cdot$	$4.9 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$	gg
43	$\text{PhCH}_2\cdot + \text{O}_2 \longrightarrow \text{PhCH}_2-\text{O}-\text{O}\cdot$	$2.4 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$	k
44		$4 \times 10^5 \text{ s}^{-1}$ 10.2 kcal/mol	hh
45	$(\text{CH}_3)_3\text{CC}\cdot=\text{O} \longrightarrow (\text{CH}_3)_3\text{C}\cdot + \text{C}\equiv\text{O}$	$3.0 \times 10^5 \text{ s}^{-1}$	ii
46	$\text{PhCH}_2\text{C}\cdot=\text{O} \longrightarrow \text{PhCH}_2\cdot + \text{C}\equiv\text{O}$	$5.2 \times 10^7 \text{ s}^{-1}$ $E_a = 7.2 \text{ kcal/mol}$	jj
47		$5.2 \times 10^5 \text{ s}^{-1}$ $E_a = 10.0 \text{ kcal/mol}$	aa
48		$11 \times 10^7 \text{ s}^{-1}$	kk
49	$\text{PhC}(\text{CH}_3)_2\text{O}\cdot \longrightarrow \text{PhC}(\text{CH}_3)_2\text{O} + \text{CH}_3\cdot$	$7 \times 10^5 \text{ s}^{-1}$	ll
50	$\text{Ph}\cdot + \text{CCl}_4 \longrightarrow \text{PhCl} + \cdot\text{CCl}_3$	$2.3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$	kk
51	$\text{CH}_3(\text{CH}_2)_3\cdot + \text{BrCCl}_3 \longrightarrow \text{CH}_3(\text{CH}_2)_3\text{Br} + \cdot\text{CCl}_3$	$2.6 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ (80°C)	mm
52	$\text{Ph}\cdot + \text{BrCCl}_3 \longrightarrow \text{PhBr} + \cdot\text{CCl}_3$	$1.6 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$	nn
53	$\text{CH}_2=\text{CHCH}_2\cdot + \text{ClOC}(\text{CH}_3)_3 \longrightarrow \text{CH}_2=\text{CHCH}_2\text{Cl} + (\text{CH}_3)_3\text{CO}\cdot$	$2.6 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$	nn
54	$\text{C}_8\text{H}_{19}\cdot + \text{PhSeCH}_2\text{CO}_2\text{C}_2\text{H}_5 \longrightarrow \text{C}_8\text{H}_{19}\text{SePh} + \cdot\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$	$1.0 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	oo
55	$\text{C}_8\text{H}_{19}\cdot + \text{PhSeC}(\text{CH}_3)(\text{CO}_2\text{C}_2\text{H}_5)_2 \longrightarrow \text{C}_8\text{H}_{19}\text{SePh} + \text{CH}_3\text{C}(\text{CO}_2\text{C}_2\text{H}_5)_2\cdot$	$8 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	oo

a. Unless otherwise noted, the rates are for temperatures near 25°C. The reference should be consulted for precise temperature and other conditions.

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
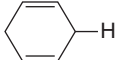
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11.2.3. Structure-Reactivity Relationships

11.2.3.1. Hydrogen Abstraction Reactions In hydrogen atom abstraction reactions, the strength of the bond to the reacting hydrogen is a major determinant of the rate at which reaction occurs. Table 11.4 gives some bond dissociation energies (BDE) that are particularly relevant to free radical reactions.

Generally, the ease of hydrogen atom abstraction parallels the BDE. Several of the trends, such as those for hydrocarbons and alkyl halides were discussed in Sections 3.1.2 and 3.4.3. The general tendency for functional groups to weaken α -CH bond is illustrated by the values for methanol, diethyl ether, acetone, and acetonitrile. The bond order relationship $\text{Si-H} > \text{Ge-H} > \text{Sn-H}$ is particularly important in free radical chemistry. Entries 16 and 18 in Table 11.3 provide abstraction rates for silanes. The comparison between Entries 6 and 16 and 14 and 18 shows that silanes are somewhat less reactive than stannanes. Trisubstituted stannanes are among the most reactive hydrogen atom donors. As indicated by Entries 6 to 8, hydrogen abstractions from stannanes proceed with rates higher than $10^7 \text{ M}^{-1}\text{s}^{-1}$ and have very low activation energies. This high reactivity correlates with the low bond strength of the Sn-H bond (78 kcal) For comparison, Entries 1 to 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 reaction with the phenyl radical

Table 11.4. Selected Bond Dissociation Energies (kcal/mol)^a

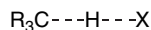
Bond	BDE	Bond	BDE
CH ₃ -H	105.0	CH ₃ S-H	87
CH ₃ CH ₂ -H	100.5	PhS-H	83
(CH ₃) ₂ CH-H	98.1	(CH ₃) ₃ Si-H	93
(CH ₃) ₃ C-H	95.7	(CH ₃) ₃ Ge-H	87
CH ₂ =CH-H	111	(C ₄ H ₉) ₃ Sn-H	78
	106		
	76	[CH ₃ C(=O)O-] ₂	30
HOCH ₂ -H	96	(CH ₃) ₃ CO-OH	44
C ₂ H ₅ OCH(CH ₃)-H	93	CH ₃ S-SCH ₃	65
CH ₃ C(=O)CH ₂ -H	96	C ₂ H ₅ -F	113
N-CCH ₂ -H	96	C ₂ H ₅ -Cl	84
F ₃ C-H	107	C ₂ H ₅ -Br	70
Cl ₃ C-H	94	C ₂ H ₅ -I	56
F-H	136	F-F	38
Cl-H	102	Cl-Cl	57
Br-H	87	Br-Br	45
I-H	71	I-I	36

a. From Y.-R. Luo, *Bond Dissociation Energies of Organic Compounds*, CRC Press, Boca Raton, FL, 2003.

(Entries 1 and 8), tri-*n*-butylstannane is about 100 times more reactive than tetrahydrofuran as a hydrogen atom donor. Thiols are also quite reactive as hydrogen atom donors, as indicated by Entries 10 and 11. Phenylselenol is an even more reactive hydrogen atom donor than tri-*n*-butylstannane (see Entry 12).

Entries 4 and 5 point to another important aspect of free radical reactivity. The data given indicate 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. Another case is chlorination in bromomethane, where the pri:sec: text selectivity increases to 1:8.8:38.⁸⁵ 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.

The TS for hydrogen atom abstraction is pictured as having the hydrogen partially bonded to the donor carbon and the abstracting radical. Generally, theoretical models of such reactions indicate a linear alignment, although there are exceptions:



The Bell-Evans-Polanyi relationship and the Hammond postulate (see Section 3.3) provide a basic framework within which to discuss structure-reactivity relationships. The Bell-Evans-Polanyi equation implies that there will be a linear relationship between E_a and the C-H BDE.

$$E_a = \alpha \Delta H_r + E_0 \quad (11.4)$$

⁸⁵. A. Dneprovskii, D. V. Kuznetsov, E. V. Eliseenkov, B. Fletcher, and J. M. Tanko, *J. Org. Chem.*, **63** 8860 (1998).

which can be rearranged to

$$E_a = \alpha(BDE) + \beta \quad (11.5)$$

We would therefore expect the E_a to decrease as the reacting C–H bond becomes weaker. The Hammond postulate relates position on the reaction coordinate to TS structure. Hydrogen atom abstractions with early TS will be reactant-like and those with late TS will be radical-like. We expect highly exothermic atom transfers to have early TSs and to be less sensitive to radical stability factors. Energy neutral reactions should have later TSs.

Table 11.5 summarizes some activation energies and relative reactivity data for some of the types of radicals that we are discussing, including alkyl, allyl, phenyl, benzyl, halomethyl, and hydroxyl radicals, and halogen atoms. These data provide confirmation of the widely recognized reactivity order *tert* > *sec* > *pri* for formation of alkyl radicals by hydrogen atom abstraction. They also provide some examples of the *reactivity-selectivity principle*, which is the premise that the most reactive radicals are the least selective and vice versa. The halogens are a familiar example of this idea. Chlorine atom selectivity is low, corresponding to very small E_a values and an early TS. Bromine, by contrast, has a significant E_a and is quite selective. The hydroxyl and alkoxy radicals are only modestly selective, whereas the $\text{CF}_3\cdot$ and $\text{CCl}_3\cdot$ radicals have higher E_a and greater selectivity.

Relative reactivity information such as that in Table 11.5 can be used in interpreting and controlling reactivity. For example, the high selectivity of the $\text{CBr}_3\cdot$ and $\text{CCl}_3\cdot$ is the basis for a recently developed halogenation procedure that is especially

Table 11.5. Activation Energies (kcal/mol) and Approximate Selectivity Ratios for Hydrogen Atom Abstraction Reactions

Radical	$\text{CH}_3\text{--H}$	$\text{CH}_3\text{CH}_2\text{--H}$	$(\text{CH}_3)_2\text{CH--H}$	$(\text{CH}_3)_3\text{C--H}$	$\text{PhCH}_2\text{--H}$	$\text{CH}_2=\text{CHCH}_2\text{--H}$	<i>pri:sec:tert</i>
$\text{CH}_3^{\cdot,a,b,c}$	14.0	11.6	9.6	8.1	9.5	7.7	1.0:4.8:61
$\text{C}_2\text{H}_5^{\cdot,d}$		13.3	11.4	10.0	9.3		
$(\text{CH}_3)_2\text{CH}^{\cdot,d}$				10 ± 2			
$(\text{CH}_3)_3\text{C}^{\cdot,d}$				10.5	10.3		
$\text{Ph}^{\cdot,d,e,f}$	10.3	4.4		3.0	2.0		1:8.5:40
$\text{PhCH}_2^{\cdot,d}$					17.0		
$\text{HC}\equiv\text{C}^{\cdot,g}$	~ 2.5	0	0	0			
$\text{CF}_3^{\cdot,a}$	10.9	8.0	6.5	4.9	5.8		
$\text{CCl}_3^{\cdot,c}$	17.9	14.2	10.6	7.7			
$\text{F}^{\cdot,c}$	1–1.5	< 1		< 1			
$\text{Cl}^{\cdot,c}$	3.4	1.1					1:2.8:2.1
$\text{Br}^{\cdot,g}$	17.5	13.0	9.5	6.9			1:250:6300
$\text{HO}^{\cdot,c}$	3.6	1.0	0.6	0.3			
$\text{CH}_3\text{O}^{\cdot,a}$	10.1	7.1		2.4			
$(\text{CH}_3)_3\text{CO}^{\cdot,c}$					3.5 ^h		1:12:50

a. B. P. Roberts and A. J. Steel, *J. Chem. Soc., Perkin Trans. 2*, 2155 (1994).

b. N. Kobko and J. J. Dannenberg, *J. Phys. Chem. A*, **105**, 1944 (2001).

c. A. A. Fokin and P. Schreiner, *Chem. Rev.*, **102**, 1551 (2002); see also P. A. Hooshiyar and H. Niki, *Int. J. Chem. Kinetics*, **27**, 1197 (1995).

d. A. A. C. C. Pais, L. G. Arnaut, and S. J. Formosinho, *J. Chem. Soc., Perkin Trans. 2*, 2577 (1998).

e. J. Park, D. Chakraborty, D. M. Bhusari, and M. C. Lin, *J. Phys. Chem. A*, **103**, 4002 (1999). T. Yu and M. C. Lin, *J. Phys. Chem.*, **99**, 8599 (1995).

f. B. Ceursters, H. M. T. Nguyen, J. Peeters and M. T. Nguyen, *Chem. Phys. Lett.*, **329**, 412 (2000). R. J. Hoobler, B. J. Opansky, and S. R. Leone, *J. Phys. Chem. A*, **101**, 1338 (1997). J. Parks, S. Gheys, and M. C. Lin, *Int. J. Chem. Kinetics*, **33**, 64 (2001).

g. A. F. Trotman-Dickenson, *Adv. Free Radical Chem.*, **1**, 1 (1965).

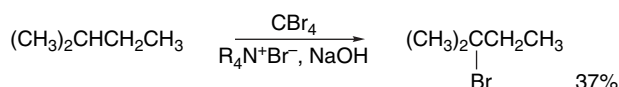
h. M. Finn, R. Friedline, N. K. Suleman, G. J. Wohl, and J. M. Tanko, *J. Am. Chem. Soc.*, **126**, 7578 (2004).

applicable to polycyclic hydrocarbons such as cubane, which do not react cleanly by direct halogenation. The reactions are carried out under phase transfer conditions using CBr_4 or CCl_4 as the halogen source and the $\text{CBr}_3\cdot$ and $\text{CCl}_3\cdot$ as the chain carriers. The reactions are initiated by electron transfer from hydroxide ion.

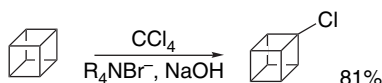
Initiation



Propagation

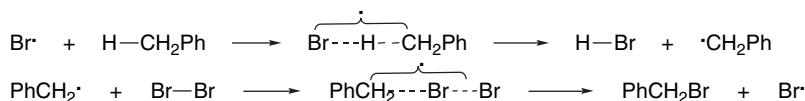


Ref. 86



Ref. 87

Many free radical reactions respond to introduction of polar substituents, just as do heterolytic processes that involve polar or ionic intermediates. The case of toluene bromination can be used to illustrate this point.



The substituent effects on toluene bromination are correlated by the Hammett equation, which gives a ρ value of -1.4 , indicating that the benzene ring acts as an electron donor in the TS.⁸⁸ Other radicals, for example, the *t*-butyl radical, show a positive ρ for hydrogen abstraction reactions involving toluene,⁸⁹ which indicates that radicals can exhibit either electrophilic or nucleophilic character. Why do free radical reactions involving neutral reactants and intermediates respond to substituent changes that modify electron distribution? One explanation is based on the idea that there is some polar character in the TS because of the electronegativity differences of the reacting atoms.⁹⁰



⁸⁶ P. R. Schreiner, O. Lauenstein, I. V. Kolomitsyn, S. Nadi, and A. A. Fokin, *Angew. Chem. Int. Ed. Engl.*, **37**, 1895 (1998).

⁸⁷ A. A. Fokin, O. Lauenstein, P. A. Gunchenko, and P. R. Schreiner, *J. Am. Chem. Soc.*, **123**, 1842 (2001).

⁸⁸ 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 (1984); 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).

⁸⁹ 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 R. H. Tang, *Frontiers of Free Radical Chemistry*, W. A. Pryor, ed., Academic Press, New York, 1980, pp. 355–380.

⁹⁰ E. S. Huyser, *Free Radical Chain Reactions*, Wiley-Interscience, New York, 1970, Chap. 4; G. A. Russell, in *Free Radicals*, Vol. 1, J. Kochi, ed., Wiley, New York, 1973, Chap. 7.

This idea receives support from the fact that the most negative ρ values are found for more electronegative radicals such as $\text{Br}\cdot$, $\text{Cl}\cdot$, and $\text{Cl}_3\text{C}\cdot$. 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.⁹¹ Thus the extent of bond cleavage and formation at the TS may be different for various radicals. Successful interpretation of substituent effects in radical reactions therefore requires consideration of factors such as the electronegativity and polarizability of the radicals as well as 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 can appear to be more complicated than those for heterolytic reactions, where substituent effects are usually dominated by the electron-releasing or electron-donating capacity of the substituent.⁹²

11.2.3.2. Addition Reactions Section B of Table 11.3 gives some rates of addition reactions involving carbon-carbon double bonds and aromatic rings. Comparison of Entries 23 and 24 shows that the phenyl radical is much more reactive toward addition to alkenes than the benzyl radical. Comparison of Entries 26 and 27 shows the same effect on additions to an aromatic ring. Delocalized benzyl and cumyl radicals have somewhat reduced reactivity.⁹³ Additions to aromatic rings are much slower than additions to alkenes (compare Entries 23 and 27). This kinetic relationship shows that it is more difficult to disrupt an aromatic ring than an alkene π bond.

Despite their overall electrical neutrality, carbon-centered radicals can show pronounced electrophilic or nucleophilic character, depending on the substituents present.⁹⁴ This electrophilic or nucleophilic character is reflected in rates of reaction with nonradical species, for example, in additions to substituted alkenes. Alkyl radicals and α -alkoxyalkyl radicals are distinctly nucleophilic in character and react most rapidly with alkenes having EWG substituents. Even methyl radicals with a single EWG, such as *t*-butoxycarbonyl or cyano are weakly nucleophilic.⁹⁵ Radicals having two EWGs, such as those derived from malonate esters, react preferentially with double bonds having ERG substituents.⁹⁶ Perfluoro radicals are electrophilic and are about 10^3 more reactive than alkyl radicals.⁹⁷

These substituent effects are consistent with an FMO interpretation with a dominant SOMO-LUMO interaction.⁹⁸ As shown in Figure 11.6, ERG substituents will raise the energy of the radical SOMO and increase the strength of interaction with the relatively low-lying LUMO of alkenes having electron-withdrawing groups. When

⁹¹ A. A. Zavitsas and J. A. Pinto, *J. Am. Chem. Soc.*, **94**, 7390 (1972); W. M. Nau, *J. Phys. Org. Chem.*, **10**, 445 (1997).

⁹² W. H. Davis, Jr., and W. A. Pryor, *J. Am. Chem. Soc.*, **99**, 6365 (1972); 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).

⁹³ M. Walbinder, J. Q. Wu, and H. Fischer, *Helv. Chim. Acta*, **78**, 910 (1995).

⁹⁴ B. Giese, *Angew. Chem. Int. Ed. Engl.*, **22**, 753 (1983); H. Fischer and L. Radom, *Angew. Chem. Int. Ed. Engl.*, **40**, 1340 (2001).

⁹⁵ K. Heberger and A. Lopata, *J. Org. Chem.*, **63**, 8646 (1998).

⁹⁶ B. Giese, H. Horler, and M. Leising, *Chem. Ber.*, **119**, 444 (1986).

⁹⁷ D. V. Avila, K. U. Ingold, J. Luszyk, W. R. Dolbier, and H. Q. Pan, *J. Am. Chem. Soc.*, **115**, 1577 (1993).

⁹⁸ U. Berg, E. Butkus, and A. Stoncius, *J. Chem. Soc., Perkin Trans. 2*, 97 (1995); M. W. Wong, A. Pross, and L. Radom, *J. Am. Chem. Soc.*, **116**, 6284 (1994).

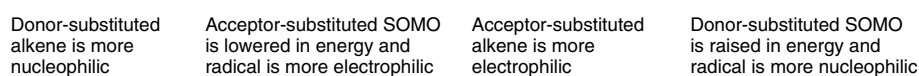


Fig. 11.6. Frontier orbital interactions between different combinations of substituted radicals and alkenes showing enhanced interaction relative to unsubstituted systems.

the radical site is substituted by an electron-attracting group, the SOMO is lower. A complementary interaction between the radical and alkene is possible.

The TS for radical additions is quite early and correlates with ground state characteristics of the reactant alkene. In particular there is a strong correlation between relative reactivity and the LUMO energy of the reactant alkene for addition reactions of the *t*-butyl radical, as shown in Figure 11.7.⁹⁹ The rate constants range over ten ln exponents and the correlation coefficient is 0.971. π -Donor substituents

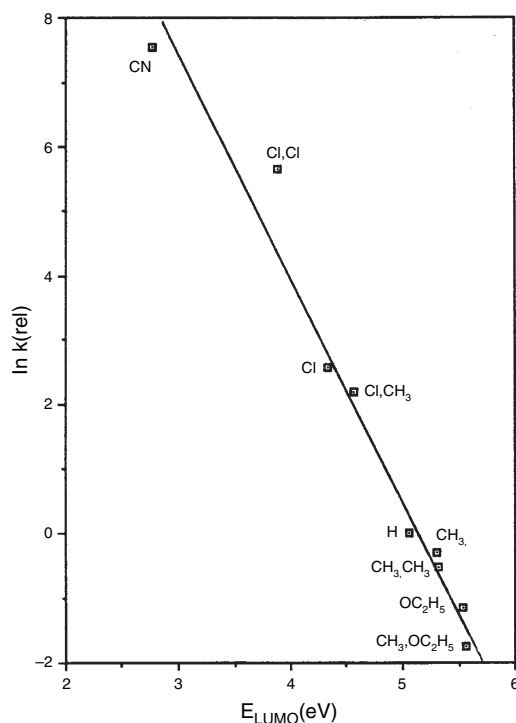


Fig. 11.7. Correlation between relative rates of addition reactions of *t*-butyl radicals and E_{LUMO} for alkenes. Reproduced from *J. Org. Chem.*, **57**, 1139 (1992), by permission of the American Chemical Society.

⁹⁹ D. J. Pasto, *J. Org. Chem.*, **57**, 1139 (1992).

(e.g., OR) retard reaction, whereas EWGs (e.g., CN) accelerate reaction, which is in agreement with the classification of alkyl radicals as nucleophilic. A relationship was also found between reactivity and the ground state stabilization of the alkene. Certain substituent combinations (e.g., CN,CN or Cl,Cl) significantly destabilize the alkene, and these compounds are highly reactive toward alkyl radicals. On the other hand, the (OC₂H₅, CH₃) combination stabilizes the alkene and such compounds are less reactive toward alkyl radicals. These results are consistent with an early TS for radical addition controlled by SOMO-LUMO interactions. The regiochemistry, which generally involves addition at the β -carbon, also correlates with the coefficient of the LUMO, as would be expected for an FMO-controlled reaction.

Some other representative rate data are given in Table 11.6. Methyl radicals are somewhat more reactive toward alkenes bearing EWG substituents than with ERG substituents. Secondary cyclohexyl radicals show a stronger trend in this direction. Some of this effect can be attributed to the stabilizing influence that these substituents have on the product radical. There is a strong correlation of reaction rate with the overall exothermicity of the reaction.¹⁰⁰

Related trends are seen in data for radicals with functional group substituents. Hydroxymethyl and 2-hydroxy-2-propyl radicals show nucleophilic character.¹⁰¹ The hydroxymethyl radical shows a slightly enhanced rate toward acrylonitrile and acrolein, but a sharply decreased rate toward ethyl vinyl ether. The more electrophilic cyanomethyl radical shows reactivity enhancement not only with radical-stabilizing EWGs, but also with ERGs. Table 11.7 gives some of the reactivity data.

α -Fluoro substituents enhance reactivity toward alkene addition. The effect of polyfluorination is more than cumulative. The rates of RCH₂ \cdot (1) ; RCHF \cdot (3.5); RCF₂ \cdot

Table 11.6. Relative Rates of Radical Additions as a Function of Alkene Substitution^a

A. Addition to substituted ethenes, CH₂=CH-X

X	CH ₃ \cdot	CH ₃ CH ₂ \cdot	<i>c</i> -C ₆ H ₁₁ \cdot
CN	2.2	5.1	24
COCH ₃	2.3		13
CO ₂ CH ₃	1.3	1.9	6.7
Ph	1.0	1.0	1.0
O ₂ CCH ₃		0.05	0.016

B. Additions to α -substituted styrenes. CH₂=CXPh

X	<i>c</i> -C ₆ H ₁₁ \cdot	\cdot CH(CO ₂ C ₂ H ₅) ₂
CN	122	
CO ₂ C ₂ H ₅	11.7	0.28
Ph	1.0	1.0
CH ₃	0.28	1.06
CH ₃ O		0.78
(CH ₃) ₂ N		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).

¹⁰⁰. M. W. Wong, A. Pross, and L. Radom, *J. Am. Chem. Soc.*, **115**, 11050 (1993); R. Arnaud, N. Bugaud, V. Vetere, and V. Barone, *J. Am. Chem. Soc.*, **120**, 5733 (1998).

¹⁰¹. J. Q. Wu and H. Fischer, *Int. J. Chem. Kinetics*, **27**, 167 (1995); S. N. Batchelor and H. Fischer, *J. Chem. Phys.*, **100**, 9794 (1996).

Table 11.7. Absolute Rates of Addition Reactions of Methyl, Cyanomethyl, and Hydroxymethyl Radicals toward Substituted Alkenes, CH₂=CHX

X	$k(M^{-1}s^{-1})$		
	$\cdot\text{CH}_3^a$	$\cdot\text{CH}_2\text{CN}^b$	$\cdot\text{CH}_2\text{OH}^c$
H	3.5×10^3	3.3×10^3	4.1×10^2
Ph	2.6×10^5	3.8×10^3	2.3×10^4
CN	6.1×10^5	1.1×10^5	1.1×10^6
CH=O	7.4×10^5	2.5×10^4	2.1×10^6
CO ₂ CH ₃	3.4×10^5	1.1×10^5	7.1×10^5
OC ₂ H ₅	1.4×10^4	1.2×10^4	1.8×10^2
CH ₃	4.3×10^3	1.2×10^4	2.7×10^2

a. T. Zytowski and H. Fischer, *J. Am. Chem. Soc.*, **118**, 437 (1996); T. Zytowski and H. Fischer, *J. Am. Chem. Soc.*, **119**, 12869 (1997).

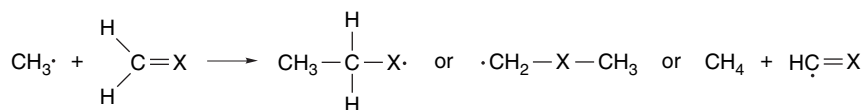
b. J. Q. Wu and H. Fischer, *Int. J. Chem. Kinet.*, **27**, 167 (1995).

c. J. Q. Wu, I. Beranek, and H. Fischer, *Helv. Chim. Acta*, **78**, 194 (1995).

SECTION 11.2
Characteristics of
Reactions Involving
Radical Intermediates

(20); and CF₃· (300) show this trend.¹⁰² Further accumulation of fluorine enhances this effect still further and the perfluoro-*t*-butyl radical is typically eight to ten times more reactive than CF₃· toward alkenes.

Computational studies have also compared some of the fundamental substituent effects on addition reactions for other functional groups. The relative barriers for addition and hydrogen abstraction were compared for ethene, formaldehyde, methylene imine, and formaldehyde nitron. The data shown below are the result of B3LYP/6-311+G(2df,p) calculations, but G2 and CBS calculations were carried out in some cases.¹⁰³



X	Addition at C		Addition at X		H Abstraction	
	ΔH	ΔH^\ddagger	ΔH	ΔH^\ddagger	ΔH	ΔH^\ddagger
=CH ₂	-20	+ 7	-20	+ 7	+ 5	+ 15
=O	-13	+4.5	-7.4	+15	-17	+ 5
=NH	-18	+6.5	-19	+9.5	-18	+4
=N ⁺ (O ⁻)H	-44	+ 1.7	+ 6.2	+ 22	-34	-1

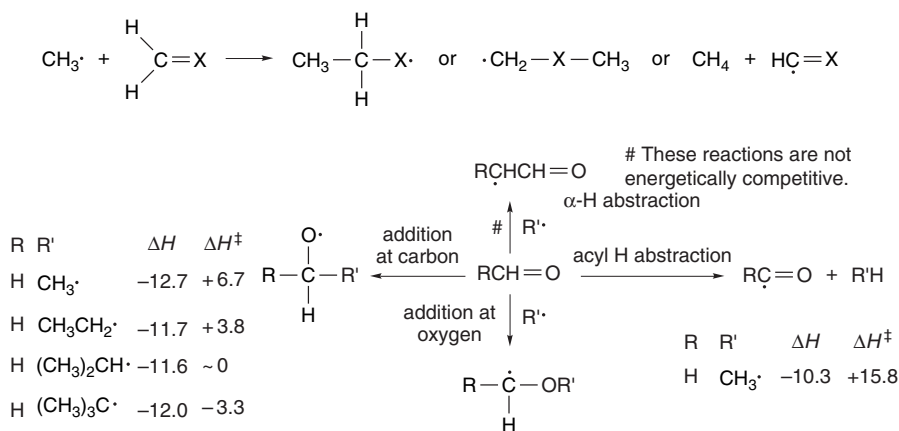
Addition is preferred to hydrogen atom abstraction for alkenes. Addition at carbon and hydrogen abstraction are competitive for aldehydes and imines. Both addition at carbon and hydrogen abstraction reactions are very exothermic for nitrones and are calculated to have low barriers. There are two possible modes of addition for the unsymmetrical systems. For the carbonyl and nitron groups, addition at the carbon is preferred. The same is true for imines, but the balance is much closer. The activation

^{102.} D. V. Avila, K. U. Ingold, J. Luszyk, W. R. Dolbier, Jr., and H.-Q. Pan, *J. Org. Chem.*, **61**, 2027 (1996); D. Avila, K. U. Ingold, J. Luszyk, W. R. Dolbier, Jr., and H.-Q. Pan, *Tetrahedron*, **52**, 12351 (1996).

^{103.} S. L. Boyd and R. J. Boyd, *J. Phys. Chem. A*, **105**, 7096 (2001).

The energetics of addition reactions of alkyl radicals with aldehyde groups have been studied as a function of radical structure.¹⁰⁵ According to G3(MP2) computations, alkyl radicals show a lower barrier to carbonyl addition as they become more substituted. As shown in Figure 11.8, these reactions interrelate acyl, alkoxyalkyl, and alkoxy radicals. For the simplest system, the addition at O is also energetically favorable, but the activation barrier is higher. Experimental studies indicate that the barrier for H abstraction from formaldehyde by primary radicals is around 7.5 kcal/mol, which is significantly lower than is calculated. Hydrogen abstraction from the α -position is calculated to have a significantly higher barrier and is not competitive.

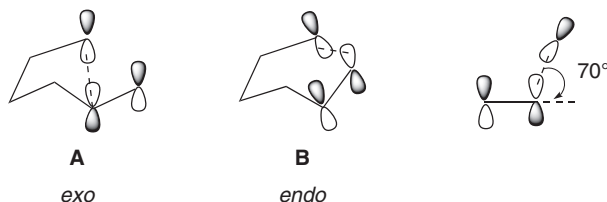
Entry 30 is the case of ring opening of the cyclopropylmethyl radical, which was discussed on p. 973. Note that the activation energy is somewhat higher than a normal single bond rotation but less than that for cyclohexane inversion. Entry 32 shows that



105. H. Hippler and B. Viskolcz, *Phys. Chem. Chem. Phys.*, **4**, 4663 (2002).

the stabilization by a phenyl substituent shifts the cyclopropyl \rightleftharpoons butenyl equilibrium to favor the cyclic form.

The cyclization of the 5-hexenyl radical to cyclopentylmethyl (Entry 33) is a commonly observed reaction. The E_a is 6 kcal/mol. The cyclization shows a preference for *exo* cyclization to a five-membered ring over *endo* cyclization to a six-membered ring,¹⁰⁶ 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. 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.¹⁰⁷



When this stereoelectronic requirement is included with a calculation of the steric and angle strain imposed on the TS, as determined by MM-type calculations, preferences of the *exo* versus *endo* modes of cyclization are predicted to be as summarized in Table 11.8.

The observed results agree with the calculated trend. Relative rates of cyclization are in the order 5-*exo* > 6-*endo* \sim 6-*exo* > 7-*endo*.¹⁰⁸ The relationship holds only for terminal double bonds. An additional alkyl substituent at either end of the double bond reduces the relative reactivity by a steric effect. The underlying conformational and stereoelectronic effects can be modified by both steric and electronic effects of substituents. For example, a 5-methoxycarbonyl substituent promotes the 6-*endo* mode of cyclization by an electronic effect.¹⁰⁹ The reactivity of the β -carbon is enhanced by the substituent.

Table 11.8. Regioselectivity of Radical Cyclization as a Function of Ring Size^a

Ring size	<i>exo:endo</i> Ratio	
	Calculated	Found
5:6	10:1	50:1
6:7	> 100 : 1	10:1
7:8	1:5.8	< 1 : 100

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

¹⁰⁶. 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).

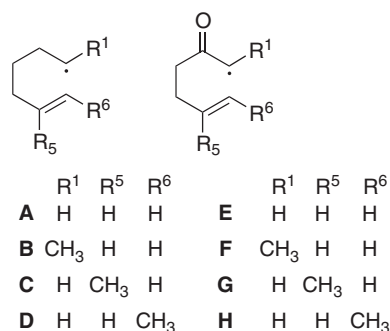
¹⁰⁷. M. J. S. Dewar and S. Olivella, *J. Am. Chem. Soc.*, **100**, 5290 (1978); D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.*, **52**, 959 (1987).

¹⁰⁸. A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, **41**, 3925 (1985).

¹⁰⁹. E. W. Della, C. Kostakis, and P. A. Smith, *Org. Lett.*, **1**, 363 (1999).

¹¹³. A. G. Leach, R. Wang, G. E. Wohlhieter, S. I. Khan, M. E. Jung, and K. N. Houk, *J. Am. Chem. Soc.*, **125**, 4271 (2003).

were included in the study. There is a change to a preference from 5-*exo* to 6-*endo* with the introduction of the 2-oxo group.



Experimentally, it is found that the hexenyl radicals prefer the 5-*exo* route, whereas the α -keto radicals prefer the 6-*endo* path. This effect is mirrored in the calculations, which find the 5-*exo* route strongly favored in the 5-hexenyl system (except for the 5-methyl derivative **C**), whereas for the α -keto radicals the 6-*endo* TS is preferred, although again the steric effect of a 6-methyl group somewhat disfavors this mode. Figure 11.9 shows various TSs. The conjugation present in the α -keto radicals imparts a planarity to the radical that favors the *endo* structure.¹¹⁴

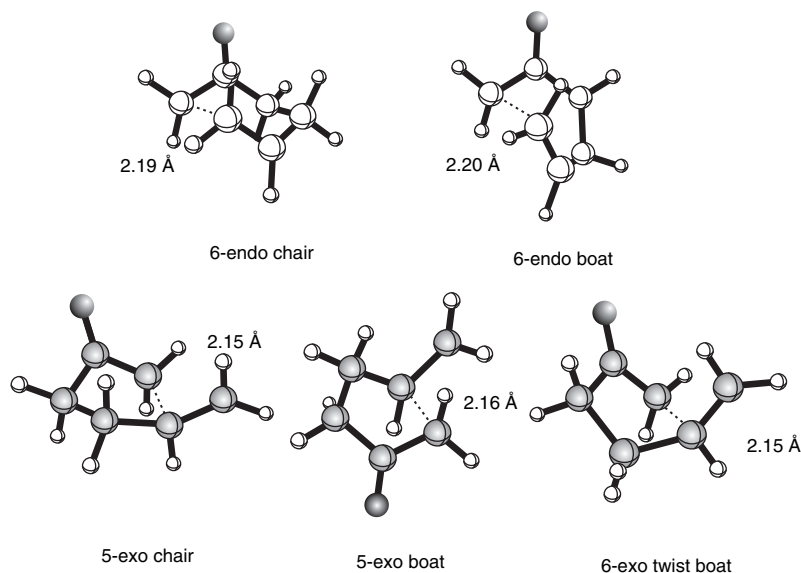
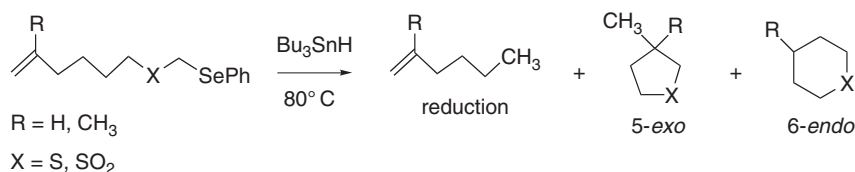


Fig. 11.9. Structures for various conformations of the radical cyclization transition structures for 2-oxo-5-hexenyl radical. Reproduced from *J. Am. Chem. Soc.*, **125**, 4271 (2003), by permission of the American Chemical Society.

¹¹⁴. J. L. Broecker and K. N. Houk, *J. Org. Chem.*, **56**, 3651 (1991).

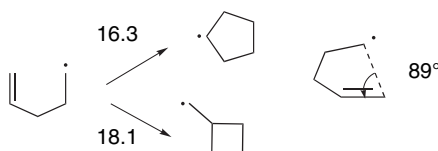
	Computed Transition Structure Energy (kcal/mol)				
	5- <i>exo</i> (chair)	5- <i>exo</i> (boat)	6- <i>endo</i> (chair)	6- <i>endo</i> (boat)	<i>endo:exo</i> ratio
A	6.4	8.1	9.1	11.6	1:99
B	7.0	8.7	9.6	12.2	1:99
C	9.1	10.3	8.4	10.7	75:25
D	6.5	8.1	9.8	12.5	1:99
E	13.3	12.6	10.0	16.5	98:2
F	15.9	14.4	12.6	19.1	95:5
G	15.8	14.7	8.6	15.2	> 99 : 1
H	12.7	12.1	10.9	17.2	84:16

Competition between 5-*exo* and 6-*endo* has also been examined for the 2-thia and 2-sulfonyl analogs of the 5-hexenyl radicals.¹¹⁵ As in the case of the parent radical, a 5-methyl substituent favors the 6-*endo* mode and this is reinforced in the case of the sulfonyl substituent, where the electrophilic radical prefers the more electron-rich alkene position.



R	X	Product composition		
		Reduction	5- <i>exo</i>	6- <i>endo</i>
H	S	17.1	70.1	12.8
H	SO ₂	3.8	73.1	23.1
CH ₃	S	38.6	7.1	54.3
CH ₃	SO ₂	3.9	2.5	93.6

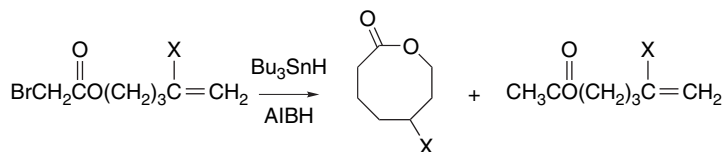
The 4-pentenyl radical can undergo 4-*exo* or 5-*endo* cyclization. UB3LYP/6-31G* calculations find a preference of 1.8 kcal/mol for the 5-*endo* TS. The angle to approach to the double bond is found to be about 89°.¹¹⁶



¹¹⁵ E. W. Della and S. D. Graney, *Org. Lett.*, **4**, 4065 (2002); E. W. Della and S. D. Graney, *J. Org. Chem.*, **69**, 3824 (2004).

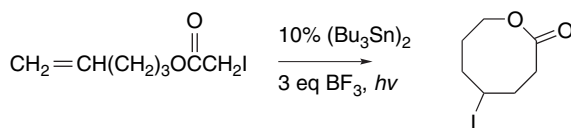
¹¹⁶ P. S. Engel, S. L. He, and W. B. Smith, *J. Am. Chem. Soc.*, **119**, 6059 (1997); C. Chatgililoglu, C. Ferreri, M. Guerra, V. Timokhin, G. Froudakis, and T. Gimisis, *J. Am. Chem. Soc.*, **124**, 10765 (2002).

Reactions of 4-substituted 4-pentenyl bromoacetates with tri-*n*-butylstannane resulted in modest yields of eight-membered *endo*-cyclization products, along with reduction products.¹¹⁷



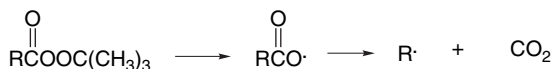
X	Product yield	
	Cyclization	Reduction
H	38%	31%
CH ₃	38%	18%
(CH ₃) ₃ Si	54%	32%

This type of cyclization can be further improved by use of a BF₃ catalyst.¹¹⁸



Systems with the potential for forming nine-, ten-, or sixteen-membered rings gave only reduction. The relatively favorable formation of eight-membered rings is attributed to the *s-trans* conformation of the ester group. The relative energies of the 8-*endo* and 7-*exo* TS were calculated for both the *s-trans* and *s-cis* conformations by ROHF/MP2/3-21G computations.¹¹⁷ The most favorable TS is the 8-*endo-cis* structure. The relative energies are shown in Figure 11.10. The general pattern that emerges from these experimental and computational results is that trajectory of approach, steric effects, and reactant conformation are the controlling factors in the ring size selectivity for radical cyclizations.

11.2.3.4. Other Radical Reactions Section D of Table 11.3 includes several examples of *radical fragmentation reactions*. Entries 44, 48, and 49 are examples of *β-scission reactions*. The facile decarboxylation of acyloxy radicals is an example.



¹¹⁷ E. Lee, C. H. Yoon, T. H. Lee, S. Y. Kim, T. J. Ha, Y. Sung, S.-H. Park, and S. Lee, *J. Am. Chem. Soc.*, **120**, 7469 (1998).

¹¹⁸ J. Wang and C. Li, *J. Org. Chem.*, **67**, 1271 (2002).

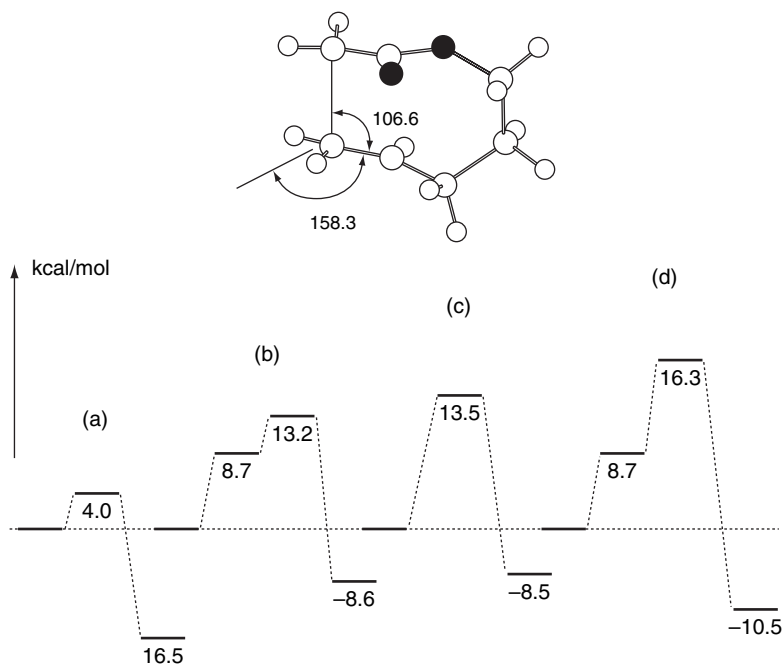
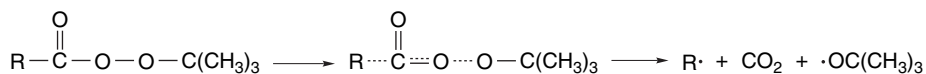


Fig. 11.10. Comparison of energies of (a) 8-endo-*s*-cis, (b) 8-endo-*s*-trans, (c) 7-exo-*s*-cis, and (d) 7-exo-*s*-trans transition structures. The *s*-trans conformation is 8.7 kcal/mol less stable than its *s*-cis. Reproduced from *J. Am. Chem. Soc.*, **120**, 7469 (1998), by permission of the American Chemical Society.

The rate of decarboxylation of aroyloxy radicals is about 10^6 s^{-1} near room temperature.¹¹⁹ Decarboxylation of alkanoyloxy radicals is even faster. Thus only very rapid reactions can compete with decarboxylation. Hydrogen abstraction from very reactive hydrogen atom donors, such as triethylsilane, can compete with decarboxylation at moderate temperatures.

These radical stability effects can be observed in the *rates of formation of radicals as well as their lifetimes*. It has already been indicated that radical structure and stability determines the temperature at which azo compounds undergo decomposition with elimination of nitrogen (see Section 11.1.4). 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.¹²⁰ These data clearly indicate that the bonding changes involved in the rate-determining step are not localized in the O—O bond. Radical character must also be developing at the alkyl group by partial cleavage of the alkyl-carbonyl bond.



¹¹⁹ J. Chateaufneuf, J. Luszyk, and K. U. Ingold, *J. Am. Chem. Soc.*, **110**, 2886 (1988); H. Misawa, K. Sawabe, S. Takahara, H. Sakuragi, and K. Tokumaru, *Chem. Lett.*, 357 (1988).

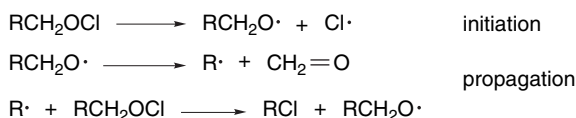
¹²⁰ P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.*, **80**, 1398 (1958).

R	Relative rate at 60°C
CH ₃	1
C ₆ H ₅	17
PhCH ₂	290
(CH ₃) ₃ C	1,700
Ph ₂ CH	19,300
Ph(CH ₃) ₂ C	41,500
PhCHCH=CH ₂	125,000

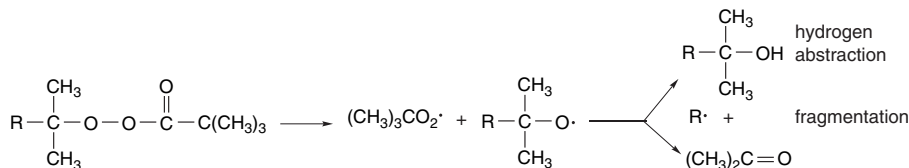
Another common fragmentation reaction is the cleavage of an alkoxy radical to an alkyl radical and a carbonyl compound.¹²¹



This type of fragmentation is involved in the chain decomposition of alkyl hypochlorites.¹²² In this reaction, too, the stability of the radical being eliminated is the major factor in determining the rate of fragmentation.



Radical trapping by a nitroxide was used to determine the ratio between β -fragmentation and hydrogen abstraction by alkoxy radicals generated by thermal decomposition of peroxy pivalate esters.¹²³ The ratio of fragmentation:hydrogen abstraction increased sharply with radical substitution and stability.



R	Fragmentation relative to CH ₃	Rate of decomposition (60°C, $\times 10^{-5} \text{ s}^{-1}$)
CH ₃	1	2.95
CH ₃ CH ₂	252	3.51
CH ₃ CH ₂ CH ₂	254	3.37
(CH ₃) ₃ CCH ₂	2670	6.18
(CH ₃) ₂ CH	3300	5.14
Cyclohexyl	28000	5.72
(CH ₃) ₃ C	86400	9.10
PhCH ₂		9.91
Ph		10.32

¹²¹. P. Gray and A. Williams, *Chem. Rev.*, **59**, 239 (1959).

¹²². 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).

¹²³. T. Nakamura, Y. Watanabe, S. Suyama, and H. Tezuka, *J. Chem. Soc., Perkin Trans. 2*, 1364 (2002).

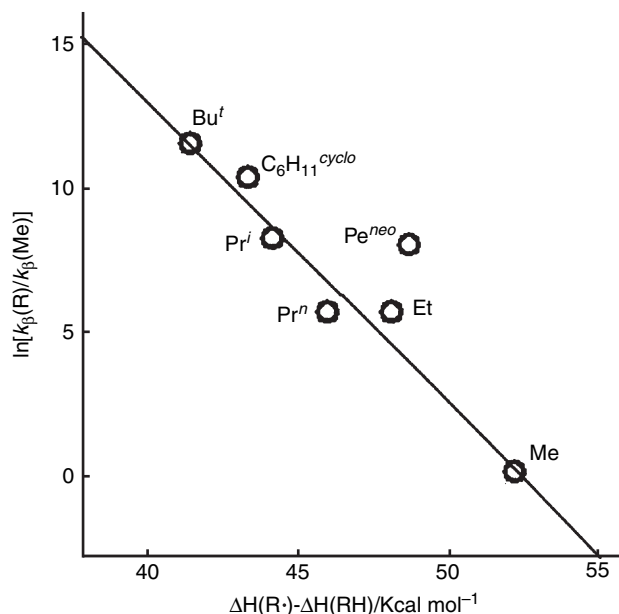
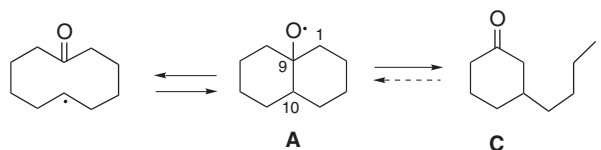


Fig. 11.11. Correlation between fragmentation of 2-alkyl-2-propoxy radicals and radical stability as measured by $\Delta H(R\cdot) - \Delta H(R-H)$. Reproduced from *J. Chem. Soc., Perkin Trans. 2*, 1364 (2002), by permission of the Royal Society of Chemistry.

As shown in Figure 11.11, there is a strong correlation between the ratio and radical stability, as measured by the difference in the enthalpy of formation. The outlying value for neopentyl can be improved by a correction for steric strain. On the other hand, the *rate of decomposition of the peroxy ester* is nearly independent of the nature of R, even for the stabilized benzyl or destabilized phenyl cases.¹²⁴ This is in marked contrast to a strong dependence on the structure of the acyl group (see above) and indicates that the fragmentation of the alkoxy radical is not concerted with the peroxy bond cleavage, but must be a separate step.

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

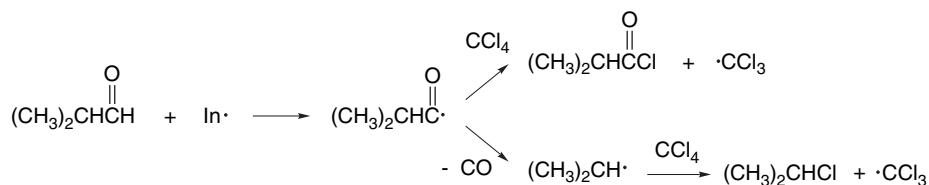


By using various trapping reagents it has been deduced that the transannular fragmentation is rapidly reversible. The cyclization of the fragmented radical C is less favorable and it is trapped at rates that exceed recyclization under most circumstances.¹²⁵

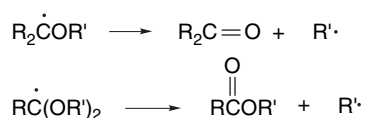
¹²⁴ T. Nakamura, W. K. Busfield, I. D. Jenkins, O. Rizzardo, S. H. Thang, and S. Suyama, *J. Org. Chem.*, **65**, 16 (2000).

¹²⁵ A. L. J. Beckwith, R. Kazlauskas, and M. R. Syner-Lyons, *J. Org. Chem.*, **48**, 4718 (1983).

Acyl radicals can fragment by loss of carbon monoxide. Decarbonylation is slower than decarboxylation, but the rate also depends on the stability of the radical that is formed.¹²⁶ For example, rates for decarbonylations giving tertiary benzylic radicals are on the order of 10^8 s^{-1} , whereas the benzoyl radical decarbonylates to phenyl radical with a rate on the order of 1 s^{-1} (see also Table 11.3, Entries 45 to 48). When reaction of isobutyraldehyde with carbon tetrachloride is initiated by *t*-butyl peroxide, both isopropyl chloride and isobutyryl chloride are formed, indicating that decarbonylation is competitive with the chlorine atom transfer.

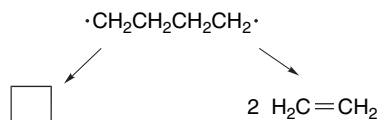


Radicals derived from ethers and acetals by hydrogen abstraction are subject to β -scission, with formation of a ketone or ester, respectively.

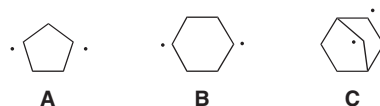


These fragmentations are sufficiently slow that the initial radicals can undergo reactions such as addition to alkenes at rates that are competitive with fragmentation.

A special case of fragmentation is that of 1,4-diradicals, where it can lead to two alkene molecules. In the case of 1,4-diradicals without functional group stabilization, reclosure to cyclobutanes is competitive with fragmentation to two molecules of alkene. The most recent of many detailed computational studies indicates that there is no barrier between the diradical and either the cyclization or fragmentation products.¹²⁷



A study of the lifetimes of the triplet biradicals **A**, **B**, and **C**, which were generated from the corresponding photoexcited azo compounds, gave the order of lifetime **A** > **B** > **C**. The lifetime of **A** is about 2.6×10^{-7} s, which is quite long for a 1,4-diradical.¹²⁸

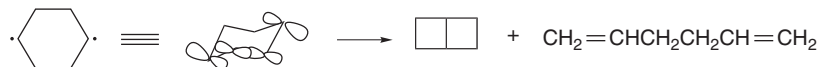


¹²⁶ D. E. Applequist and L. Kaplan, *J. Am. Chem. Soc.*, **87**, 2194 (1965); W. H. Urry, D. J. Trecker, and H. D. Hartzler, *J. Org. Chem.*, **29**, 1663 (1964); H. Fischer and H. Paul, *Acc. Chem. Res.*, **20**, 200 (1987).

¹²⁷. E. Ventura, M. Dallos, and H. Lischka, *J. Chem. Phys.*, **118**, 10963 (2003).

128. W. Adam, K. Hannemann, and R. M. Wilson, *J. Am. Chem. Soc.*, **106**, 7646 (1984); W. Adam, K. Hannemann, and R. M. Wilson, *Angew. Chem. Int. Ed. Engl.*, **24**, 1071 (1985); W. Adam, H. Platsch, J. Sendelbach, and J. Wirz, *J. Org. Chem.*, **58**, 1477 (1993).

The major factor identified in controlling the lifetimes of these diradicals is the orientation of the singly occupied orbitals with respect to one another. One factor determining the lifetime is the rate of conversion (intersystem crossing) to the singlet biradical. The rate of conversion is dependent on the orientation of the orbitals having the unpaired electrons. In **A** the orbitals are essentially parallel, which is a poor orientation for intersystem crossing. Diradical **B** is more flexible and the triplet is converted more rapidly to the singlet diradical, which reacts rapidly to give the cyclization and fragmentation products.



The geometry of the bicyclic ring system in radical **C** directs the half-filled orbitals toward one another and its lifetime is less than 1×10^{-10} s.¹²⁹

11.3. Free Radical Substitution Reactions

11.3.1. Halogenation

The basic reactivity and selectivity relationships for halogenation of alkanes can be understood in terms of bond dissociation energies. Bond dissociation energies such as those in Part B of Table 3.2 can be used to estimate 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 because only reactions with low activation energies are fast enough to sustain a chain process. If individual steps are identified as being endothermic by more than a few kcal, it is unlikely that a chain mechanism can operate.

Example 11.1 Calculate the enthalpy for each step in the bromination of ethane by bromine atoms from molecular bromine. Determine the overall enthalpy of the reaction.

				bond energy (kcal/mol)	
initiation	$\text{Br}-\text{Br}$	\longrightarrow	$2 \text{ Br}\cdot$	$\text{Br}-\text{Br}$	+45
propagation	$\text{Br}\cdot + \text{CH}_3\text{CH}_3$	\longrightarrow	$\text{H}-\text{Br} + \text{CH}_3\text{CH}_2\cdot$	$\text{H}-\text{Br}$	-87
				$\text{H}-\text{C}$	+100.5
					+13.5
	$\text{CH}_3\text{CH}_2\cdot + \text{Br}-\text{Br}$	\longrightarrow	$\text{CH}_3\text{CH}_2\text{Br} + \text{Br}\cdot$	$\text{Br}-\text{Br}$	+45
				$\text{Br}-\text{C}$	-70
					-25
				total	-11.5

The enthalpy of the reaction is given by the sum of the propagation steps and is -11.5 kcal/mol. Analysis of the enthalpy of the individual steps indicates that the first step is somewhat endothermic (+13.5 kcal). This endothermicity is the lower limit of the E_a for the step. An E_a of 14.0 ± 0.25 kcal/mol has been reported.¹³⁰

Radical chain processes depend on a series of fast steps that maintain the reactive intermediates at low concentration. Since termination reactions are usually very fast,

¹²⁹ W. Adam, S. Grabowski, and R. M. Wilson, *Acc. Chem. Res.*, **23**, 165 (1990).

¹³⁰ K. D. King, D. M. Golden, and S. W. Benson, *Trans. Faraday Soc.*, **66**, 2794 (1970).

the presence of an endothermic step in a chain sequence means that the chains will be short. The value for ethane is borderline, which suggests that radical bromination of ethane will exhibit only short chain lengths. As the enthalpy of the corresponding steps for abstraction of secondary or tertiary hydrogen is less positive, the bromination selects for 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, since these depend on the energy of the TS. The bond dissociation energies can therefore provide only permissive, not definitive, conclusions. For single atom abstraction reactions such as these involved in hydrocarbon halogenation, the enthalpy correlates with E_a for both steps.

—	CH ₄ (105.0)	+18.0
—	C ₂ H ₅ (100.5)	+13.5
—	(CH ₃) ₂ CH ₂ (98.1)	+11.1
—	(CH ₃) ₃ CH(95.7)	+9.7

The thermochemistry of radical chain halogenations varies strongly with the halogens. Fluorination is strongly exothermic and difficult to control. Iodination is endothermic and cannot sustain a chain reaction. Both chlorination and bromination are moderately exothermic and chain reactions with hydrocarbons are feasible. Figure 11.12 summarizes these energies for reaction with methane, ethane, propane, and isobutane. By tracking each hydrocarbon-halogen combination, the energy profile can be obtained. From these data we can, for example, determine and compare the minimum E_a for chlorination and bromination at C(2) in propane.

Cl₂ : H abstraction $\Delta H = -4.9$ kcal/mol Cl abstraction $\Delta H = -23$ kcal/mol

Br₂ : H abstraction $\Delta H = +11.1$ kcal/mol Br abstraction $\Delta H = -26.5$ kcal/mol

The two energy profiles are significantly different in that bromination, but not chlorination, has an endothermic step.

Free radical bromination is an important method of selective functionalization of hydrocarbons.¹³¹ 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. Based on BDE (see Table 3.2, p. 258), the enthalpy requirements for abstraction of hydrogen from methane, ethane (primary), propane (secondary), and isobutane (tertiary) by bromine atoms are +18.0, +13.5, +11.1, and +9.7 kcal/mol, respectively (see Figure 11.12).¹³² These differences are reflected in the E_a and there is a substantial kinetic preference for hydrogen abstraction in the order tertiary > secondary > primary. Substituents that promote radical stability, such as phenyl, vinyl, or carbonyl groups, also lead to kinetic selectivity in radical brominations. Bromination at benzylic positions is a particularly efficient process.

In addition to Br₂, *N*-bromosuccinimide is an important reagent for radical chain bromination, especially at allylic and benzylic positions. Mechanistic investigations have established that Br₂ is the active halogenating agent under the conditions used

¹³¹. W. A. Thaler, *Meth. Free Radical Chem.*, **2**, 121 (1969); A. Nechvatal, *Adv. Free Radicals*, **4**, 175 (1972).

¹³². E. S. Huyser, *Free Radical Chain Reactions*, Wiley-Interscience, New York, 1970, p. 91.

Hydrogen atom abstraction step

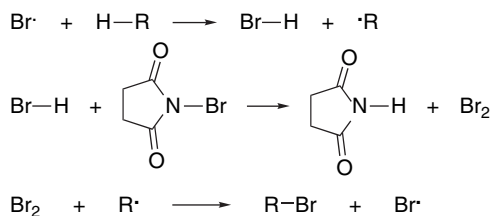
$R_3CH + X\cdot \longrightarrow R_3C\cdot + H-X$			
	+34.0	— M	X = I
	+29.5	— E	
	+27.1	— P	
	+24.7	— <i>i</i> B	
	+18.0	— M	X = Br
	+13.5	— E	
	+11.1	— P	
	+9.7	— <i>i</i> B	
0 —	+3.0	— M	X = Cl
	-2.5	— E	
	-4.9	— P	
	-7.3	— <i>i</i> B	
	-29.0	— M	X = F
	-33.5	— E	
	-35.9	— P	
	-38.3	— <i>i</i> B	

Halogen atom abstraction step

$R_3C\cdot + X-X \longrightarrow R_3CX + X\cdot$			
-18.3	—	<i>iB</i>	X = I
-19.8	—	E	
-20.1	—	P	
-21.1	—	M	
-25.0	—	M, E, <i>iB</i>	X = Br
-26.5	—	P	
-26.7	—	M	X = Cl
-27.1	—	<i>iB</i>	
-27.2	—	E	
-27.6	—	P	
~~~~~			
-70.0	—	M	X = F
-75.1	—	E	
-77.4	—	<i>iB</i> , P	

Fig. 11.12. Thermochemical relationships for steps in radical chain halogenation M = methane, E = ethane, P = propane, and *i*B = isobutane.

for NBS bromination.¹³³  $Br_2$  is maintained at a low concentration during the course of the reaction by formation from NBS and HBr.

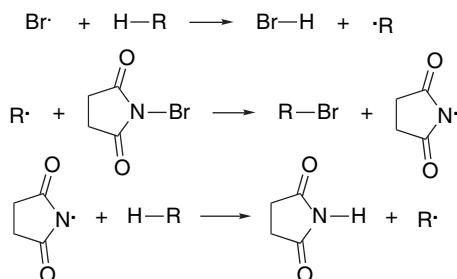


¹³³ R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.*, **85**, 354, 3142 (1963); G. A. Russell, C. DeBoer, and K. M. Desmond, *J. Am. Chem. Soc.*, **85**, 365 (1963); J. H. Incremona and J. C. Martin, *J. Am. Chem. Soc.*, **92**, 627 (1970); J. C. Day, M. J. Lindstrom, and P. S. Skell, *J. Am. Chem. Soc.*, **96**, 5616 (1974).

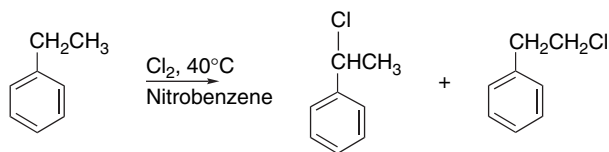


The fact that the  $\text{Br}_2$  concentration remains at very low levels is important to the success of the allylic halogenation process. The allylic bromination of alkenes must compete with polar addition of bromine via a bromonium ion intermediate. The reactions differ in their dependence on bromine concentration. The allylic substitution is one-half order in bromine, whereas the addition reaction follows a first- or second-order dependence on  $[\text{Br}_2]$  (see Section 5.3). Therefore a low concentration of  $\text{Br}_2$  favors substitution over addition.¹³⁴

NBS can also be used to brominate alkanes. For example, cyclopropane, cyclopentane, and cyclohexane give the corresponding bromides when irradiated with NBS in dichloromethane.¹³⁵ Under these conditions, the succinimidyl radical appears to be involved as the hydrogen-abstracting intermediate.



Significant differences are seen with the reactions of the other halogens relative to bromination. In the case of chlorination, although the same chain mechanism is operative, there is a key difference in the *diminished selectivity of the chlorination*. For example, the *pri:tert* selectivity in 2,3-dimethylbutane for chlorination is 1:3.6 in typical solvents.¹³⁶ Owing to the greater reactivity of the chlorine atom, abstractions of primary, secondary, and tertiary hydrogens are all *exothermic* (see Figure 11.12). As a result of this exothermicity, the stability of the product radical has less influence on the  $E_a$ . In terms of the Hammond postulate (Section 3.3.2.2), the TS is expected to be more *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.¹³⁷



(4.25:1, ratio is solvent dependent)

Isotope effect and relative rate studies also suggest an early TS for benzylic chlorination and bromination. The benzylic position is only moderately activated toward uncomplexed chlorine atoms. Relative to ethane, toluene reactivity is increased only by a factor of 3.3.¹³⁷ The kinetic isotope effect observed for bromination¹³⁸ and chlorination¹³⁹ of toluene suggest little rehybridization at the TS.

¹³⁴. C. C. Wamser and L. T. Scott, *J. Chem. Educ.*, **62**, 650(1985); D. W. McMillen and J. B. Grutzner, *J. Org. Chem.*, **59**, 4516 (1994).

¹³⁵. J. G. Traynham and Y.-S. Lee, *J. Am. Chem. Soc.*, **96**, 3590 (1974).

¹³⁶. K. D. Raner, J. Luszyk, and K. U. Ingold, *J. Org. Chem.*, **53**, 5220 (1988).

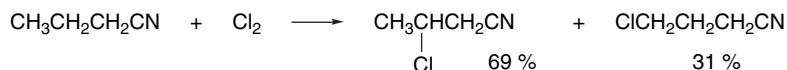
¹³⁷. G. A. Russell, A. Ito, and D. G. Hendry, *J. Am. Chem. Soc.*, **85**, 2976 (1963).

¹³⁸. R. P. Hanzlik, A. R. Schaefer, J. B. Moon, and C. M. Judson, *J. Am. Chem. Soc.*, **109**, 4926 (1987).

¹³⁹. K. B. Wiberg and L. H. Slaugh, *J. Am. Chem. Soc.*, **80**, 3033 (1958).

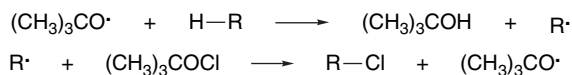
The selectivity of chlorination is influenced by solvents. For example, the chlorination of 2,3-dimethylbutane shows increased preference for the tertiary position in benzene.¹⁴⁰ The complexation with solvent attenuates the reactivity of chlorine atoms. Halogenated solvents also give evidence of complex formation. Brominated solvents lead to greater selectivity.¹⁴¹

Radical chlorination shows a substantial polar effect. Positions substituted by EWG are relatively unreactive toward chlorination, even though the substituents are capable of stabilizing the radical intermediate.¹⁴² For example, butanonitrile is chlorinated at C(3) and C(4), but not at C(2), despite the greater stability of the C(2) radical.



Similarly, carboxylic acid and ester groups tend to direct chlorination to the  $\beta$ - and  $\gamma$ -positions, because attack at the  $\alpha$ -position is electronically disfavored. The polar effect is attributed to the fact that the chlorine atom is an electrophilic species, and the relatively electron-poor methylene group adjacent to the EWG is avoided. Because the chlorine atom is highly reactive, the reaction is expected to have a very early TS and the electrostatic effect predominates over the stabilizing effect of the substituent on the intermediate. The electrostatic effect is the dominant factor in the *kinetic selectivity* of the reaction and the relative stability of the radical intermediate has little influence.

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.



For this reason, selectivity and product composition is different from direct chlorination. The *t*-butoxy radical is intermediate in selectivity between chlorine and bromine atoms. The selectivity is also solvent and temperature dependent. A typical ratio in chlorobenzene as the solvent is *tert:sec:pri* = 60:10:1.¹⁴³

Radical substitution reactions by iodine are not practical because the abstraction of hydrogen from hydrocarbons by iodine is endothermic, even for stable radicals. The enthalpy of the overall reaction is also slightly endothermic (see Figure 11.12). Thus, both because of the kinetic problem precluding a chain reaction and an unfavorable equilibrium constant for substitution, iodination does not proceed by a radical chain mechanism.

Fluorination presents problems at the other extreme. Both steps in the substitution chain reaction are exothermic and the reaction is violent if not performed under

¹⁴⁰ G. A. Russell, *J. Am. Chem. Soc.*, **80**, 4987, 4997, 5002 (1958); C. Walling and M. F. Mayahi, *J. Am. Chem. Soc.*, **81**, 1485 (1959).

¹⁴¹ A. S. Dneprovskii, D. V. Kuznetsov, E. V. Eliseenkov, B. Fletcher, and J. M. Tanko, *J. Org. Chem.*, **63**, 8860 (1998).

¹⁴² 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).

¹⁴³ C. Walling and P. J. Wagner, *J. Am. Chem. Soc.*, **86**, 3368 (1964).

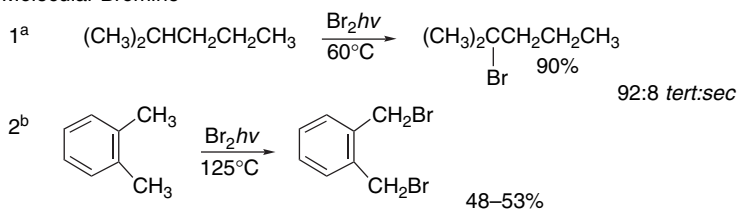
carefully controlled conditions. Furthermore, fluorine atoms are capable of cleaving carbon-carbon bonds.



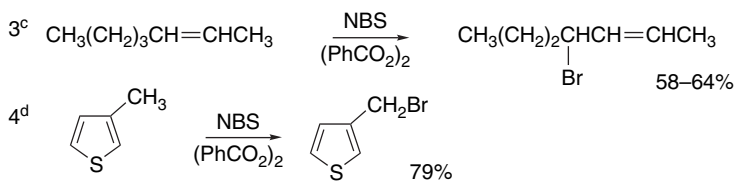
Saturated hydrocarbons such as neopentane, norbornane, and cyclooctane have been converted to the corresponding perfluoro derivatives in 10–20% yield by reaction

### Scheme 11.4. Radical Chain Halogenation

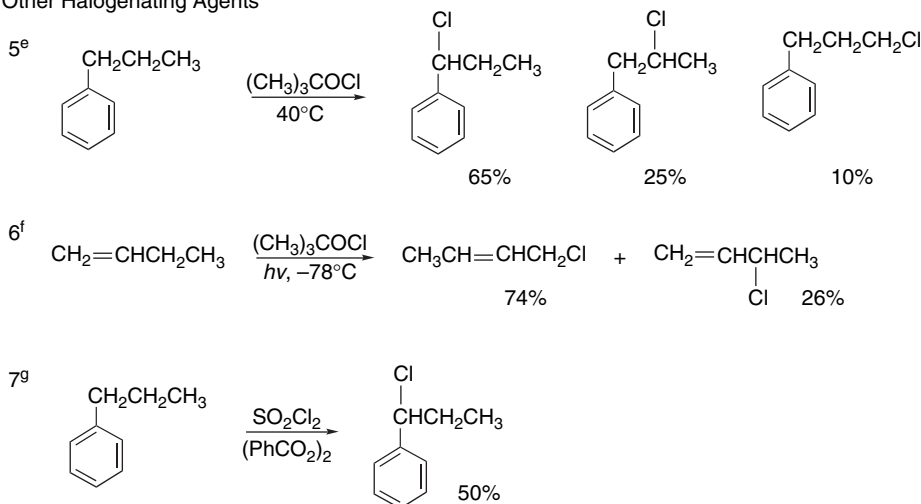
#### Molecular Bromine



#### N-Bromosuccinimide



#### Other Halogenating Agents



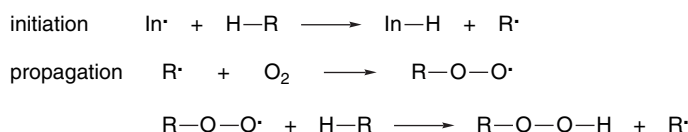
- a. G. A. Russell and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 4025 (1955).  
 b. E. F. M. Stephenson, *Org. Synth.*, **IV**, 984 (1963).  
 c. F. L. Greenwood, M. D. Kellert, and J. Sedlak, *Org. Synth.*, **IV**, 108 (1963).  
 d. E. Campaigne and B. F. Tullar, *Org. Synth.*, **IV**, 921 (1963).  
 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).

with fluorine gas diluted with helium at  $-78^{\circ}\text{C}$ .¹⁴⁴ Simple ethers can be completely fluorinated under similar conditions.¹⁴⁵ Crown polyethers can be fluorinated by passing a  $\text{F}_2/\text{He}$  stream over a solid mixture of sodium fluoride and the crown ether.¹⁴⁶ Liquid phase fluorination of hydrocarbons has also been observed, but the reaction is believed to be ionic, rather than radical, in character.¹⁴⁷

Scheme 11.4 illustrates some representative halogenation reactions. The reaction in Entry 1 was conducted by slow addition of bromine to excess 2-methylpentane at  $60^{\circ}\text{C}$ , with irradiation from a tungsten light bulb. The reaction in Entry 2 is a typical benzylic bromination, carried out at  $125^{\circ}\text{C}$  with irradiation from a sun lamp. Entries 3 and 4 are examples of NBS bromination using benzoyl peroxide as the initiator. Entry 3 is interesting in that none of the allylic isomer 2-bromo-3-heptene is found. Entries 5 and 6 are examples of chlorination by *t*-butyl hypochlorite in which the *t*-butoxy radical is the chain carrier. Note that in Entry 6, both the primary and secondary allylic products are formed. The reaction in Entry 7 uses sulfuryl chloride as the halogenation reagent. Note that in contrast to chlorination with  $\text{Cl}_2$  (see p. 1021), the reaction shows selectivity for the benzylic position.

### 11.3.2. Oxygenation

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



The reaction of oxygen with most radicals is very fast because of the triplet character of molecular oxygen (see Table 11.2, Entries 42 and 43). The ease of autoxidation is therefore governed by the rate of hydrogen abstraction in the second step of the propagation sequence. The alkylperoxyl radicals that act as the chain carriers are fairly selective. Positions that are relatively electron rich or provide particularly stable radicals are the most easily oxidized. Benzylic, allylic, and tertiary positions are the most susceptible to oxidation. This selectivity makes radical chain oxidation a preparatively useful reaction in some cases.

The reactivity of a series of hydrocarbons toward oxygen measured under a standard set of conditions gives some indication of the susceptibility of various structural units to autoxidation.¹⁴⁸ Table 11.9 gives the results for a series of hydrocarbons. These data indicate the activating effect of alkyl, vinyl, and phenyl substituents.

¹⁴⁴. N. J. Maraschin, D. B. Catsikis, L. H. Davis, G. Jarvinen, and R. J. Lagow, *J. Am. Chem. Soc.*, **97**, 513 (1975).

¹⁴⁵. D. F. Persico, H.-N. Huang, R. J. Lagow, Jr., and L. C. Clark, Jr., *J. Org. Chem.*, **50**, 5156 (1985).

¹⁴⁶. W.-H. Lin, W. I. Bailey, Jr., and R. J. Lagow, *J. Chem. Soc., Chem. Commun.*, 1350 (1985).

¹⁴⁷. C. Gal and S. Rozen, *Tetrahedron Lett.*, **25**, 449 (1984).

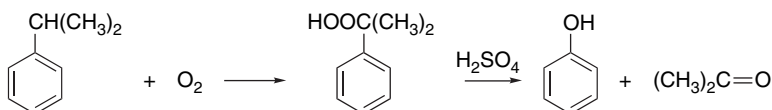
¹⁴⁸. G. A. Russell, *J. Am. Chem. Soc.*, **78**, 1047 (1956).

**Table 11.9. Relative Reactivities of Some Aromatic Hydrocarbons toward Oxygen**

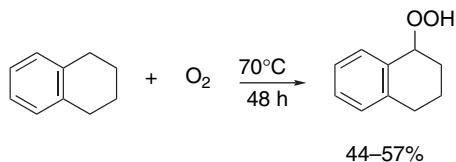
$\text{PhCH}(\text{CH}_3)_2$	1.0	$\text{PhCH}_2\text{CH}_3$	0.18
$\text{PhCH}_2\text{CH}=\text{CH}_2$	0.8	$\text{PhCH}_3$	0.015
$\text{Ph}_2\text{CH}_2$	0.35		

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

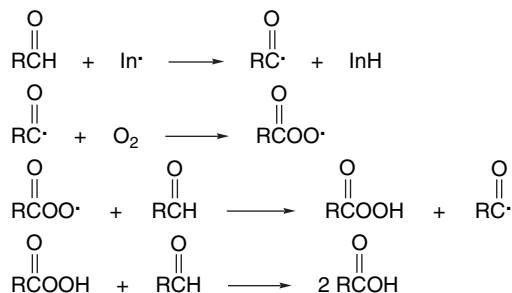
The best preparative results from autoxidation are obtained when only one relatively reactive hydrogen is available for abstraction. The oxidation of isopropylbenzene (cumene) is carried out on an industrial scale with the ultimate products being acetone and phenol.



The benzylic position in tetralin can be selectively oxidized to the hydroperoxide.¹⁴⁹

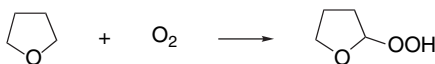


Functional groups that stabilize radicals are expected to increase susceptibility to autoxidation. This is illustrated by two cases that have been relatively well studied. Aldehydes, in which abstraction of the formyl hydrogen is facile, are easily autoxidized. The autoxidation initially forms a peroxy-carboxylic acid, but usually the corresponding carboxylic acid is isolated because the peroxy acid oxidizes additional aldehyde in a parallel heterolytic reaction. The final step is an example of the Baeyer-Villiger reaction, which is discussed in Section 12.5.2.1 of Part B.



Similarly, the  $\alpha$ -position in ethers is autoxidized quite readily to give  $\alpha$ -hydroperoxy ethers.

¹⁴⁹ H. B. Knight and D. Swern, *Org. Synth.*, **IV**, 895 (1963).



This reaction is the cause 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 air. Since the hydroperoxides are less volatile than the ethers, they are concentrated by evaporation or distillation and the concentrated peroxide solutions may explode. For this reason, storage of ethers that have been exposed to oxygen is extremely hazardous.

## 11.4. Free Radical Addition Reactions

### 11.4.1. Addition of Hydrogen Halides

As with halogen substitution, thermochemical relationships impose limits on free radical chain addition reactions of the hydrogen halides. These relationships are summarized in Figure 11.13. There are significant endothermic steps for HF and HI and a slightly endothermic step for HCl. 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 is favorable. In the case of hydrogen fluoride, the abstraction of hydrogen from hydrogen fluoride is energetically prohibitive. Only in the case of HBr is the thermochemistry consistent with a radical chain process. The HBr addition has one thermal neutral step and an

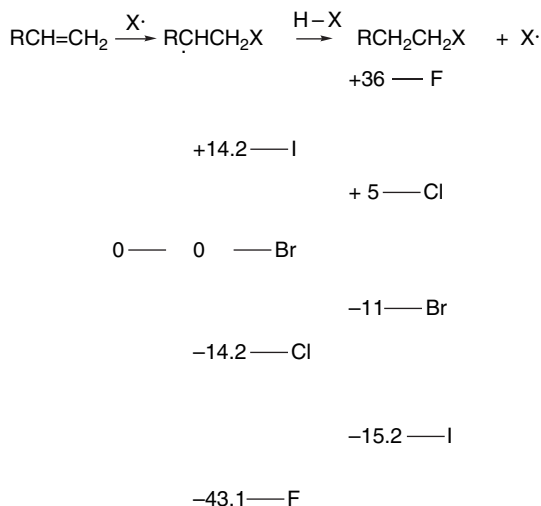
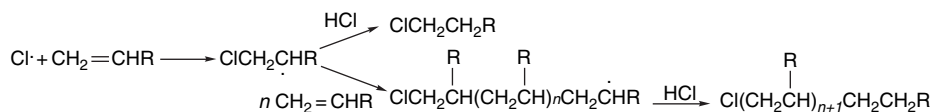
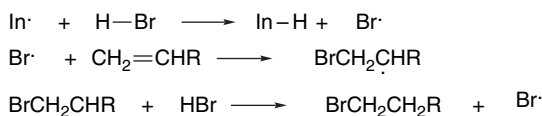


Fig. 11.13. Thermochemistry for the steps in radical chain additions of the hydrogen halides to alkenes. The C=C and C-H bond energies were taken as 70 and 98 kcal/mol, respectively, and primary C-X bond energies were used.

exothermic step. Because of the relatively slow second step, polymerization competes with addition of the hydrogen halide in the case of HCl.

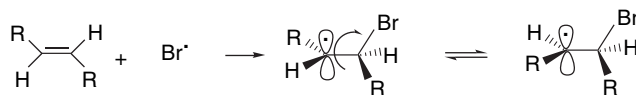


The reaction with HBr is also significant in terms of regiochemistry. The reaction results in the anti-Markovnikov orientation, with the bromine adding to the less-substituted carbon of the double bond. The anti-Markovnikov addition of HBr to alkenes was one of the earliest free radical reactions to be put on a firm mechanistic basis. In the presence of a suitable initiator, such as a peroxide, a radical chain mechanism becomes competitive with the ionic mechanism for addition of HBr.



The bromine atom adds to the less-substituted carbon of the double bond, generating the more stable radical intermediate. The regioselectivity of radical chain hydrobromination is opposite to that of ionic addition. (See Section 5.3 for discussion of the ionic mechanism.) The early work on the radical mechanism of addition of HBr was undertaken to understand why Markovnikov's rule was violated under certain circumstances. The cause was found to be conditions that initiated the radical chain process, such as peroxide impurities or light. Some examples of radical chain additions of hydrogen bromide to alkenes are discussed in Section 11.4.5.

The stereochemistry of radical addition of hydrogen bromide to alkenes has been studied with both acyclic and cyclic alkenes.¹⁵⁰ *Anti* addition is favored.^{151, 152} This is contrary to what would be expected if the  $sp^2$  carbon of the radical intermediate was rapidly rotating or inverting with respect to the remainder of the molecule, which should result in stereorandomization and a mixture of *syn* and *anti* products.



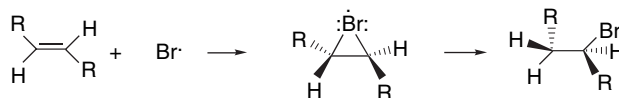
The stereoselectivity of the radical addition can be explained in terms of a bridged structure similar to that involved in ionic bromination of alkenes.¹⁵³

¹⁵⁰. B. A. Bohm and P. I. Abell, *Chem. Rev.*, **62**, 599 (1962).

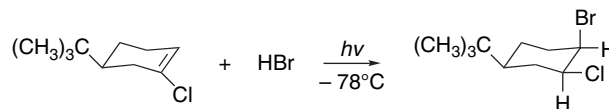
¹⁵¹. P. S. Skell and P. K. Freeman, *J. Org. Chem.*, **29**, 2524 (1964).

¹⁵². H. L. Goering and D. W. Larsen, *J. Am. Chem. Soc.*, **81**, 5937 (1959).

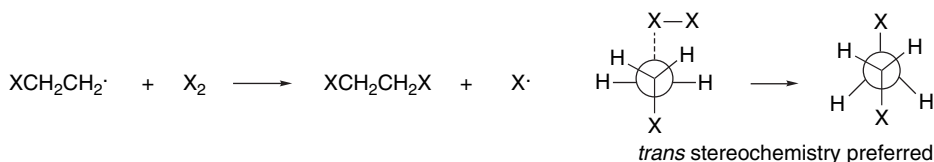
¹⁵³. P. S. Skell and J. G. Traynham, *Acc. Chem. Res.*, **17**, 160 (1984).



*trans*-Diaxial addition is the preferred stereochemical mode for addition to cyclohexene and its derivatives.¹⁵⁴ This stereochemistry, too, can be explained in terms of a bromine-bridged intermediate.



The issue of the role of bridged radicals in the stereochemistry of halogenation has recently been examined computationally and a new interpretation offered.¹⁵⁵ The structure, rotational barriers, and  $E_a$  for halogen atom abstraction for  $\beta$ -haloethyl radicals were studied. For the reactions where  $X = \text{Cl}$  or  $\text{Br}$ , the halogen atom abstraction reaction shows a preference for a *trans* TS.



The results also indicate that the chlorine and bromine abstraction steps are faster than rotational equilibration, so the stereochemistry can be explained without requiring a bridged radical.

The nature of bridging and migration involving chlorine has been explored computationally for the 3-chloro-2-butyl radical.¹⁵⁶ B3LYP/aug-cc-pVD2 calculations found an open radical to be the most stable form. The symmetrically bridged radical is a TS for chlorine atom migration. The energy of the TS varied from 2.4 to 7.0 kcal/mol, depending on the computational method. The methods also give differing values for the barrier to single-bond rotation. The chlorine has considerable negative charge ( $-0.351e$ ) in the bridged radical, compared to the open radical ( $-0.189e$ ) by NPA analysis. The spin density also increases at chlorine in the TS. These results suggest partial heterolytic character for the migration. The energy profile for rotation and migration derived from the B3LYP energies is given in Figure 11.14.

In contrast to the  $\beta$ -chloro radical, bromine-bridged radicals are calculated to be stable relative to open radicals at the MP2/6-31G** and B3LYP/6-31G** level of computation.¹⁵⁷ The 2-fluoroethyl radical shows no bridging and only a low barrier to single-bond rotation ( $<0.5$  kcal/mol). Bridging was also found to be unfavorable for the other second-row substituents OH and  $\text{NH}_2$ .¹⁵⁸ These computational results suggest that significant bridging is to be expected in  $\beta$ -bromo radicals, whereas  $\beta$ -chloro radicals should be subject to facile 1,2-migration.

¹⁵⁴. 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. Read 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).

¹⁵⁵. Z.-H. Li, K.-N. Fan, and M. W. Wong, *J. Phys. Chem. A*, **105**, 10890 (2001).

¹⁵⁶. B. Neumann and H. Zipse, *Org. Biomol. Chem.*, **1**, 168 (2003).

¹⁵⁷. H. Ihee, A. H. Zewail, and W. A. Goddard, III, *J. Phys. Chem. A*, **103**, 6638 (1999).

¹⁵⁸. M. Guerra, *J. Am. Chem. Soc.*, **114**, 2077 (1992).



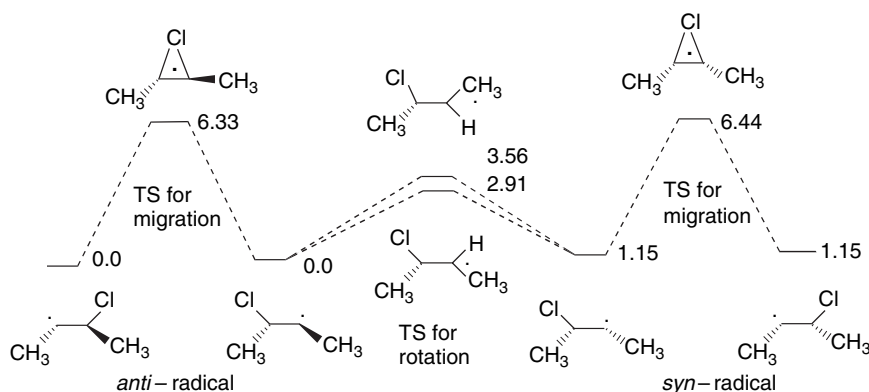
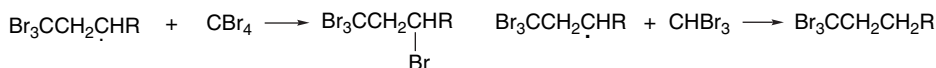
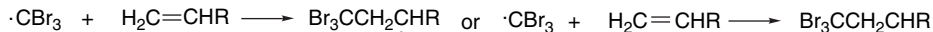


Fig. 11.14. Energy profile for chlorine migration and rotation in the 3-chloro-2-butyl radical.

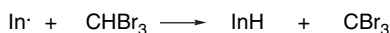
#### 11.4.2. Addition of Halomethanes

One of the oldest preparative free radical reactions is the addition of polyhalomethanes to alkenes. Examples of addition of carbon tetrabromide, carbon tetrachloride, and bromoform have been recorded.¹⁵⁹ The reactions are chain processes that depend on facile abstraction of halogen or hydrogen from the halomethane.

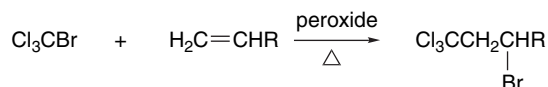
##### ADDITION OF TETRABROMOMETHANE



##### ADDITION OF TRIBROMOMETHANE

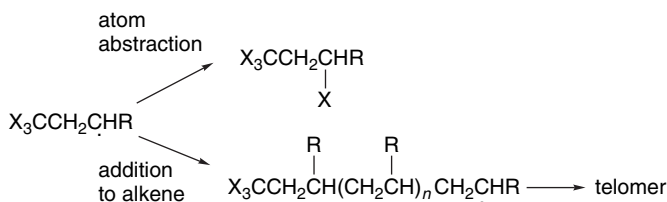


Bromotrichloromethane can also be used effectively in the addition reaction. Because of the preferential abstraction of bromine, a trichloromethyl unit is added to the less-substituted carbon atom of the alkene.

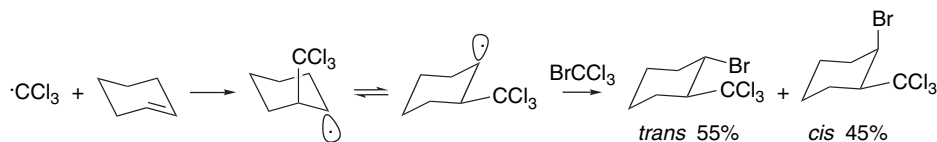


The order of reactivity of the halomethanes is  $\text{CBr}_4 > \text{CBrCl}_3 > \text{CCl}_4 > \text{CH}_2\text{Cl}_2 > \text{CHCl}_3$ . The efficiency of 1:1 addition for a given alkene also depends on the ease with which it undergoes radical chain polymerization, since polymerization can compete with 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.

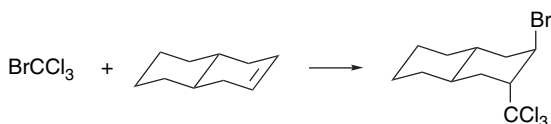
¹⁵⁹ E. Sosnovsky, *Free Radical Reactions in Preparative Organic Chemistry*, Macmillan, New York, 1964, Chap. 2.



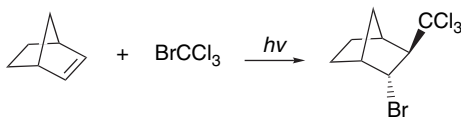
The addition of bromotrichloromethane to cyclohexene gives a nearly 1:1 mixture of the two possible stereoisomers.¹⁶⁰



This result indicates that the initially added trichloromethyl group has little influence on the stereochemistry of the subsequent bromine atom abstraction. The intermediate 2-(trichloromethyl)cyclohexyl radical presumably relaxes to the equatorial conformation faster than the occurrence of bromine atom abstraction, and there is little preference for axial or equatorial approach. In contrast, with  $\Delta^{2,3}$ -octahydronaphthalene, the addition is exclusively *trans*-diaxial.

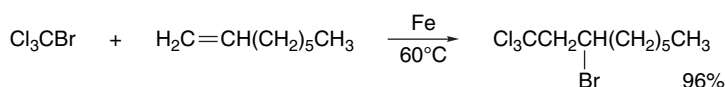


The *trans*-fused decalin system is conformationally rigid and the stereochemistry of the product indicates that the initial addition of the trichloromethyl radical is from an axial direction. This is expected on stereoelectronic grounds because the radical should initially interact with the  $\pi^*$  orbital. The axial trichloromethyl group then shields the adjacent radical position and directs the bromine abstraction in the *trans* sense. 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.

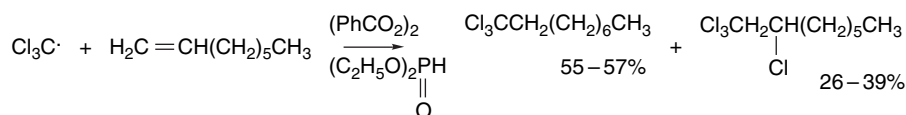


The addition of bromotrichloromethane to terminal alkenes occurs in reasonable yield in THF without the addition of a specific initiator.¹⁶¹ Bromotrichloromethane additions are effectively catalyzed by Fe(0), which acts as an initiator by one-electron reduction.¹⁶²

162. F. Bellesia, L. Forti, F. Ghelfi, and U. M. Pagnoni, *Synth. Commun.*, **27**, 961 (1997).

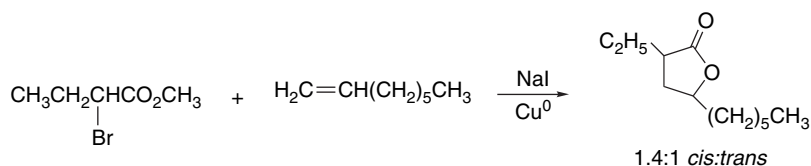


The combination of  $\text{CCl}_4$  and diethyl phosphite with a peroxide initiator gives competitive addition of  $\text{H}-\text{CCl}_3$ . In this case the phosphite acts as a hydrogen donor.¹⁶³



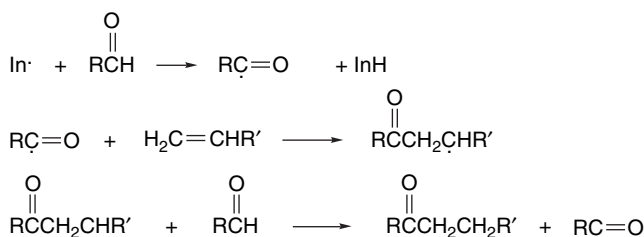
Section 11.4.5 provides some other examples of additions of tetrahalomethanes.

There are examples of other halomethanes that can undergo radical addition.  $\alpha$ -Haloesters have been successfully added to alkenes in the presence of copper metal. The copper serves as an electron transfer initiator. The  $\gamma$ -haloester adduct cyclizes to a lactone. The reaction works best when NaI is also used to convert the bromide to the more reactive iodide.¹⁶⁴



### 11.4.3. Addition of Other Carbon Radicals

Other functional groups 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 3.17 (p. 315), the acyl radicals are somewhat stabilized. The C–H BDE for acetaldehyde, which is 88.3 kcal/mol, decreases slightly with additional substitution but increases for  $\text{CF}_3$ .¹⁶⁵ The chain process results in formation of a ketone by addition of the aldehyde to an alkene



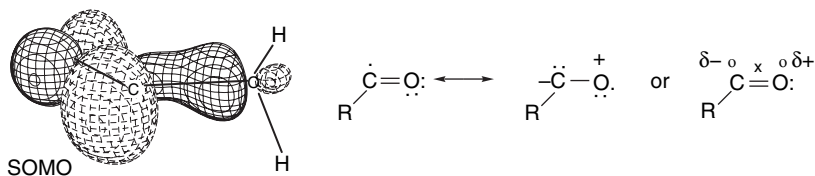
Acyl radicals are strongly bent with a nearly trigonal angle, according to MP2/6-31G* computations. The C=O bond length is just under 1.200 Å, somewhat shorter than a normal carbonyl bond. The SOMO orbital is in the plane of the molecule and

¹⁶³ J. M. Barks, B. C. Gilbert, A. F. Parsons, and B. Upeandran, *Synlett*, 1719 (2001).

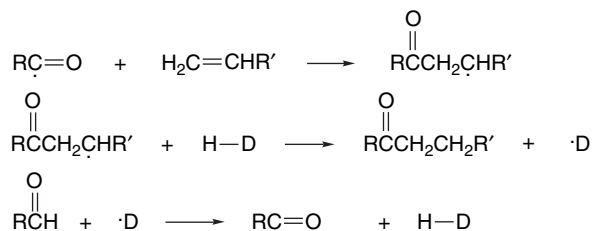
¹⁶⁴ J. O. Metzger, R. Mahler, and G. Franke, *Liebigs Ann. Recueil*, 2303 (1997).

¹⁶⁵ B. Viskolcz and T. Berces, *Phys. Chem. Chem. Phys.*, **2**, 5430 (2000); C. W. Bauschlicher, Jr., *J. Chem. Phys.*, **98**, 2564 (1994).

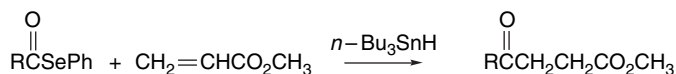
centered mainly on carbon, but also on the oxygen.¹⁶⁶ Acyl radicals are *nucleophilic*, based on their reactivity toward protonated heterocyclic molecules.¹⁶⁷ The acyl radical is isoelectronic with  $\text{N}=\text{O}$  and a similar Linnett structure can be drawn.



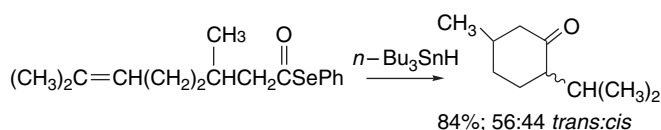
The efficiency of aldehyde additions can be improved by adding an alternative hydrogen atom donor, such as methyl thioglycolate or *N*-hydroxysuccinimide.¹⁶⁸



Acyl radicals can also be generated from acyl selenides and *tri-n*-butylstannane.¹⁶⁶



Intramolecular versions of this reaction have been used to form both common and macrocyclic rings.



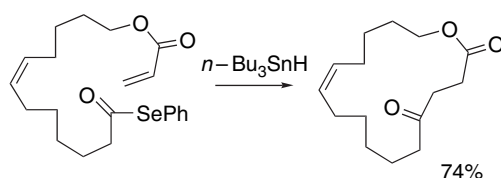
The latter reactions are carried out under high-dilution conditions and require an activating EWG substituent.¹⁶⁹

¹⁶⁶. D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, **57**, 1429 (1992).

¹⁶⁷. M. Bellatti, T. Caronna, A. Citterio, and F. Minisci, *J. Chem. Soc., Perkin Trans. 2*, 1835 (1976); F. Minisci, *Top. Current Chem.*, **62**, 1 (1976).

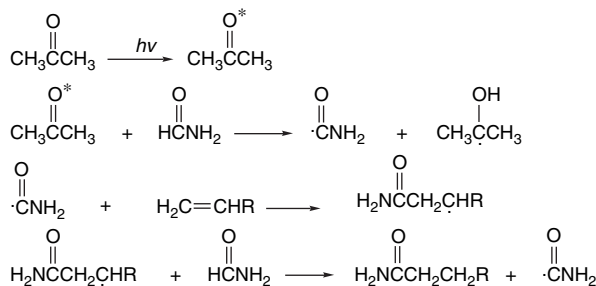
¹⁶⁸. V. Paul, B. P. Roberts, and C. R. Willis, *J. Chem. Soc., Perkin Trans. 2*, 1953 (1989); S. Tsujimoto, I. Iwahama, S. Sakaguchi, and Y. Ishii, *Chem. Commun.*, 2352 (2001); S. Tsujimoto, S. Sakaguchi, and Y. Ishii, *Tetrahedron Lett.*, **44**, 5601 (2003).

¹⁶⁹. D. L. Boger and R. J. Mathvink, *J. Am. Chem. Soc.*, **112**, 4008 (1990).



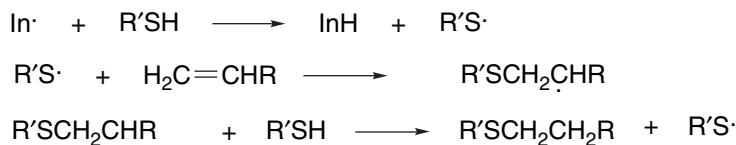
Some other examples of acyl radical additions are discussed in Section 11.4.5.

The chain addition of formamide to alkenes is a closely related reaction and results in the formation of primary amides.¹⁷⁰ The reaction is carried out with irradiation in acetone. The photoexcited acetone initiates the chain reaction by abstracting hydrogen from formamide.



#### 11.4.4. 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.¹⁷¹ The mechanism is analogous to that for hydrogen bromide addition. The energetics of both the hydrogen abstraction and addition steps are favorable. The reaction exhibits anti-Markovnikov regioselectivity.



The preferred stereochemistry of addition to cyclic alkenes is *anti*,¹⁷² but the additions are not as highly stereoselective as for hydrogen bromide addition.

#### 11.4.5. Examples of Radical Addition Reactions

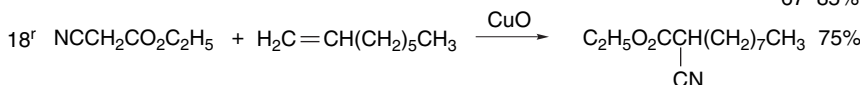
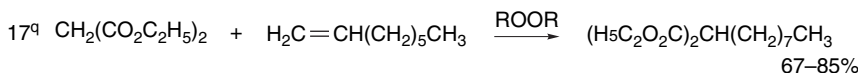
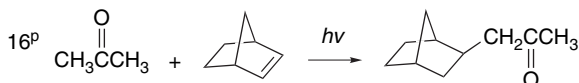
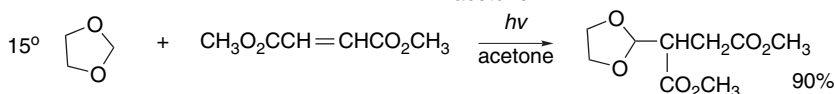
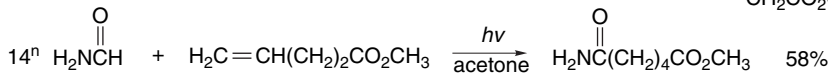
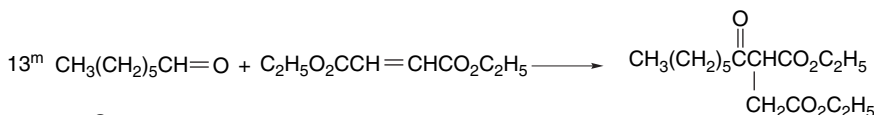
Scheme 11.5 gives some examples of these radical addition reactions. Entries 1 to 3 show anti-Markovnikov addition of HBr. The reaction in Entry 1 was carried out by passing HBr gas into the alkene, using benzoyl peroxide as the initiator, apparently near room temperature. Entry 2 is an example of anti-Markovnikov addition to

¹⁷⁰. D. Elad and J. Rokach, *J. Org. Chem.*, **29**, 1855 (1964).

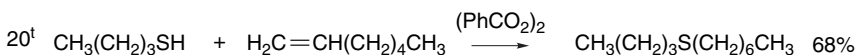
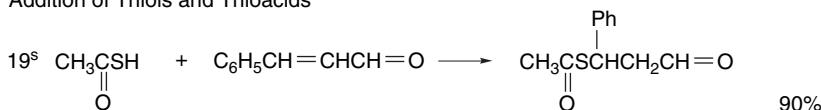
¹⁷¹. K. Griesbaum, *Angew. Chem. Int. Ed. Engl.*, **9**, 273 (1970).

¹⁷². N. A. LeBel, R. F. Czaja, and A. DeBoer, *J. Org. Chem.*, **34**, 3112 (1969); P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 759 (1966); F. G. Bordwell, P. S. Landis, and G. S. Whitney, *J. Org. Chem.*, **30**, 3764 (1965); E. S. Huyser, H. Benson, and H. J. Sinnige, *J. Org. Chem.*, **32**, 622 (1962).

### Free Radical Reactions



## D. Addition of Thiols and Thioacids

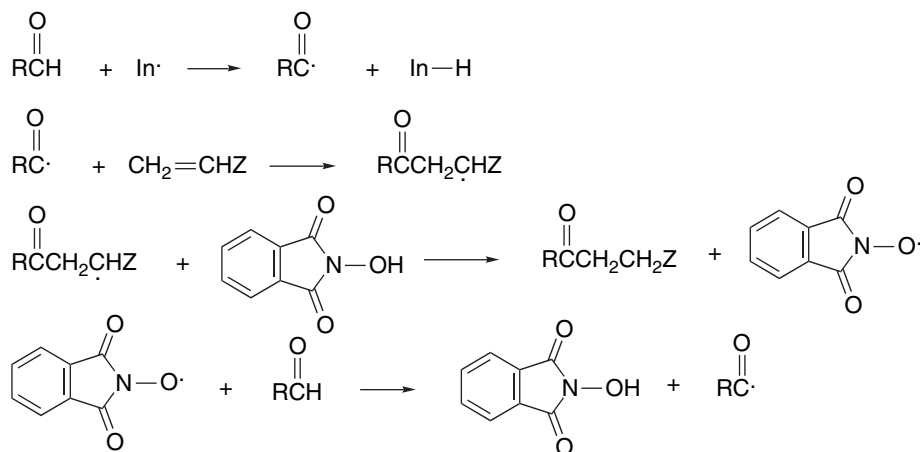


- a. W. J. Bailey and S. S. Hirsch, *J. Org. Chem.*, **28**, 2894 (1963).  
 b. R. Neumann, F. de la Vega, and A. Bar-On, *J. Org. Chem.*, **60**, 1315 (1995).  
 c. H. O. House, C.-Y. Chu, W. V. Phillips, T. S. B. Sayer, and C.-C. Yau, *J. Org. Chem.*, **42**, 1709 (1977).  
 d. M. S. Kharasch, E. W. 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 Aukun, 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. F. Bellesia, L. Forti, F. Ghelfi, and U. M. Pagnoni, *Synth. Commun.*, **27**, 961 (1997).  
 i. M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949).  
 j. E. C. Macias, J. M. G. Molinillo, G. M. Massanet, and F. Rodriguez-Luis, *Tetrahedron*, **48**, 3345 (1992).  
 k. S. Tsushimoto, S. Sakaguchi, and Y. Ishii, *Tetrahedron Lett.*, **44**, 5601 (2003).  
 l. H.-S. Dang and B. P. Roberts, *J. Chem. Soc. Perkin Trans. 1*, 67 (1998).  
 m. T. M. Patrick, Jr., and F. B. Erickson, *Org. Synth.*, **IV**, 430 (1963).  
 n. D. Elad and J. Rokach, *J. Org. Chem.*, **29**, 1855 (1964).  
 o. I. Rosenthal and D. Elad, *J. Org. Chem.*, **33**, 805 (1968).  
 p. W. Reusch, *J. Org. Chem.*, **27**, 1882 (1962).  
 q. J. C. Allen, J. I. G. Cadogan, B. W. Harris, and D. H. Hey, *J. Chem. Soc.*, 4468 (1962).  
 r. A. Hajek and J. Malek, *Synthesis*, 454 (1977).  
 s. R. Brown, W. E. Jones, and A. R. Pinder, *J. Chem. Soc.*, 2123 (1951).  
 t. D. W. Grattan, J. M. Locke, and S. R. Wallis, *J. Chem. Soc., Perkin Trans. 1*, 2264 (1973).

a mercury lamp. Entries 4 to 8 involve additions of tetrahalomethanes. In Entry 4 the ratio of reactants was 1.00  $\text{CCl}_4$ , 0.33 alkene, and 0.02 peroxide. Similar ratios were used in Entries 6 and 7. Entry 5 was done with irradiation from a mercury lamp. Entry 6 demonstrates the exclusive *exo* addition of the trichloromethyl radical and dominant *endo* abstraction of chlorine. Entry 8 is an example of a recently developed procedure in which iron powder acts both as an initiator and catalyst.

Entries 9 to 16 show additions of various carbon radicals. Entry 9 involves addition of acetaldehyde to a terminal alkene. The reaction was done under mercury

lamp irradiation and the conversion was rather low. Higher yields were obtained using heptanal. Entries 10 and 11 demonstrate that alkenes with EWG substituents are suitable reactants, which is consistent with the nucleophilic character of acyl radicals. The reaction in Entry 10 was carried out under irradiation from a mercury lamp. These reactions were found to be facilitated by  $O_2$ , which is thought to be involved in the initiation phase of the reaction. Entry 11 uses *N*-hydroxyphthalimide as the chain transfer agent in a process called *polarity reversal catalysis*. The adduct radical abstracts hydrogen from *N*-hydroxyphthalimide. The resulting radical is much more reactive toward hydrogen abstraction from the aldehyde than is the adduct radical. In the example cited, the ratio of reactants used was aldehyde 7.5, alkene 1.0, *N*-hydroxyphthalimide 0.1, benzoyl peroxide 0.1.



The reaction in Entry 12 is related and uses thioglycolate esters as a chain transfer agent. In this particular reaction involving an electron-rich alkene, the yield is only 8% in the absence of the thioglycolate. Entry 13 is another example of the addition of an acyl radical to relatively electrophilic alkene. Entry 14, involving the addition of formamide was done with acetone photosensitization. The 2-dioxolanyl radical involved in Entry 15 would be expected to be nucleophilic in character and higher yields were obtained with diethyl maleate than with typical terminal alkenes. The addition of 1,3-dioxolane to various enones has been done using benzophenone sensitization.¹⁷⁴ The radicals in Entries 17 and 18 are electrophilic in character. Entries 19 and 20 are examples of thiol additions.

Intramolecular addition reactions are quite common when radicals are generated in molecules with unsaturation in a sterically favorable position.¹⁷⁵ We will encounter several examples of intramolecular additions in the next section. Cyclization reactions based on intramolecular addition of radical intermediates are synthetically useful and several specific cases are considered in Section 10.3.3 of Part B.

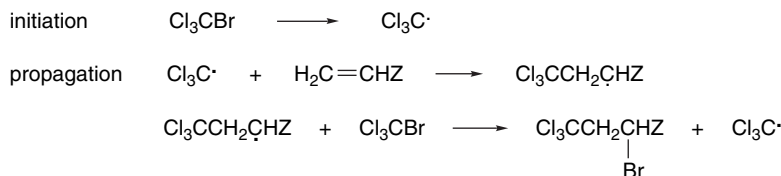
¹⁷⁴. C. Manfrotto, M. Mella, M. Freccero, M. Fagnoni, and A. Albini, *J. Org. Chem.*, **64**, 5024 (1999).

¹⁷⁵. A. L. J. Beckwith, *Tetrahedron*, **37**, 3073 (1981).

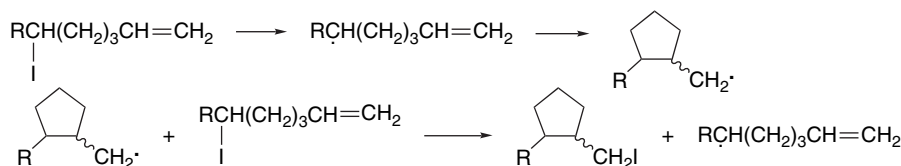


## 11.5.1. Halogen, Sulfur, and Selenium Group Transfer Reactions

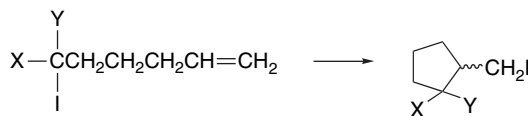
Other atoms and groups apart from hydrogen are susceptible to abstraction by free radicals. The most important from a synthetic point of view are bromine, iodine, sulfur, and selenium substituents.¹⁷⁶ Group transfer reactions can occur inter- or intramolecularly. Indeed, we have already encountered one example in the addition of polyhalogenated methanes to alkenes. The chain is propagated by a bromine atom transfer.



Cyclizations involving iodine atom transfers have been developed, and among the most effective examples are reactions involving the cyclization of 6-iodohexene derivatives.¹⁷⁷ The 6-hexenyl radical generated by iodine atom abstraction rapidly cyclizes to a cyclopentylmethyl radical. The chain is propagated by iodine atom transfer.



Various functionalized derivatives can be cyclized, including  $\alpha$ -iodoesters,  $\alpha$ -iodoketones, and  $\alpha$ -iodomalonates.¹⁷⁸ These substituents make the radical more electrophilic and reactive toward the alkene and also facilitate the iodine abstraction step.



Similarly, 6-iodoalkyne derivatives cyclize to iodomethylenecyclopentanes.¹⁷⁹ The chain is propagated by abstraction of iodine by the cyclized vinyl radical intermediate.

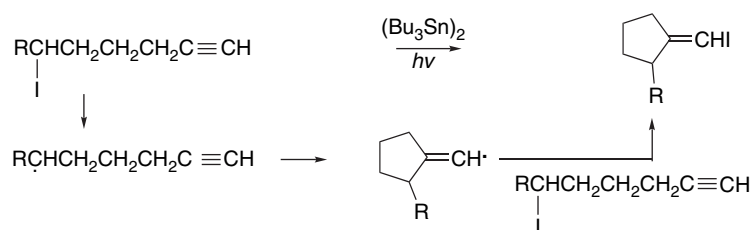
¹⁷⁶. J. Byers, in *Radicals in Organic Synthesis*, P. Renaud and M. P. Sibi, eds., Wiley-VCH, Weinheim, 2001, Vol. 1, Chap. 1.5.

¹⁷⁷. D. P. Curran and D. Kim, *Tetrahedron Lett.*, **27**, 5821 (1986).

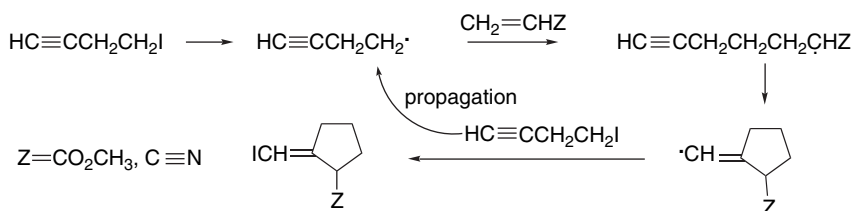
¹⁷⁸. D. P. Curran and C. T. Chang, *Tetrahedron Lett.*, **28**, 2477 (1987).

¹⁷⁹. D. P. Curran, M.-H. Chen, and D. Kim, *J. Am. Chem. Soc.*, **108**, 2489 (1986).

This sequence of reactions benefits from the high reactivity of the intermediate alkenyl reaction in the iodine transfer step.

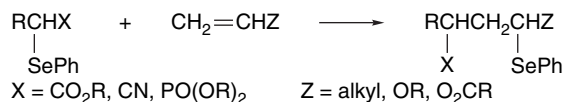


The hexabutyldistannane used in this reaction is not involved in the propagation sequence but may be involved in initiation or scavenging of potential chain termination radicals. With 4-iodobutyne, the intermediate radicals can be trapped by activated alkenes, which leads to cyclized products.¹⁸⁰



For all of these reactions, the reagents and reaction conditions must be chosen to meet the fundamental requirement for successful chain reactions. Each step in the sequence must be fast and exothermic to permit chain propagation.¹⁸¹

Aryl selenides have also proven to be excellent reagents in group transfer reactions.¹⁸² Photolysis of selenides in an inert solvent such as benzene can initiate chain reactions. Various substituted radicals can be generated in this manner by using  $\alpha$ -selenenyl derivatives of esters,¹⁸³ nitriles,¹⁸⁴ malonates,¹⁸⁵  $\beta$ -ketoesters,¹⁸³  $\alpha$ -methoxyesters,¹⁸⁶ and phosphonates.¹⁸⁷ The resulting radicals undergo addition to alkenes to generate  $\gamma$ -seleno derivatives.



¹⁸⁰. D. P. Curran and M.-H. Chen, *J. Am. Chem. Soc.*, **109**, 6558 (1987).

¹⁸¹. D. P. Curran, *Synthesis*, 417, 511 (1988); C. P. Jasperse, D. P. Curran, and T. L. Fervig, *Chem. Rev.*, **91**, 1237 (1991).

¹⁸². L. Castle and M. J. Perkins, in *The Chemistry of Organic Selenium and Tellurium Compounds*, Part 2, S. Patai, ed., Wiley, Chichester, 1987, Chap. 16.

¹⁸³. J. H. Byers and B. C. Harper, *Tetrahedron Lett.*, **33**, 6953 (1992).

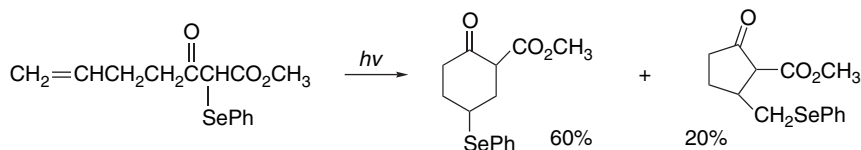
¹⁸⁴. D. P. Curran and G. Thoma, *J. Am. Chem. Soc.*, **114**, 4436 (1992).

¹⁸⁵. J. H. Byers and G. C. Lane, *J. Org. Chem.*, **58**, 3355 (1993).

¹⁸⁶. P. Renaud and S. Abazi, *Synthesis*, 253 (1996).

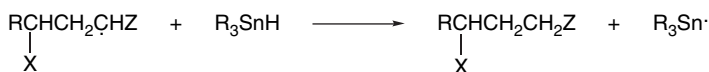
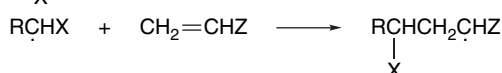
¹⁸⁷. P. Balczewski, W. M. Pietrzykowski, and M. Mikolajczyk, *Tetrahedron*, **51**, 7727 (1995); J. H. Byers, J. G. Thissell, and M. A. Thomas, *Tetrahedron Lett.*, **36**, 6403 (1995).

Appropriately substituted selenides can undergo cyclization reactions via a group transfer process.¹⁸⁸

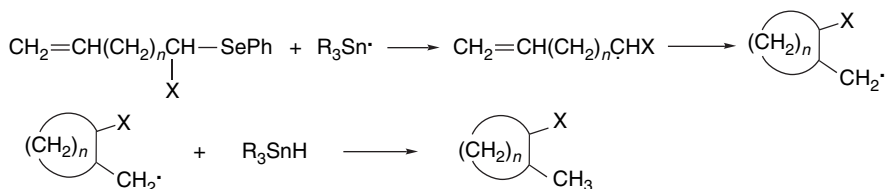


If selenide additions are carried out in the presence of tri-*n*-butylstannane, the radical generated by addition is reduced by hydrogen abstraction. The chain is then continued by selenide abstraction by the stannyl radical, which leads to reduced addition and cyclization products.

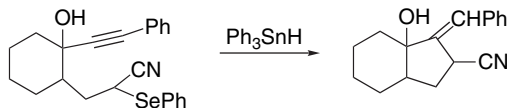
*Intermolecular addition:*



*Intramolecular addition:*

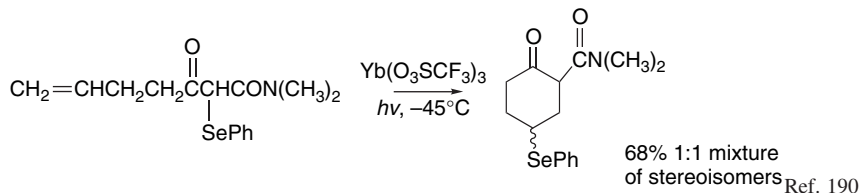


This reaction can also be applied to alkynes.



Ref. 189

Certain of these phenylselenenyl radical transfer reactions are catalyzed by Lewis acids. The regioselectivity depends on reactant structure, and related compounds give 5-*exo* and 7-*endo* products. The catalysis is believed to be the result of complexation at the carbonyl, which enhances the electrophilicity of the radical.



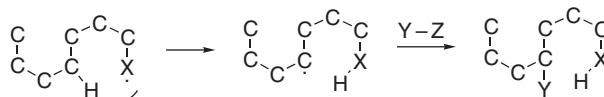
¹⁸⁸. J. H. Byers, T. G. Gleason, and K. S. Knight, *J. Chem. Soc., Chem. Commun.*, 354 (1991).

¹⁸⁹. D. J. L. Clive, T. L. B. Boivin, and A. G. Angoh, *J. Org. Chem.*, **52**, 4943 (1982).

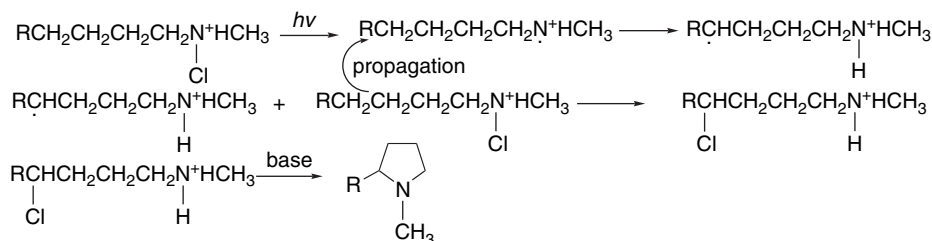
¹⁹⁰. D. Yang, Q. Gao, and O.-Y. Lee, *Org. Lett.*, **4**, 1239 (2002).

## 11.5.2. Intramolecular Hydrogen Atom Transfer Reactions

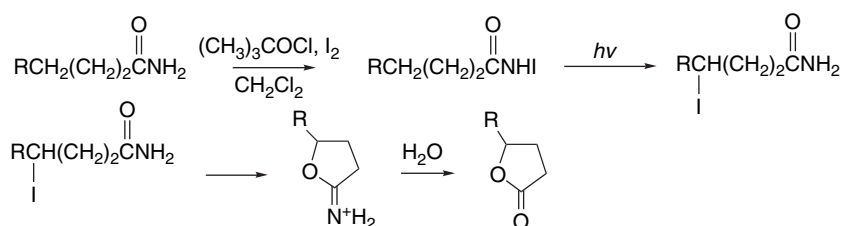
We have seen that substitution, addition, and group transfer reactions can occur intramolecularly. Intramolecular substitution reactions that involve hydrogen abstraction have some unique synthetic applications because they permit functionalization of carbon atoms relatively remote from the initial reaction site.¹⁹¹ The preference for a six-membered cyclic TS in the hydrogen abstraction step imparts position selectivity to the process.



There are several reaction sequences that 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*.¹⁹² The reaction leads to  $\gamma$ -haloamines, but these are usually converted to pyrrolidines by intramolecular nucleophilic substitution.



There are related procedures involving *N*-haloamides that lead to lactones via iminolactone intermediates.¹⁹³



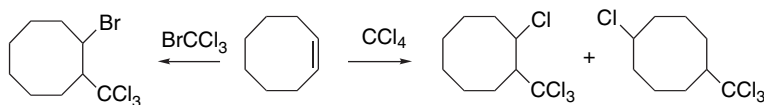
Intramolecular hydrogen abstraction reactions have also been observed in medium-sized rings. The reaction of cyclooctene with carbon tetrachloride and bromotrichloromethane is an interesting case. As shown in the equations below,

¹⁹¹ G. Majetich and K. Wheless, *Tetrahedron*, **51**, 7095 (1995).

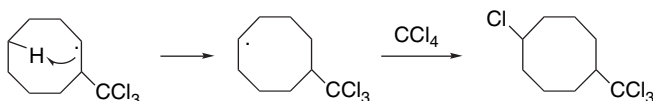
¹⁹² M. E. Wolff, *Chem. Rev.*, **63**, 55 (1963).

¹⁹³ 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).

bromotrichloromethane adds in a completely normal manner, but carbon tetrachloride gives some 4-chloro-1-trichloromethylcyclooctane, as well as the expected product.¹⁹⁴



In the case of carbon tetrachloride, the radical intermediate undergoes two competing reactions; transannular hydrogen abstraction is competitive with abstraction of a chlorine atom from carbon tetrachloride. The former reaction leads to the 1,5-disubstituted product.

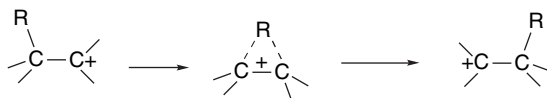


No product derived from the transannular hydrogen abstraction is observed in the addition of bromotrichloromethane because bromine atom transfer is sufficiently fast to prevent effective competition from the intramolecular hydrogen abstraction.

The selectivity observed in most intramolecular functionalizations depends on the preference for a six-membered TS in the hydrogen atom transfer step. Appropriate molecules can be constructed in which steric or conformational effects dictate a preference for selective abstraction of a hydrogen that is more remote from the reactive radical.

### 11.5.3. Rearrangement Reactions of Free Radicals

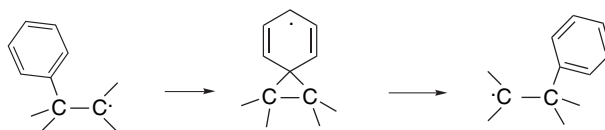
Compared with carbocations, rearrangements of radical intermediates are much less common. However, migrations can occur for specific structural types. The groups that are usually involved in migration in free radical intermediates include aryl, vinyl, acyl, and other unsaturated substituents. Migration of saturated groups is unusual and there is a simple structural reason for this. With carbocations, migration occurs through a bridged TS (or intermediate) that involves a three-center two-electron bond.



In a free radical, there is a third electron in the system that cannot occupy the same orbital as the other two electrons and must instead be in an antibonding level. As a result, the TS for migration is much less favorable than for the corresponding carbocation. The more facile migration of aryl and other unsaturated groups involves

¹⁹⁴ 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).

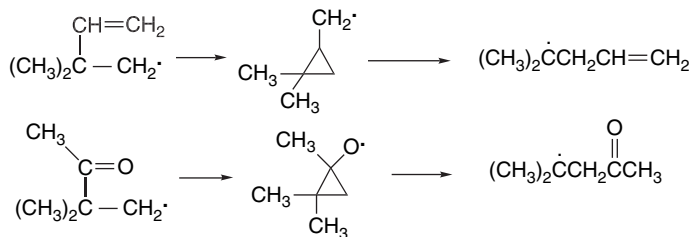
bridged radicals formed by an addition process. In the case of aryl migration, the bridged intermediate is a cyclohexadienyl radical.



It has been possible to measure absolute rates and  $E_a$  for rearrangement in a series of 2-substituted 2,2-dimethylethyl radicals. The rates at 25° C and the  $E_a$  for several substituents are as indicated below.¹⁹⁵

X	$k$ (s ⁻¹ )	$E_a$ (kcal/mol)	
Ph	$7.6 \times 10^2$	11.8	
CH ₂ =CH	$10^7$	5.7	
(CH ₃ ) ₃ CC≡C	9.3	12.8	
(CH ₃ ) ₃ CC=O	$1.5 \times 10^5$	7.8	
N≡C	9.0	16.4	

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



The vinyl rearrangement is an example of reversible cyclopropylcarbinyl radical formation and ring opening. The acyl migration occurs through cyclopropoxy radicals. The energy profile of the cyclopropoxy radical has been compared computationally to that of the cyclopropylcarbinyl radical (see Section 11.1.3 and Figure 11.3). At the UMP3/6-31G* level, the cyclopropyloxy radical is a TS, rather than an intermediate.¹⁹⁶ The energy profile for the formation of the 2-oxocyclopentylmethyl radical and its rearrangement to the 3-oxocyclohexyl radical by acyl migration has been explored,¹⁹⁷ and the results are shown in Figure 11.15. The rearrangement is found to be exothermic and the calculated barrier for the rearrangement is 20.3 kcal/mol, which is slightly less than that for the initial cyclization. This calculation, too, indicates that the cyclopropoxy radical fragments with no barrier.

Aryl migration is considerably slower because of the diminished susceptibility of the aryl ring to radical addition. Aryl migrations are promoted by steric crowding at the initial radical site. This trend is illustrated by data from the thermal decomposition

¹⁹⁵. D. A. Lindsay, J. Luszyk, and K. U. Ingold, *J. Am. Chem. Soc.*, **106**, 7087 (1984).

¹⁹⁶. A. L. Cooksy, H. F. King, and W. H. Richardson, *J. Org. Chem.*, **68**, 9441 (2003).

¹⁹⁷. I. Ryu, H. Fukushima, T. Okuda, K. Matsu, N. Kombe, N. Sonada, and M. Komatsu, *Synlett*, 1265 (1997).

	$E_a$	$E_b$	$E_c$	$E_d$	$E_e$
UMP3/6-31G**/UMP3/3-21G	30.7	20.3	17.0	16.4	-4.8

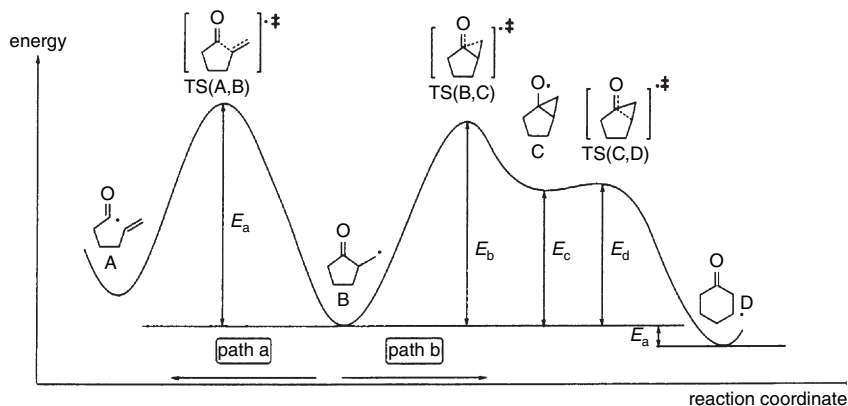
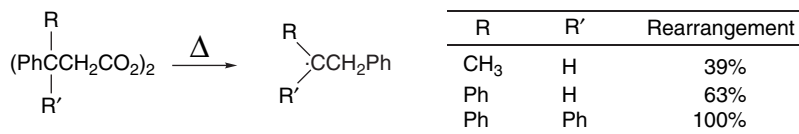


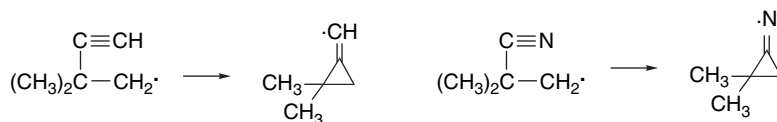
Fig. 11.15. Relative energies of the 5-hexenyl, 2-oxocyclopentylmethyl, and 3-oxocyclohexyl radicals and the transition structures separating them. Reproduced from *Synlett*, 1265 (1997), by permission of G. Thieme Verlag.

of a series of diacyl peroxides. The amount of product derived from rearrangement increases with the size and number of the substituents.¹⁹⁸



The aryl migration has been modeled computationally at the UB3PW91/G-31G(*d,p*) level.¹⁹⁹ The bridged cyclohexadienyl radical is found to be a short-lived intermediate that is 10.1 kcal/mol above the open radical. The barrier for return to the open radical is 4.0 kcal/mol. The relative stability of the bridged radical is increased by most *para*-substituents, since they provide stabilization of the cyclohexadienyl radical.

The much slower rearrangement of alkynyl and cyano substituents can be attributed to the reduced stability of the intermediate derived by cyclization of the triply bound substituents.

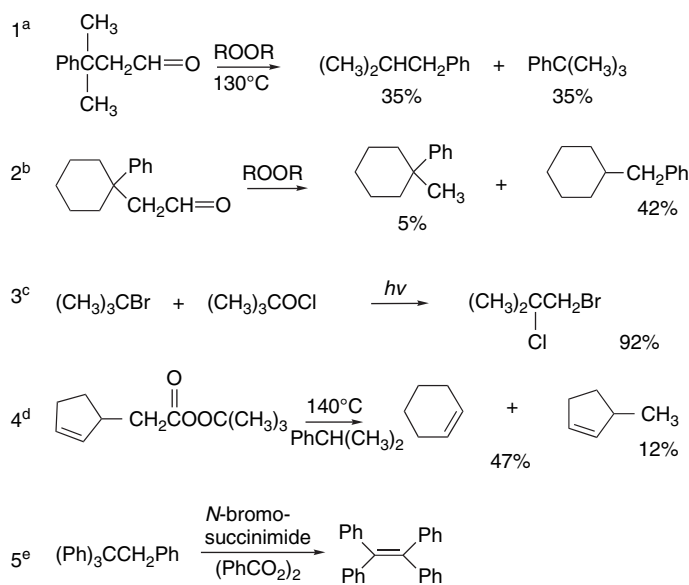


Scheme 11.6 gives some examples of reactions in which free radical rearrangements have been observed. Entries 1 and 2 are phenyl group migrations in primary alkyl radicals generated by decarbonylation. The migration is competitive with the

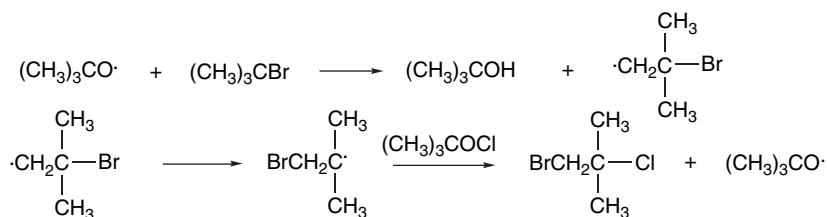
¹⁹⁸. W. Rickatson and T. S. Stevens, *J. Chem. Soc.*, 3960 (1963).

¹⁹⁹. A. Asensio and J. J. Dannenberg, *J. Org. Chem.*, **66**, 5996 (2001).

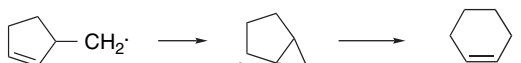
## Scheme 11.6. Free Radical Rearrangements

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. Constanza, and J. Strelitz, *J. Org. Chem.*, **33**, 3221 (1968).

hydrogen abstraction reaction that gives unrearranged product. The reaction in Entry 3 occurs by hydrogen abstraction followed by bromine migration.



Entry 4 is an alkenyl migration that presumably occurs through a bicyclic radical.



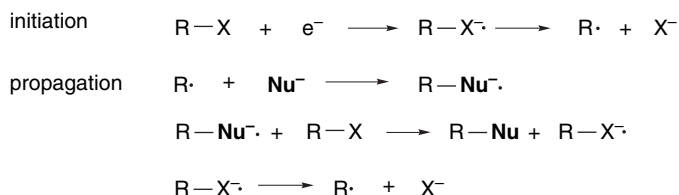
The reaction in Entry 5 involves a phenyl migration. The rearranged radical undergoes hydrogen atom elimination rather than the usual abstraction of bromine.

11.6.  $S_{RN}1$  Substitution Processes

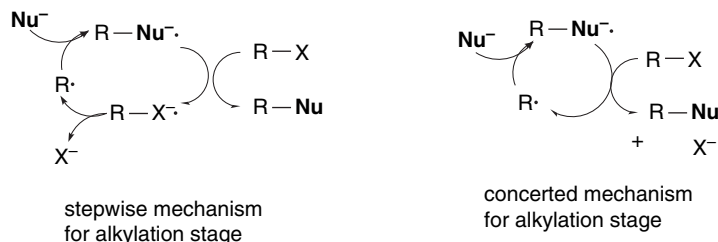
The mechanistic description  $S_{RN}1$  refers to a nucleophilic substitution via a radical intermediate that proceeds by unimolecular decomposition of a radical anion derived from the reactant. There are two families of such reactions that have been developed



to a stage of solid mechanistic understanding as well as synthetic utility. The common mechanistic pattern of  $S_{RN}1$  involves electron transfer to the reactant that generates a radical anion, which then expels the leaving group. A chain process occurs if the radical generated by expulsion of the leaving group can react with the nucleophile to give a radical anion capable of sustaining a chain reaction.



A key to the efficiency of  $S_{RN}1$  reactions is the electron transfer to the alkylating reagent.²⁰⁰ This process can be stepwise if the radical anion that is formed is sufficiently stable, but can also be concerted. The concerted path is the most likely one for alkyl halides. The combination reaction between the radical and nucleophile is very fast.



The  $S_{RN}1$  reaction was first discovered and developed for nitroalkane anions, but it is applicable to several other types of nucleophiles. The  $S_{RN}1$  reaction is applicable to various aryl and tertiary alkyl halides and has also been extended to other leaving groups. The reaction has found a number of synthetic applications, especially in substitution of aryl and bridgehead alkyl halides that are resistant to other substitution mechanisms.²⁰¹

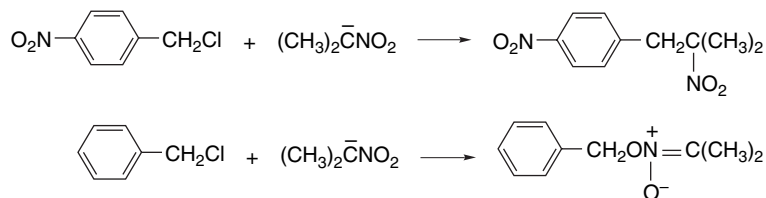
### 11.6.1. $S_{RN}1$ Substitution Reactions of Alkyl Nitro Compounds

The  $S_{RN}1$  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 understand the mechanistic basis for high-yield carbon alkylation of the 2-nitropropane anion by *p*-nitrobenzyl chloride. The corresponding

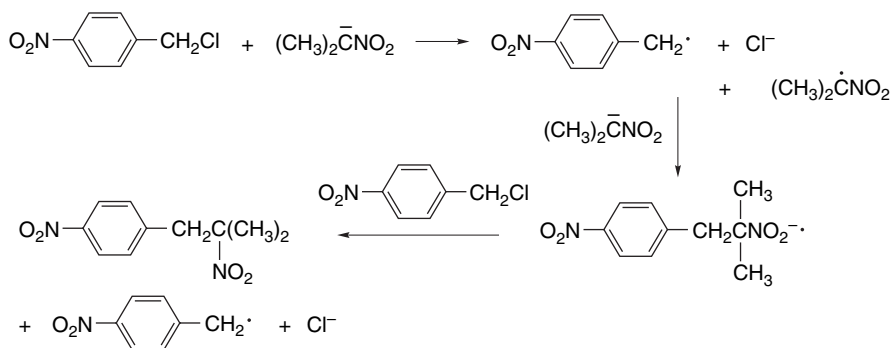
²⁰⁰ J.-M. Saveant, *J. Phys. Chem.*, **98**, 3716 (1994); R. A. Rossi, A. B. Pierini, and G. L. Borosky, *J. Chem. Soc., Perkin Trans. 2*, 2577 (1994).

²⁰¹ R. A. Rossi, *Current Org. Chem.*, **7**, 747 (2003); R. A. Rossi, A. B. Pierini, and A. N. Santiago, *Org. React.*, **54**, 1 (1999); R. A. Rossi, A. B. Pierini and A. B. Penenory, *Chem. Rev.*, **103**, 71 (2003).

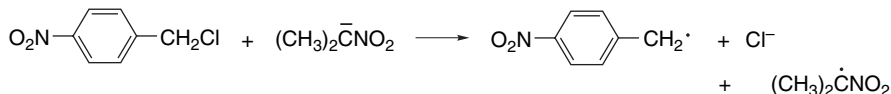
bromide and iodide, as well as benzyl halides that do not contain a nitro substituent give mainly the unstable oxygen alkylation product with this ambident anion.²⁰²



A mixture of carbon and oxygen alkylation would be expected for an  $S_N2$  substitution process. The high preference for carbon alkylation suggested that a different mechanism operates with *p*-nitrobenzyl chloride. This conclusion was further strengthened by the fact that the chloride is more reactive than would be predicted by application of the usual  $I > Br > Cl$  reactivity trend for leaving groups in  $S_N2$  reactions. The involvement of a free radical process was indicated by ESR studies and by demonstrating that typical free radical inhibitors decrease the rate of the carbon alkylation process. The mechanism proposed is a free radical chain process initiated by electron transfer from the nitronate anion to the nitroaromatic compound.²⁰³ This process is the dominant reaction only for the chloride, because, with the better leaving groups bromide and iodide, a direct  $S_N2$  process is faster.

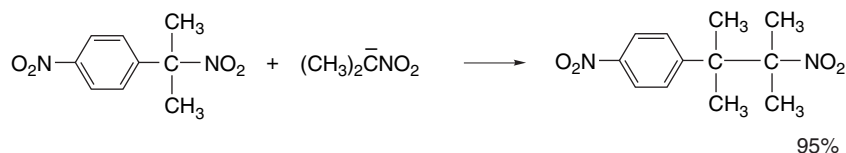


The absolute rate of dissociation of the *p*-nitrobenzyl chloride radical anion has been measured as  $4 \times 10^3 \text{ s}^{-1}$ . The *m*-nitro isomer does not undergo a corresponding reaction,²⁰⁴ owing to the fact that the *m*-nitro group does not provide any resonance stabilization of the benzylic radical. The kinetics of the overall reaction supports a concerted electron transfer involving dissociation at the stage of electron transfer from the nitronate to the benzylic halide.²⁰⁵



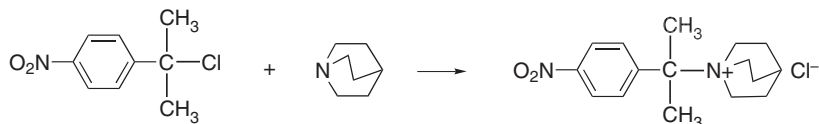
- ²⁰² N. Kornblum, *Angew. Chem. Int. Ed. Engl.*, **14**, 734 (1975); N. Kornblum, in *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*, S. Patai, ed., Interscience, New York, 1982, Chap. 10.
- ²⁰³ N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Am. Chem. Soc.*, **88**, 5662 (1966); G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.*, **88**, 5663 (1966).
- ²⁰⁴ R. K. Norris, S. D. Baker, and P. Neta, *J. Am. Chem. Soc.*, **106**, 3140 (1984).
- ²⁰⁵ C. Costentin, P. Hapiot, M. Medebielle, and J.-M. Saveant, *J. Am. Chem. Soc.*, **121**, 4451 (1999).

The synthetic value of the  $S_{RN}1$  substitution reaction was developed from this mechanistic understanding. The reaction is capable of providing highly substituted carbon skeletons that would be inaccessible by normal  $S_N2$  processes. For example, tertiary *p*-nitrocumyl halides can act as alkylating agents in high yield. The nucleophile need not be a nitroalkane anion, but can be anions such as thiolate, phenolate, or a carbanion such as those derived from malonate esters.²⁰⁶ The same mechanism operates as for the nitronate anion. Furthermore, the leaving group need not be a halide. Displacement of nitrite ion from  $\alpha$ ,*p*-nitrocumene occurs with good efficiency.²⁰⁷



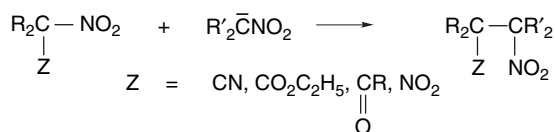
Azido, sulfonyl, and quaternary nitrogen groups can also be displaced by this mechanism.

An  $S_{RN}1$  mechanism has been proposed for the alkylation of amines by *p*-nitrocumyl chloride.^{208, 209}



Clearly, the tertiary nature of the chloride would make a  $S_N2$  mechanism highly unlikely. 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 cannot easily be formed by an  $S_N2$  mechanism. The alkylating agent must contain a nitro group and a second EWG. These compounds react with nitronate anions to effect displacement of the nitro group.²¹⁰



When radical scavengers are added, the reaction is greatly retarded, which indicates that a chain reaction is involved. 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

²⁰⁶ 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).

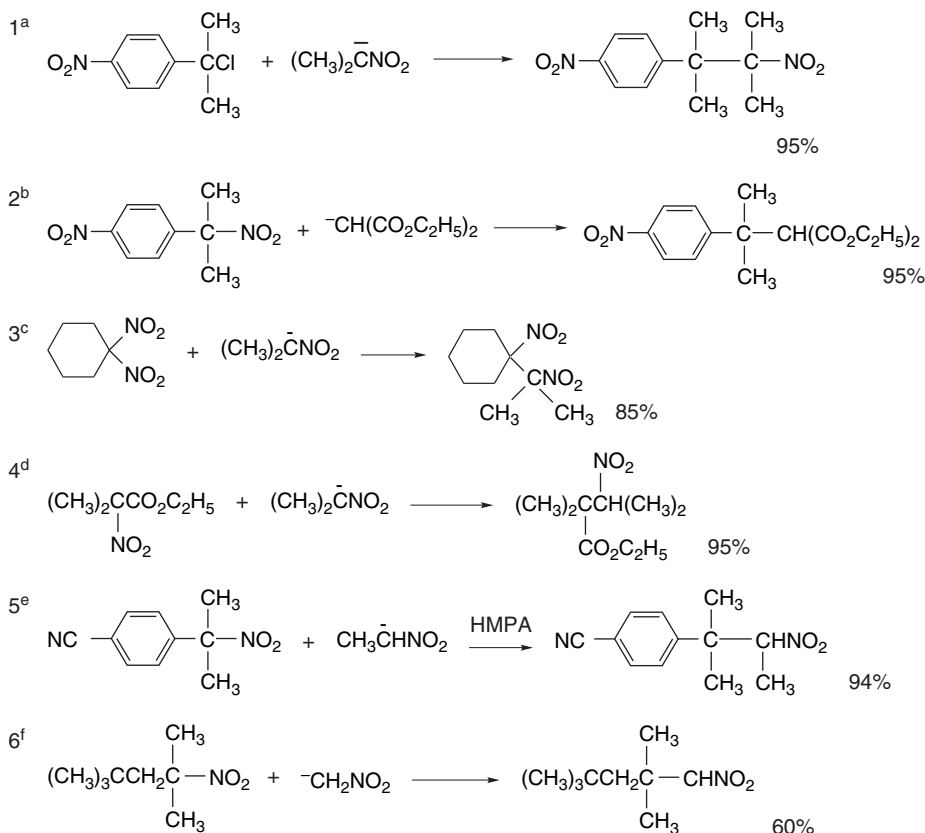
²⁰⁷ N. Kornblum, T. M. Davis, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.*, **89**, 5714 (1967).

²⁰⁸ N. Kornblum and F. W. Stuchal, *J. Am. Chem. Soc.*, **92**, 1804 (1970).

²⁰⁹ W. R. Bowman, *Chem. Soc. Rev.*, **17**, 283 (1988).

²¹⁰ N. Kornblum and S. D. Boyd, *J. Am. Chem. Soc.*, **92**, 5784 (1970).

214. 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 # 178, Washington, 1983; J.-M. Saveant, *Adv. Phys. Org. Chem.*, **26**, 1 (1990).



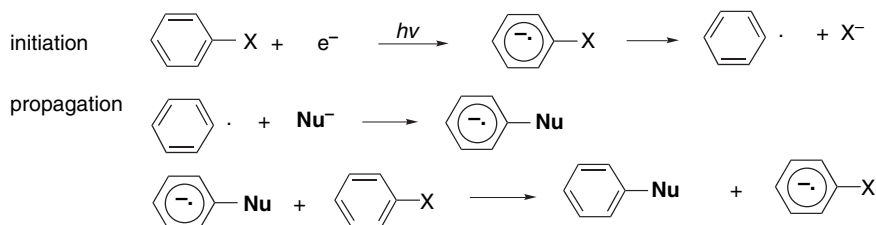
a. N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.*, **89**, 725 (1967).

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, N. 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 (1984).

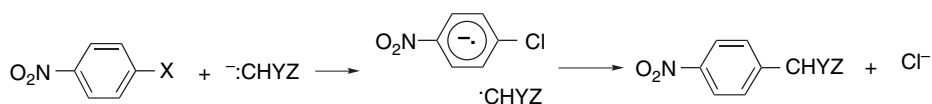


The reactions can also be initiated by a strong chemical reductant or electrochemically.²¹⁵ There are several lines of evidence that support the operation of a chain

²¹⁵ C. Amatore, J. Chaussard, J. Pinson, J.-M. Saveant, and A. Thiebault, *J. Am. Chem. Soc.*, **101**, 6012 (1979).

mechanism, one of the most general observations being that the reactions are stopped or greatly retarded by radical traps. The reactions are not particularly sensitive to the aromatic ring substituents. Both ERGs (such as methoxy) and EWGs (such as benzoyl) can be present.²¹⁶ Groups that easily undergo one electron reduction, especially the nitro group, cause the reaction to fail. The nucleophiles that have been used successfully include sulfide and phosphide anions, dialkyl phosphite anions, and certain enolates. Kinetic studies have shown that the enolate and phosphorus nucleophiles react at about the same rate.²¹⁷ This suggests that the step directly involving the nucleophile (Step 2 of the propagation sequence) occurs at essentially the diffusion-controlled rate, since there is little selectivity among the individual nucleophiles.²¹⁸ The combination of aryl radicals with diethyl phosphate anion has been measured at about  $10^9 \text{ M}^{-1} \text{ s}^{-1}$ .²¹⁹

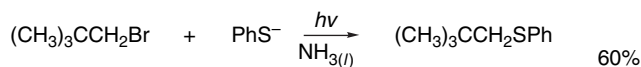
A related mechanism has been suggested for nitroarylation of enolates. An impetus for considering other mechanisms is the fact that the by-products that might be expected from aryl radicals, such as reduction products from hydrogen abstraction from the solvent or biaryls from coupling, are not observed. The alternative is that rather than being a chain process, the radicals may combine (*cage recombination*) more rapidly than they separate.



The kinetics of the reaction of *p*-nitrochlorobenzene with the sodium enolate of ethyl cyanoacetate is consistent with this mechanism. Moreover, radical scavengers have no effect on the reaction, contrary to what would be expected for a chain mechanism in which aryl radicals must encounter the enolate in a propagation step. However, the reactant, *p*-nitrophenyl chloride, is one that might also react by the addition-elimination mechanism (see Section 9.5) and the postulated mechanism is essentially the stepwise electron transfer version of the latter. The question then becomes whether the postulated radical pair is a distinct intermediate.

The synthetic value of the  $\text{S}_{\text{RN}}1$  arylation lies in the fact that other substituents that activate the halide to substitution are not required, in contrast to aromatic nucleophilic substitution that proceeds by an addition-elimination mechanism (see Section 9.5). Scheme 11.8 illustrates some typical reactions.

Substitution of hindered alkyl halides by the  $\text{S}_{\text{RN}}1$  mechanism have also been documented.²²⁰ Some examples are shown below.



Ref. 221

²¹⁶ 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).

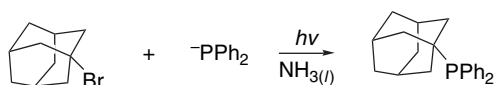
²¹⁷ X.-M. Zhang, D.-L. Yang, X.-Q. Jia, and Y.-C. Liu, *J. Org. Chem.*, **58**, 7350 (1993).

²¹⁸ 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).

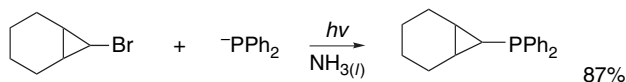
²¹⁹ A. Annunziata, C. Galli, M. Marinelli, and T. Pau, *Eur. J. Org. Chem.*, 1323 (2001).

²²⁰ S. M. Palacios, A. N. Santiago, and R. A. Rossi, *J. Org. Chem.*, **49**, 4609 (1984).

²²¹ A. B. Pierini, A. B. Penenory, and R. A. Rossi, *J. Org. Chem.*, **50**, 2739 (1985).

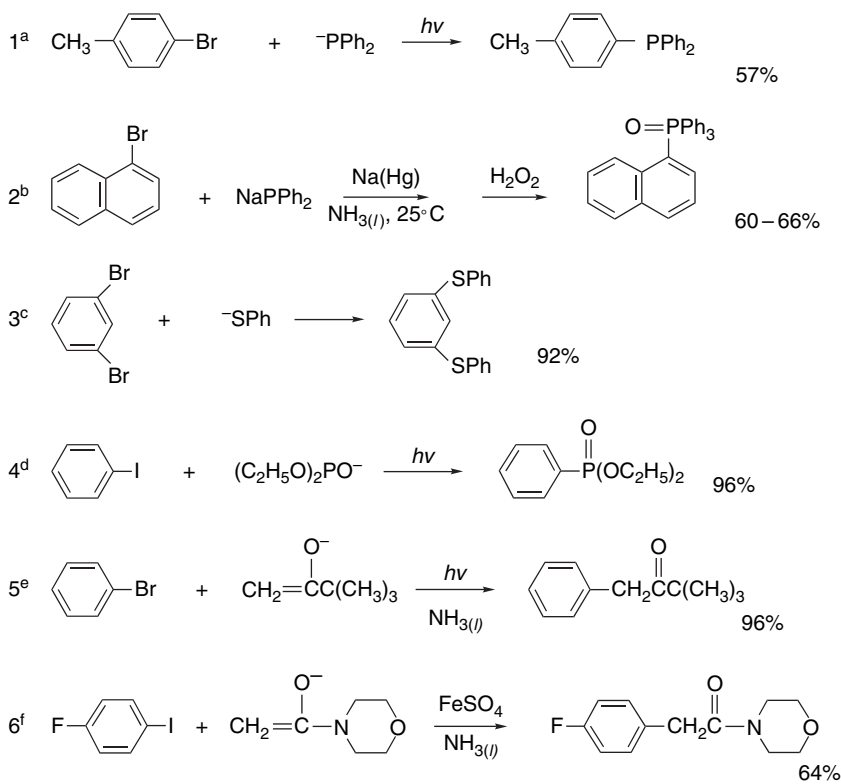


Ref. 222

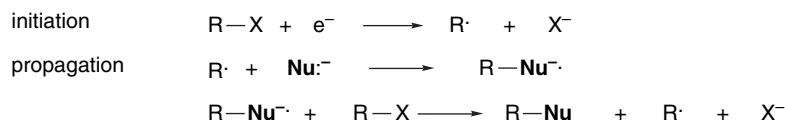


Ref. 223

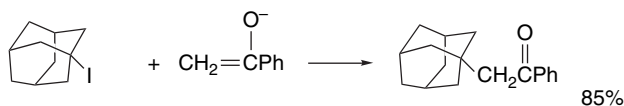
### Scheme 11.8. Aromatic Substitution by the S_{RN}1 Mechanism

a. J. E. Swartz and J. F. Bunnett, *J. Org. Chem.*, **44**, 340 (1979).b. P. G. Mabzo, S. M. Palacios, R. A. Alonso, and R. A. Rossi, *Org. Prep. Proc. Int.*, **27**, 660 (1995).c. J. E. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3611 (1974).d. J. E. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3612 (1974).e. M. F. Semmelhack and T. Bargar, *J. Am. Chem. Soc.*, **102**, 7765 (1980).f. M. van Leeuwen and A. McKillop, *J. Chem. Soc., Perkin Trans. I*, 2433 (1993).222. R. A. Rossi, S. M. Palacios, and A. N. Santiago, *J. Org. Chem.*, **47**, 4654 (1982).223. R. A. Rossi, A. N. Santiago, and S. M. Palacios, *J. Org. Chem.*, **49**, 3387 (1984).

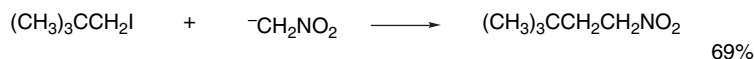
The mechanism is the same as for aryl halides, but the dissociation of the halide is probably concerted with the electron transfer.



Acetophenone enolate and nitromethane anions have also been used successfully in alkyl substitution.



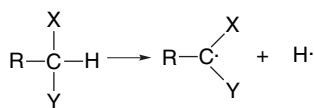
Ref. 224



Ref. 225

### Topic 11.1. Relationships between Bond and Radical Stabilization Energies

In Section 3.4.3, we discussed substituent effects on radicals in terms of radical stabilization energies (RSE). These values are defined in terms of standard bond dissociation energies. These RSE values provide a numerical assessment of some well-recognized effects, such as increasing radical stability in the order methyl < primary < secondary < tertiary and the strong stabilization of benzylic and allylic radicals. However, there are some RSE values that are less consistent with chemical experience. For example, the  $\text{CCl}_3\cdot$  radical is assigned a negative RSE of 13.79 kcal/mol, although it has a prominent place in radical chemistry. There is a general issue that pertains to radical stabilization energies from both thermochemical and computational BDE when they are defined as  $\Delta H$  for the reaction



This formulation includes any stabilization of the reactant in the value of the BDE and resulting RSE. Thus the “inherent” strength of the C–H bond is considered to be decreased to the extent that the product radical is stabilized. Further interpretation requires subdividing the BDE into its “inherent” and “extra stabilization” factors. To

²²⁴. M. A. Nazareno and R. A. Rossi, *J. Org. Chem.*, **61**, 1645 (1996).

²²⁵. A. B. Peneory and R. A. Rossi, *Gazz. Chem. Ital.*, **125**, 605 (1995).



do this, structural features that strengthen or weaken the bond *in the reactant* must be accounted for. The AIM approach (see Section 1.4.3) provides the basis for one such scheme. The intrinsic bond energy  $BE_i$  was defined in terms of the AIM energy  $E_i(r_{\text{BCP}})$  and charge density  $\rho_i(r_{\text{BCP}})$ :

$$BE_i = c_1^{\text{AB}} E_i(r_{\text{BCP}}) / [c_2^{\text{AB}} + \rho_i(r_{\text{BCP}})] - c_3^{\text{AB}} \Delta R \quad (11.6)$$

where  $c_1^{\text{AB}}$ ,  $c_2^{\text{AB}}$ , and  $c_3^{\text{AB}}$  are empirical characteristics of bond types and  $\Delta R$  is the difference between the length of the AIM bond path and the internuclear distance.²²⁶

This concept of inherent bond energy was extended by Exner and Schleyer to a wider range of structures.²²⁷ The approach reproduced atomization energies for typical alkanes and alkenes with a standard deviation of about 4.6 kcal/mol, i.e., within about 1%, although some molecules, e.g., allene and cyclopropene, fell well outside those limits. The calculated intrinsic bond energies  $BE_i$  were then compared with BDE, the energy required for homolytic dissociation. This analysis suggested that most of the dependence of BDE on structure can be attributed to the “extra stabilization” of the radicals, rather than to inherent differences in bond strength. Table 11.10 includes experimental bond energies, computed (G2) bond dissociation energies, the  $BE_i$  resulting from application of Equation (11.6), and the resulting RSE.

The data conform to familiar qualitative trends. We see the methyl < *pri* < *sec* < *tert* trend for alkyl groups. The strong stabilization of allyl radicals is evident in the value C(3)–H bond energy for propene, whereas the positive RSE for ethene, ethyne, and benzene reflect the low stability of radicals at  $sp^2$  and  $sp$  carbons. Also apparent in these data is the relative strength of C–H bonds in strained-ring compounds (cyclopropane). These results are also in accord with the concept of assigning most of the change in the BDE to radical stabilization or destabilization. The intrinsic bond energies,  $BE_i$ , show much less variation with substitution than the BDE.

**Table 11.10. Comparison of Experimental, Computational, and Calculated C–H Bond Dissociation Energies (kcal/mol)^a**

Compound	BDE (exp)	BDE (G2)	$BE_i$	RSE ^b
Methane	104.9	105.8	103.9	+1.0
Ethane	101.4	102.6	104.1	–2.7
Propane	98.6	100.3	100.3	–5.7
Isobutane	96.5	98.8	104.4	–7.9
Cyclopropane	106.3	113.0	105.8	+0.5
Cyclobutane	96.5	102.1	104.3	–7.8
Cyclopentane	94.5		103.9	–9.4
Cyclohexane	94.5		103.5	–9.0
Ethene	112.2	112.0	106.0	+5.2
Ethyne	132.8	135.0	110.4	+22.4
Propene	88.2	88.7	103.2	–15.0
Benzene	111.2		106.5	+4.7

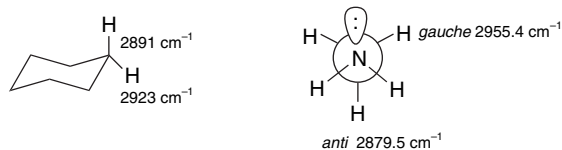
a. K. Exner and P. v. R. Schleyer, *J. Phys. Chem. A*, **105**, 3407 (2001).

b. Apparent radical stabilization from BDE (exp) –  $BE_i$  [Equation ( 11.6)]

²²⁶. S. Grimme, *J. Am. Chem. Soc.*, **118**, 1529 (1996).

²²⁷. K. Exner and P. v. R. Schleyer, *J. Phys. Chem. A*, **105**, 3407 (2001)

Larson and Cremer have explored another approach to dissecting BDE into inherent and RSE effects.²²⁸ There is a relationship between C–H BDE and the vibrational frequencies of the bonds.²²⁹ Furthermore, the vibrations can be determined for C–H bonds in specific conformations, for example, the equatorial and axial bonds in cyclohexanes or the *anti* and *gauche* bonds in amines.



Ref. 230

Ref. 231

Variation in vibrational frequencies of stereochemically distinct bonds

The measurement of the vibrational frequencies provides a means to compare the relative stabilization in radicals with effects already present in the reactant molecules. Following up on experimental work that demonstrated that spectroscopic C–H-bond-stretching frequencies correlate with bond strength,²²⁹ Larson and Cremer developed reliable computation methods for calculating C–H frequencies and from them inherent (or ideal) bond energies. The difference is the radical stabilization (or destabilization energy), as indicated in Figure 11.16.

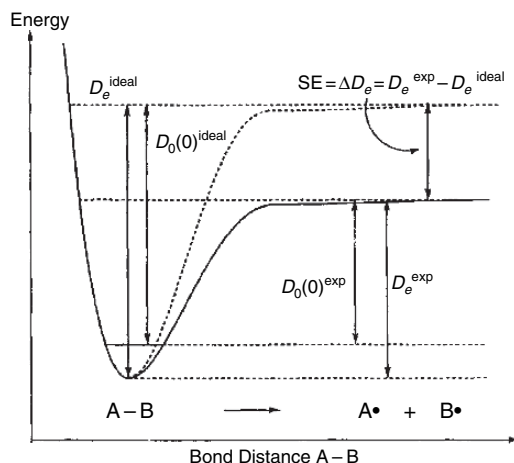


Fig. 11.16. Determination of fragment stabilization energy (SE) by comparison of  $D_e$  (exp) with  $D_e$  (ideal).  $D_0$  includes correction for zero point energy. Reproduced from *J. Mol. Struct.*, **485/486**, 385 (1999), by permission of Elsevier.

²²⁸ J. A. Larson and D. Cremer, *J. Mol. Struct.*, **485/486**, 385 (1999).

²²⁹ D. C. McKean, *Chem. Soc. Rev.*, **7**, 399 (1978); D. C. McKean, *Int. J. Chem. Kinetics*, **21**, 445 (1989).

²³⁰ J. Caillod, O. Saur, and J.-C. Lavalley, *Spectrochim. Acta*, **36A**, 185 (1980).

²³¹ J. L. Duncan, D. C. McKean, J. Torto, A. Brown, and A. M. Ferguson, *J. Chem. Soc., Faraday Trans.*, **II**, **84**, 1423 (1988).

**Table 11.11. Radical Stabilization Energy (SE) as Defined in Figure 11.16**

Structure	BE _{exp}	BE _i	SE
CH ₃ -H	112.9	112.3	0.5
CH ₃ CH ₂ -H	109.0	109.2	-0.1
CH ₃ CH ₂ CH ₂ -H	105.6	108.5	-2.9
(CH ₃ ) ₂ CH-H	102.9	106.4	-3.4
FCH ₂ -H	107.5	110.0	-3.4
HOCH ₂ -H	101.2	103.6	-2.3
H ₂ NCH ₂ -H	103.3	96.0	7.3
ClCH ₂ -H	108.6	113.4	-4.7
O=CH-H	95.1	95.4	-0.2
O=CHCH ₂ -H	101.2	107.2	-6.0
CH ₃ C(=O)-H	95.6	95.9	-0.3
NCCH ₂ -H	102.3	112.1	-9.8
H ₂ C=CH-H	118.8	118.2	0.5
HC≡C-H	140.1	140.2	-0.1
HC≡CCH ₂ -H	97.0	110.9	-13.9
C ₆ H ₅ -H	118.0	118.6	-0.6
H ₂ C=CHC(=O)-H	93.4	93.7	-0.3
O=C=CH-H	111.9	123.7	-11.7

TOPIC 11.1

*Relationships between  
Bond and Radical  
Stabilization Energies*

The RSEs found for several groups by this approach are given in Table 11.11. Among the noteworthy features of this analysis is the disappearance of the “negative stabilization energies” associated with phenyl, ethenyl, and ethynyl radicals. Nearly all the observed high BDEs in these compounds is attributed to the inherent strength of the C–H bond in the reactant. On the other hand, the stabilization of acyl radicals (see H₂C=O and CH₃CH=O) also disappear, because in this case the bonds in the reactant are inherently weaker. The various  $\pi$ -conjugating substituents such as propargyl, cyanomethyl, and the  $\alpha$ -acyl radicals show significant stabilization (a negative number by this definition). The halogens and hydroxyl groups have modest stabilizing effects according to this analysis, but an  $\alpha$ -amino group has a destabilizing effect. This is because the C–H bond in the reactant is particularly *weak*, not because the aminoalkyl radicals are unstable. The ketene ( $\cdot\text{CH}=\text{C}=\text{O}$ ) radical shows a large stabilization, but only because the reactant bond is strong and the BDE is high, so one would not expect facile reaction, despite the apparent stabilization.

Where does this leave us in terms of understanding substituent effects on radicals? The most general statement to be made is that the BDE, not the RSE, is the best indicator of reactivity of the C–H bond. This is evident in the relationship allyl  $\sim$  benzyl  $<$  *tert*  $<$  *sec*  $<$  *pri*  $<$  methyl  $<$  ethenyl  $\sim$  phenyl  $<$  ethynyl bonds to hydrogen. We also note that the statement “all substituents weaken adjacent C–H bonds” is generally true. The traditional RSE values, however, result from two substituent effects, those in the reactant and those in the radical, and ultimately depend on the definition of the inherent bond strength. The clearest guide to reactivity is the experimental BDE or its computational equivalent. We discuss the *rates of hydrogen abstraction reactions* in more detail in Topic 11.2.

## Topic 11.2. Structure-Reactivity Relationships in Hydrogen Abstraction Reactions

*Hydrogen abstraction reactions* are of considerable importance in several contexts. They play a role in determining the kinetics of combustion, which determines fuel characteristics, e.g., octane number. The rates of hydrogen abstraction reactions are also important in understanding the role of hydrocarbons and halogenated hydrocarbons in such environmental issues such as air pollution and polar ozone depletion. Hydrogen abstraction reactions are also of importance in understanding the relationship between bond dissociation energies and reactivity. The order allyl  $\sim$  benzyl  $>$  *tert*  $>$  *sec*  $>$  *pri*  $>$  aryl  $\sim$  vinyl for C–H bond reactivity is one of the fundamental structure-reactivity relationships that is developed in introductory organic chemistry. In this section we explore the empirical relationship between the rates and  $E_a$  for some hydrogen abstraction reactions from small hydrocarbons and halogenated hydrocarbons by some radicals of fundamental importance, such as the halogen atoms and hydroxyl radical. We consider some empirical, analytical, and computational approaches to understanding hydrogen atom abstraction reactions.

Owing to the importance of hydrogen abstraction reactions, there have been several approaches to developing empirical relationships that can be used to predict activation energies. These efforts are kinetic analogs of the group equivalent approach to thermodynamic properties, in that experimental data are taken as the base and predictive relationships are derived from the data. An example of an empirical approach has been reported by Ranzi et al.²³² From thermodynamic and kinetic data pertaining to radicals such as alkyl, hydroxyl, hydroperoxyl, methoxyl, and chlorine atoms, characteristic values corresponding to the  $A$  and  $E_a$  components of the Arrhenius equation were tabulated. Each reactant species was also assigned a correction factor. These characteristic values are then put into an equation that uses the reference Arrhenius parameters and correction factors to compute  $E_a$ :

$$E_a = E_{x^\circ}^\circ + E_{R-H}^C \left( \frac{E_{x^\circ}^\circ}{13500} \right)^{0.333} - \left[ 1 - \left( \frac{E_R^\circ}{13500} \right)^{0.333} \right] E_{X-H} \quad (11.7)$$

where  $E_{x^\circ}^\circ$  and  $E_R^\circ$  are the tabulated energy terms and  $E^C$  is the correction term. This equation has no theoretical basis beyond the Arrhenius equation and essentially assumes that each reactant and radical has transferable characteristics. The relative simplicity of the hydrogen atom transition state perhaps contributes to the existence of transferability. Figure 11.17 shows the correlation between calculated and experimental rate constants.

Roberts and Steel investigated the applicability of an extended Bell-Evans-Polyani relationship to a series of hydrogen abstraction reactions. They developed a correlation equation that incorporated additional terms for electronegativity differences and for radical stabilization effects:

$$E_a = E_o f + \alpha \Delta H^\circ (1 - d) + \beta \Delta \chi_{AB}^2 + \gamma (s_A + s_B) \quad (11.8)$$

where  $f = (\text{BDE}_{AH} \times \text{BDE}_{BH}) / \text{BDE}_{H_2}$ ,  $d$  is a parameter added for delocalized radicals,  $\beta$  and  $\gamma$  are parameters derived from the correlation,  $\chi$  is electronegativity, and  $s$  is a parameter that is characteristic of the atoms A and B. The inclusion of the various

²³² E. Ranzi, M. Dente, T. Faravelli, and G. Pennati, *Combust. Sci. and Tech.*, **95**, 1 (1994).

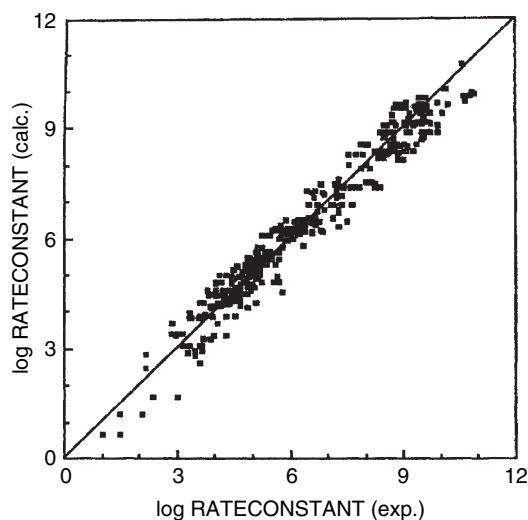
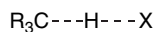


Fig. 11.17. Correlation of experimental hydrogen abstraction rates with rates calculated by Equation (11.7). Reproduced from *Combust. Sci. and Tech.*, **95**, 1 (1994) by permission of Taylor and Francis

terms has conceptual justifications; for example, the electronegativity term accounts for the increased strength of bonds between elements of differing electronegativity and the parameter  $d$  is related to the stabilization associated with delocalized radicals. For the set of 65 reactions examined, the  $E_a$  averaged to within 0.5 kcal/mol of the experimental value. The value of such an approach is that it provides for prediction of relative reactivity (in the form of  $E_a$ ) on the basis of existing BDE and electronegativity data. The numerical values of the parameters are determined by the correlation equation.²³³

Another kind of approach is based on estimates from first principles. The fundamental concept of these approaches is that the  $E_a$  of a hydrogen abstraction reaction will be determined mainly by the strength of the C–H and H–X bonds and by repulsions between  $R_3C$  and X in the transition state.



The problem is to formulate these relationships quantitatively. One approach, called the *interacting state model* (ISM) uses the Morse curves for the C–H and H–X bonds as the starting point and describes the TSs in terms of the length of the C–H and C–X bonds at the TS.²³⁴ The total bond order is taken to be 1.0 unless one of the radicals has extra (e.g., resonance) stabilization, in which case a parameter is added to the formulation. These assumptions lead to a formula that gives the TS energy from the bond lengths and force constants of the C–H and H–X bonds. These structural characteristics are available from experiment or computation. There are other methods

²³³ B. P. Roberts and A. J. Steel, *J. Chem. Soc., Perkin Trans. 2*, 2155 (1994); B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 2719 (1996).

²³⁴ L. G. Arnaut, A. A. C. C. Pais, and S. J. Formosinho, *J. Mol. Struct.*, **563**, 1 (2001).

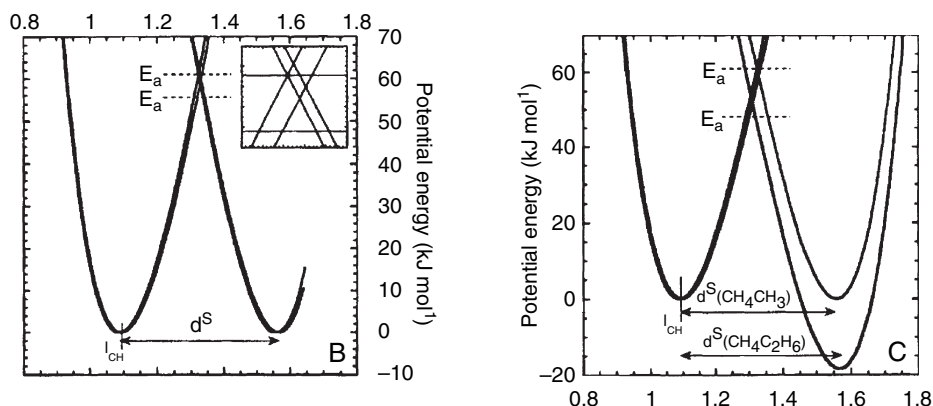


Fig. 11.18. Comparison of Morse curves from: (a)  $\text{CH}_3 \cdot + \text{CH}_4$  and  $\text{C}_2\text{H}_5 \cdot + \text{C}_2\text{H}_6$  thermoneutral; and (b)  $\text{CH}_3 \cdot + \text{C}_2\text{H}_6$  exothermic hydrogen atom transfer reactions. Reproduced from *J. Mol. Struct.*, **563**, 1 (2001), by permission of Elsevier.

of estimating or calculating  $E_a$  that use the C–H and H–X bond energies as the principal determinant of  $E_a$ .²³⁵

The qualitative interpretation of the ISM method can be illustrated by Figure 11.18. Figure 11.18a shows the equi-energy curves that pertain to the transfer of H between methyl and methane and ethyl and ethane. The curves nearly overlap, but the slightly weaker C–H bond in ethane is characterized by a smaller force constant and leads to a somewhat smaller barrier. The calculated barriers are 14.6 and 14.3 kcal/mol, respectively. The methyl-ethane reaction, shown in Figure 11.18b, is exothermic and there is a much more substantial shift in the curves. The calculated barrier is 12.4 kcal, compared with the experimental value of 11.5. Thus, the calculation moves the barriers in the right direction, although it does not reproduce the entire effect that is observed experimentally.

There have also been computational approaches using both semiempirical and ab initio MO and DFT methods. As in the treatment of isolated radicals, computational methods applied to radical transition states must use methods that are applicable for systems having unpaired electrons.²³⁶ In one study, reactant, product, and TS energies were calculated using the PM3 method.²³⁷ These were then compared with the corresponding experimental data. Figure 11.19 shows the PM3 representation of the SOMO distribution for the TS for hydrogen abstraction from propene (allylic hydrogen) by ethyl radical. Note that there is some delocalization of the SOMO distribution into the propene double bond, which is consistent with the idea that the stabilization of the allylic radical will contribute to the TS structure and lower the  $E_a$ . When the PM3 computations were applied to about 40 hydrocarbons, including some 10 benzylic and related conjugated structures, a good linear correlation was found between experimental and calculated  $E_a$ . The calculated  $E_a$  values tended to be too high by several kcal, but calibration of the linear correlation provided an average deviation of 1.5 kcal. The correlation was even better if the hydrocarbons were subdivided into structurally related groups.

²³⁵ H. S. Johnston and C. Parr, *J. Am. Chem. Soc.*, **85**, 2544 (1963); N. Agmon and R. D. Levine, *Chem. Phys. Lett.*, **52**, 197 (1977); R. D. Gilliom, *J. Am. Chem. Soc.*, **99**, 8399 (1977); A. A. Zavitsas and C. Chatgililoglu, *J. Am. Chem. Soc.*, **117**, 10645 (1995).

²³⁶ Y. Y. Chuang, E. L. Coitino, and D. G. Truhlar, *J. Phys. Chem. A*, **104**, 446 (2000).

²³⁷ X. Ma and H. H. Schobert, *Ind. Eng. Chem. Res.*, **40**, 743 (2001).

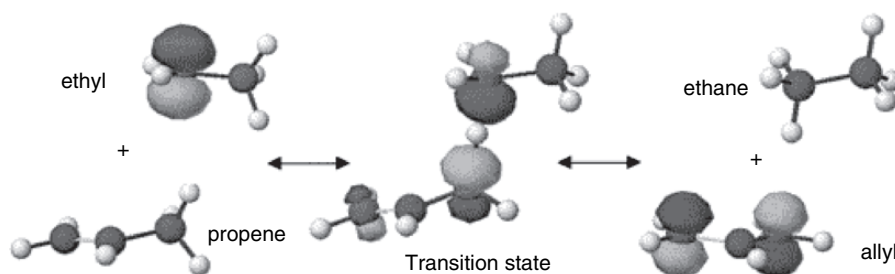


Fig. 11.19. PM3 representation of reactants, transition state, and products showing optimal geometry and distribution of SOMO orbital. Reproduced from *Int. Eng. Chem. Res.*, **40**, 743 (2001), by permission of the American Chemical Society.

These results extend those of an earlier study using AM1 and PM3 computations that showed excellent correlations within structurally similar groups, e.g., *tert*, *sec*, *pri*, and conjugated.²³⁸ These studies also showed that the barrier for identity hydrogen atom transfers (e.g., ethyl/ethane) *increased* with conjugation. This result, which at first might seem surprising, reflects the fact that there is greater conjugative stabilization in the radicals than in the transition state. Table 11.12 lists some of the computed barriers. The trend toward an increased barrier with conjugation should not be confused with the *greater* reactivity of allylic and benzylic C–H toward more reactive alkyl radicals. For example, the data for hydrogen atom abstraction from toluene and propene by the methyl radical in Table 11.5 show barriers of 9.5 and 7.7 kcal/mol, respectively.

There has been a good deal of study of the polyhalogenated methanes in hydrogen atom abstraction reactions toward hydroxyl ( $\text{HO}\cdot$ ) and chlorine radicals.²³⁹ These reactions are involved in both the atmospheric destruction of such compounds as well as their involvement in ozone depletion. Information is needed about these reactions to model the environmental impact of the compounds.

The reactions of halogenated methanes with  $\text{HO}\cdot$  are characterized by a low activation barrier and early TS. In one study the reactants, products, and TS were calculated at the 6-311G(2d,2p) level using the PMP4(SDTQ) method to remove spin contamination.²⁴⁰ Table 11.13 gives the calculated rates,  $E_a$ , and the derived atmospheric lifetimes for the halogenated methanes based on the reaction with  $\text{HO}\cdot$ . The atmospheric lifetimes are computed in relation to the known rate for  $\text{CH}_3\text{CCl}_3$ .

**Table 11.12. Computed Barriers for Identity Hydrogen Atom Abstraction Reactions**

Saturated		Conjugated	
R	$E_a$	R	$E_a$
$\text{CH}_3\cdot$	15.8	$\text{CH}_2=\text{CHCH}_2\cdot$	15.7
$\text{CH}_3\text{CH}_2\cdot$	10.1	$(\text{CH}_2=\text{CH})_2\text{CH}\cdot$	20.0
$(\text{CH}_3)_2\text{CH}\cdot$	8.3	$\text{PhCH}_2\cdot$	15.7
$(\text{CH}_3)_3\text{C}\cdot$	10.9 ^a	$\text{Ph}_2\text{CH}\cdot$	19.3

a. This value is believed to be overestimated by the PM3 method.

²³⁸ D. M. Camioni, S. T. Autrey, T. B. Salinas, and J. A. Franz, *J. Am. Chem. Soc.*, **118**, 2013 (1996).

²³⁹ R. Atkinson, *Chem. Rev.*, **86**, 69 (1986).

²⁴⁰ F. Louis, C. A. Gonzalez, R. E. Huie, and M. J. Kurylo, *J. Phys. Chem. A*, **105**, 1599 (2001).

**Table 11.13. Computed Rates,  $E_a$ , and Atmospheric Lifetimes for Halomethanes^a**

Compound	Number	$k_{298} \times 10^{-15}$	$E_a/R$	Lifetime (years)
CH ₃ F	2	21	1340	6.37
CH ₃ Cl	5	189	1015	1.55
CH ₃ Br	8	100	1190	2.47
CH ₂ F ₂	3	23	1595	3.59
CH ₂ FCl	11	80	1160	1.68
CH ₂ Cl ₂	6	433	510	0.43
CH ₂ ClBr	16	304	590	0.54
CH ₂ Br ₂	8	247	690	0.57
CHF ₃	4	0.28	2640	397
CHF ₂ Cl	12	9.1	1540	13.16
CHF ₂ Br	15	15	1375	6.03
CHFC1 ₂	13	115	765	1.18
CHCl ₃	7	870	10	0.15
CH ₂ FBr	17	30	1440	1.88
CHFBBr ₂	17	100	825	0.49
CHFC1Br	20	68	920	0.73
CHCl ₂ Br	18	264	330	0.16
CHClBr ₂	19	346	250	0.12

a. F. Louis, C. A. Gonzalez, R. E. Huie, and M. J. Kurylo, *J. Phys. Chem. A*, **105**, 1599 (2001).

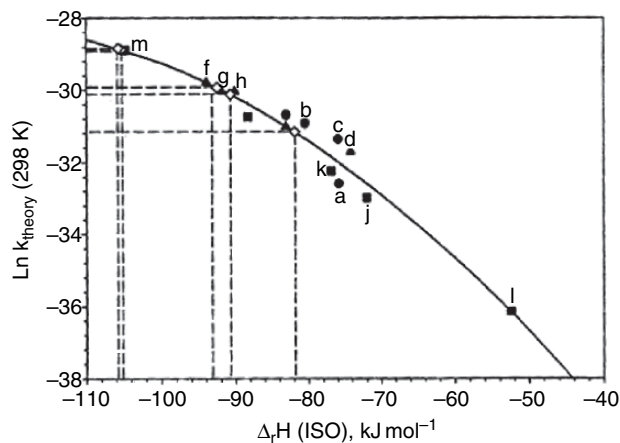


Fig. 11.20. Quadratic Evans-Polanyi relationship  $\ln k(298) = -1.368 \times 10^{-3} \Delta H_r^2 - 0.354 \Delta H_r - 50.96$ : (a) CH₃F, (b) CH₃Cl, (c) CH₃Br, (d) CH₂F₂, (e) CH₂FCl, (f) CH₂Cl₂, (g) CH₂ClBr, (h) CH₂Br₂, (i) CHF₃, (j) CHF₂Cl, (k) CHF₂Br, (l) CHFC1₂, (m) CHCl₃. From *J. Phys. Chem. A*, **105**, 1599 (2001).



**Table 11.14.** Comparison of Computed and Observed  $E_a$  (kcal/mol) for Reaction of Halomethanes with Cl.

Compound	$E_a$ (MP4/6-31G**)	$E_a$ (observed)
CH ₃ F	3.4	1.54 ± 1.0
CH ₂ F ₂	3.7	3.26 ± 1.0
CHF ₃	9.7	7.62 ± .16
CH ₃ Cl	3.9	2.50 ± 0.4
CH ₂ Cl ₂	1.6	2.7 ± 1.0
CHCl ₃	0.6	2.48 ± 1.0
CH ₂ CF	2.6	2.78 ± 1.0
CHClF ₂	5.4	4.51 ± 1.0
CHCl ₂ F	2.3	

The purpose of this study was to test the reliability of theoretical rate calculations to predict the atmospheric lifetime, an important property of these compounds:



These kinetic data lead to a quadratic rather than linear Bell-Evans-Polyani relationship:

$$\ln k_{298} = 1.368 \times 10^{-3} \Delta H^2 - 0.354 \Delta H - 50.96$$

The corresponding plot is shown in Figure 11.20.

A quadratic relationship between  $E_a$  and  $\Delta H$  was also noted for the reactions of Cl $\cdot$  and some of the same halomethanes.²⁴¹ Table 11.14 shows the computed and experimental  $E_a$  and Figure 11.21 shows the Evans-Polyani relationship. The

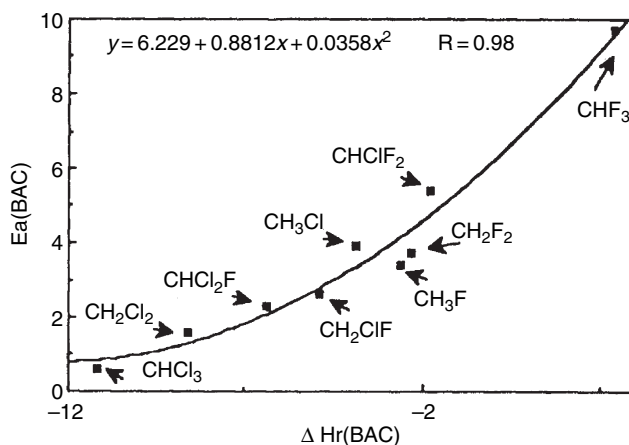


Fig. 11.21. Quadratic Evans Polyani relationship between  $E_a$  and BDE for Cl $\cdot$  and halomethanes. From *J. Phys. Chem.*, **98**, 111342 (1994).

²⁴¹ M.-T. Rayez, J.-C. Rayez, and J.-P. Sawerysyn, *J. Phys. Chem.*, **98**, 111342 (1994).

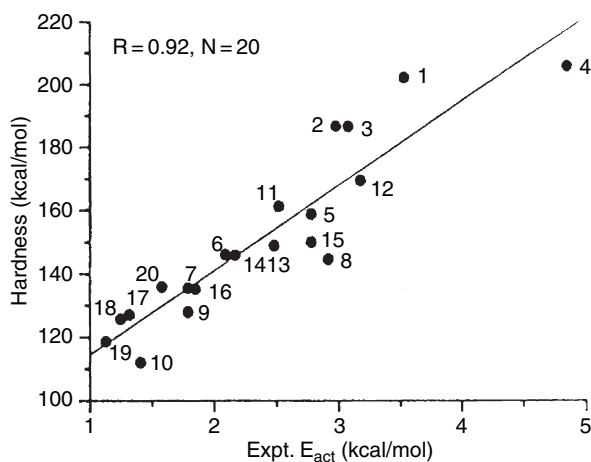


Fig. 11.22. Correlation between hardness and  $E_a$  for reaction of halomethanes with hydroxyl radical. Compounds are identified in Table 11.13. Reproduced from *Chem. Phys. Lett.*, **318**, 69 (2000), by permission of Elsevier.

observation of quadratic relationships is related to the concept of intrinsic barriers as formulated in the Marcus theory (see Section 3.3.2.3).

Chandra et al. considered the reactivity trends of the halomethanes toward  $\text{HO}\cdot$  in the DFT/hardness context.²⁴² There is a good correlation with the global hardness parameter. For  $\text{X} = \text{Cl}$  or  $\text{Br}$ , hardness decreases as more  $\text{Cl}$  and  $\text{Br}$  substituents are added. For fluorine the hardness trend is  $\text{CH}_3\text{F} = \text{CH}_2\text{F}_2 < \text{CH}_4 < \text{CHF}_3$ . This is in qualitative agreement with the rate data shown in Table 11.14. For the halomethanes, electron transfer to  $\cdot\text{OH}$  is exothermic, and  $\cdot\text{OH}$  is expected to be electrophilic in its reactions with the halomethanes. The trend of decreased reactivity with increased hardness can then be interpreted as decreased electron donation in the TS. Figure 11.22 shows the correlation between global hardness and the  $E_a$ .

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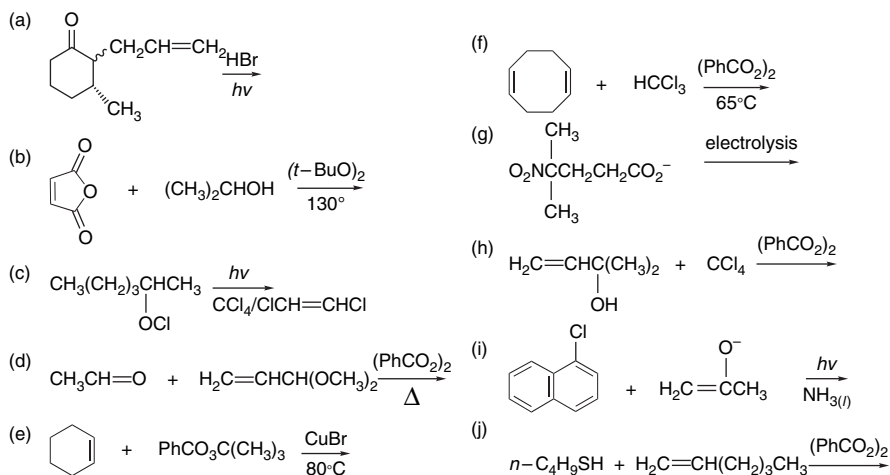
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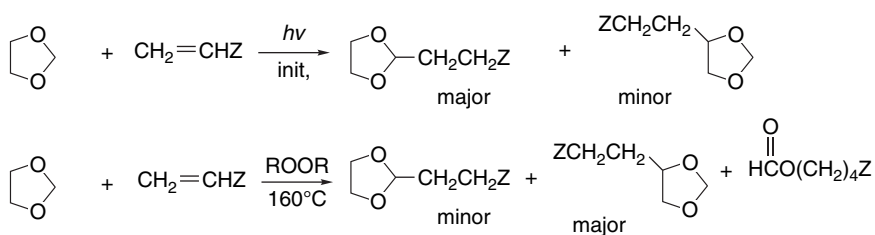
## Problems

(References for these problems will be found on page 1167.)

11.1. Predict the structure of the products of the following reactions.

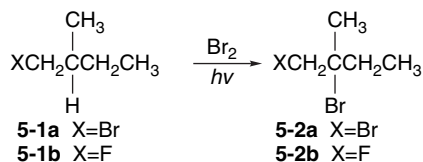


- 11.2. Using the data in Table III of Problem ref 11.2, calculate the expected product composition from gas phase chlorination and bromination of 3-methylpentane under conditions (excess hydrocarbon) that minimize polyhalogenation.
- 11.3. A careful study of the photoinitiated addition of HBr to 1-hexene established the following facts: (1) The chain length is about 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% at 4°C to about 22% at 63°C. (3) During the course of the reaction, a small amount of 2-hexene can be detected. Write a mechanism that is consistent with these results.
- 11.4. The irradiation of 1,3-dioxolane in the presence of alkenes and an initiator leads to 2-alkyldioxolanes along with small amounts of 4-alkyldioxolanes. The reaction is particularly effective with EWG-substituted alkenes such as diethyl maleate. When the reaction is done thermally with a peroxide initiator at 160°C, the product mixture is more complex and more of the 4-substituted dioxolane is formed. Account for the change in product ratio with increasing temperature.

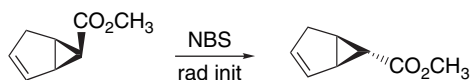


11.5. Provide a detailed mechanistic explanation for the following results.

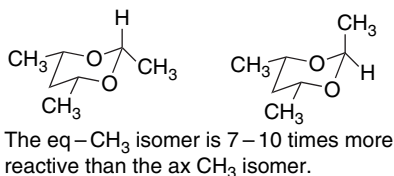
- a. Photochemically initiated bromination of resolved **5-1a**,  $\alpha_D + 4.21$ , affords **5-2a** which retains optical activity,  $\alpha_D - 3.23$ , but **5-1b** under the same conditions gives racemic **5-2b**.



- 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 the hydrogen atom at C(2) by the *t*-butoxy radical.



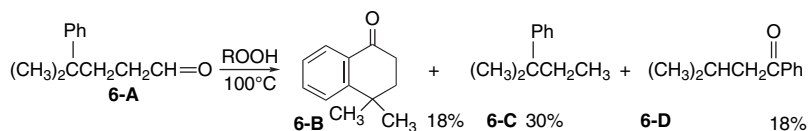
- d. Free radical chain chlorination of enantiomerically resolved 1-chloro-2-methylbutane yields six dichloro derivatives, of which four are optically active and two are not. Identify the products that are expected to fall in each group. Indicate the mechanistic significance of the identity of the optically active and inactive compounds.
- e. Irradiation of the hydrocarbon **5-A** in the presence of di-*t*-butyl peroxide generates a radical that can be identified as the 2-phenylethyl radical by its ESR spectrum. This is the only radical identified, even when the photolysis is carried out at  $-173^\circ\text{C}$ .



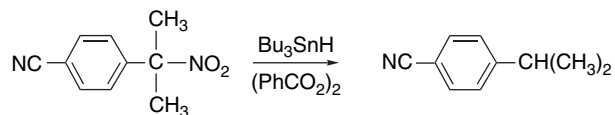
- 

- $$\begin{array}{c}
 \text{OCH}_3 \quad \text{O} \\
 \parallel \quad \parallel \\
 \text{CH}_3\text{CCCH}_2\text{COOC(CH}_3)_3 \\
 | \quad \quad \quad \mathbf{5-G} \\
 \text{Ph}
 \end{array}
 \xrightarrow{130^\circ\text{C}}
 \begin{array}{c}
 \text{OCH}_3 \quad \text{O} \\
 \parallel \quad \parallel \\
 \text{CH}_3\text{CCCH}_2\text{OC(CH}_3)_3 \\
 | \quad \quad \quad \mathbf{5-H} \\
 \text{Ph}
 \end{array}
 + \begin{array}{c}
 \text{O} \quad \text{Ph} \\
 \parallel \quad | \\
 \text{CH}_3\text{CCCH}_2\text{CHCH}_3 \\
 \mathbf{5-I}
 \end{array}
 + \begin{array}{c}
 \text{O} \quad \text{Ph} \\
 \parallel \quad | \\
 \text{CH}_3\text{CCCH}=\text{CCH}_3 \\
 \mathbf{5-J}
 \end{array}
 + \begin{array}{c}
 \text{O} \quad \text{Ph} \\
 \parallel \quad | \\
 \text{CH}_3\text{CCCH}_2\text{C}=\text{CH}_2 \\
 \mathbf{5-K}
 \end{array}$$
- 26%                      15%                      9%                      9%

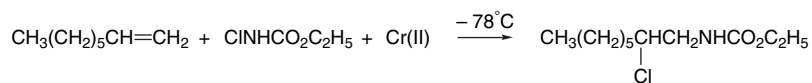
a.


$$\text{Ph}(\text{CH}_2)_3\text{CH}=\text{CH}_2 \xrightarrow[140^\circ\text{C}]{\text{ROOH}} \text{Product}$$

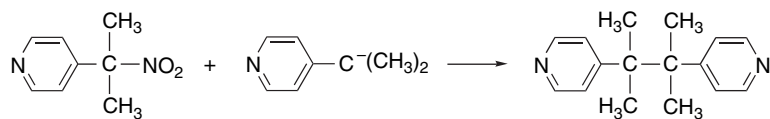
c.



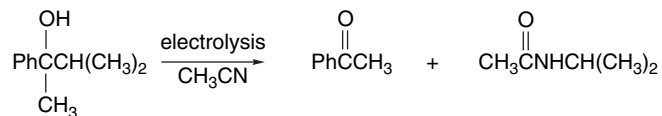
d.



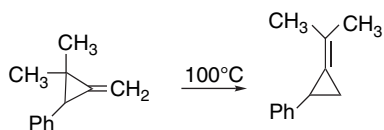
e.



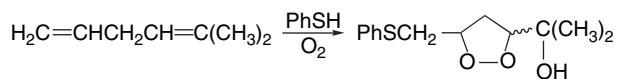
f.



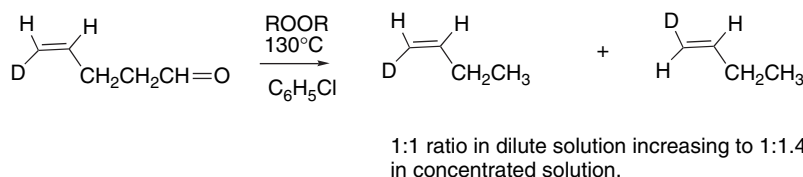
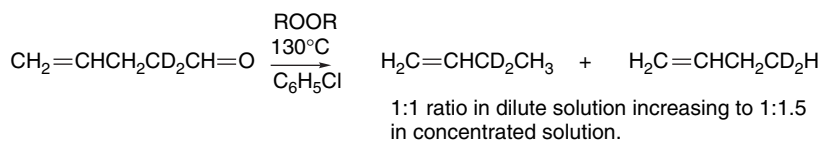
g.



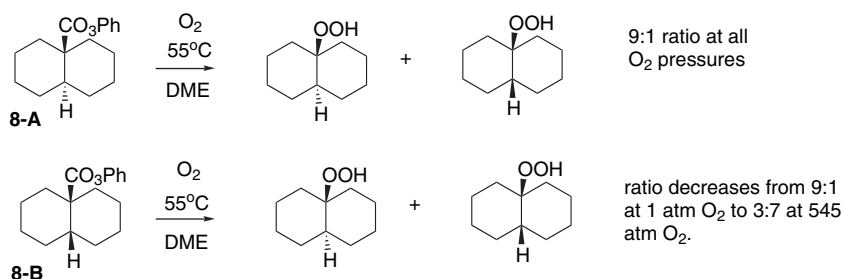
h.



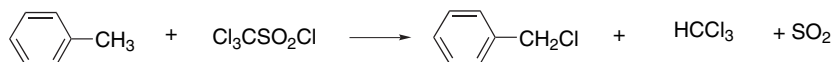
11.7. The decarbonylation of the two isotopically labeled pentenals shown below have been studied. Explain why the distribution of deuterium found in the products is affected by solution concentration.



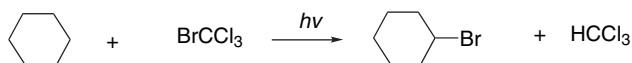
- 11.8. Decomposition of the *trans*-decalyl peroxyester **8-A** gives a 9:1 ratio of *trans*- and *cis*-hydroperoxides at all the oxygen pressures studied. The product ratio from the *cis*-peroxyester **8-B** is dependent on oxygen pressure. At 1 atm O₂ it is 9:1 *trans*:*cis*, identical to the *trans* isomer, but the ratio decreases and eventually inverts with increasing O₂ pressure. At 545 atm, the ratio is 7:3, favoring the *cis*-hydroperoxide. What deductions about the stereochemistry of the 9-decalyl radical can be made from these observations?



- 11.9 a. Trichloromethanesulfonyl chloride can chlorinate hydrocarbons as described in the stoichiometric equation below. The reaction occurs by a free radical chain process. Write at least two possible sequences for chain propagation.



- b. The chlorination has been compared with bromination by BrCCl₃ carried out under radical chain conditions. In this reaction, cyclohexane is about one-fifth as reactive as toluene, but in the chlorination by trichloromethanesulfonyl chloride, cyclohexane is about three times more reactive than toluene. Does this information permit a choice between the chain sequences you have written in part (a)?

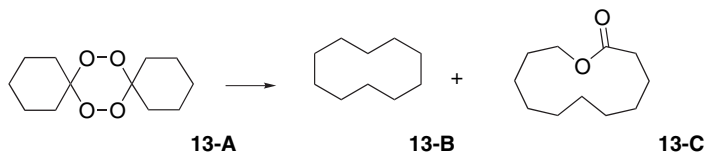


- 11.10. A highly selective photochemical chlorination of esters, amides, and alcohols can be carried out in 70–90% H₂SO₄ using *N*-chlorodialkylamines as the

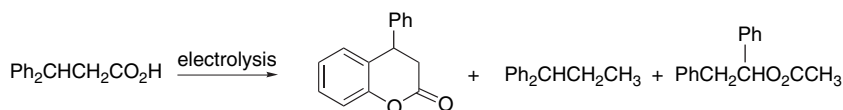
- 11.12. Write a stepwise mechanism for each of the radical rearrangement reactions listed in Scheme 11.6.



- 11.13. The *spiro* peroxide **13-A**, which is readily prepared from cyclohexanone and hydrogen peroxide, decomposes thermally to give substantial amounts of cyclodecane (**13-B**) and 11-undecanolactone (**13-C**). Account for the efficient formation of these macrocyclic compounds.

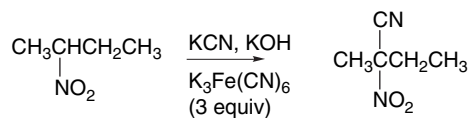


- 11.14. Methylcyclopropane shows strikingly different reactivity toward chlorine and bromine under radical chain conditions in  $\text{CH}_2\text{Cl}_2$  solution. The main product with chlorine is chloromethylcyclopropane (56%), along with smaller amounts of 1,3-dichlorobutane and 1,3-dichloro-2-methylpropane. Bromine gives only 1,3-dibromobutane. Offer a mechanistic explanation.
- 11.15. Electrolysis of 3,3-diphenylpropanoic acid in acetic acid–sodium acetate solution gives the products shown below. Propose mechanisms for the formation of each product.

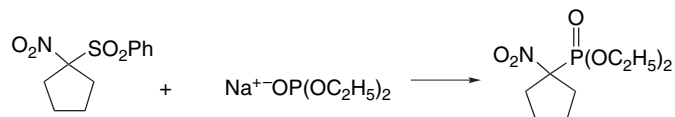


- 11.16. Write a mechanism to account for the observed product of each of the following reactions:

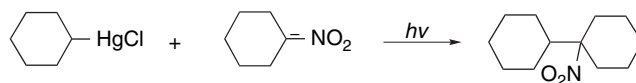
a.



b.

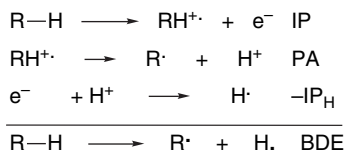


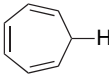



c.



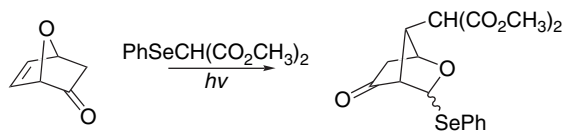
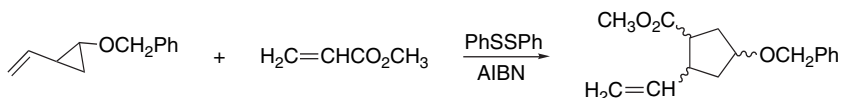
- 11.17. The *N*-benzoyl methyl esters of the amino acids glycine, alanine, and valine have been shown to react with *N*-bromosuccinimide to give the  $\alpha$ -bromo derivatives. The order of reactivity is glycine > alanine > valine in the ratio 23:8:1. Account for the formation of the products and the order of the reactivity.

- 11.18. By measurement in an ion cyclotron resonance mass spectrometer, it is possible to measure the proton affinity (PA) of free radicals. These data can be combined with ionization potential (IP) data according to the scheme below to determine the bond dissociation energy (BDE) of the corresponding C—H bond. The ionization potential of the H atom is 313.6 kcal/mol. Use the data given below to determine the relative stabilization of the various radicals relative to methyl, for which the BDE is 104 kcal/mol. Compare the BDE determined in this way with the comparable values given in Table 3.20.



	IP	PA
PhCH ₂ —H	203	198
 —H	190	200
 —H	198	199
 —H	224	180
CH ₂ =CHCH ₂ —H	224	180
 —H	232	187
CH ₂ =CH—H	242	183

- 11.19. Provide stepwise mechanisms for the following reactions:

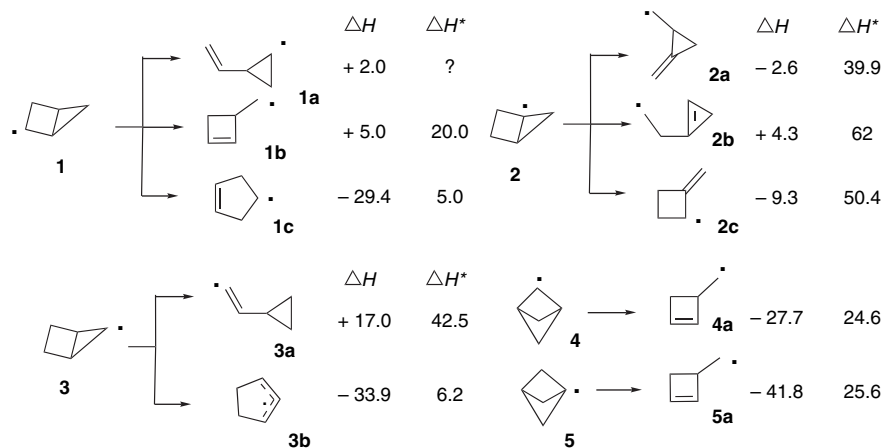


- 11.20. The energy of some free radicals derived from small strained hydrocarbons has been calculated at the MINDO/3 level. The  $\Delta H$  and  $\Delta H^\ddagger$  were calculated for several possible fragmentations and are given below. Consider the stereoelectronic and steric

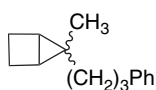
factors involved in the various fragmentations. Explain the large variations in  $\Delta H$  and  $\Delta H^\ddagger$  and identify structural features that lead to facile fragmentation.

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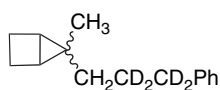
PROBLEMS



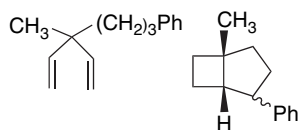
- 11.21. The pyrolysis of a mixture of the two stereoisomers of 5-methyl-5-(3-phenylpropyl)bicyclo[2.1.0]pentane leads to a mixture of three products. The two reactants equilibrate under the reaction conditions at a rate that exceeds product formation. When deuterium is introduced into the propyl side chain, there is no intermolecular deuterium scrambling. Write a mechanism for formation of each product and indicate how the deuterium results help to define the mechanism. What can be said about the lifetime of the intermediates in your mechanism?



reactants



deuterated reactants



products