2 Small-Radical Chemistry

MARTIN NEWCOMB

University of Illinois at Chicago, Chicago, Illinois

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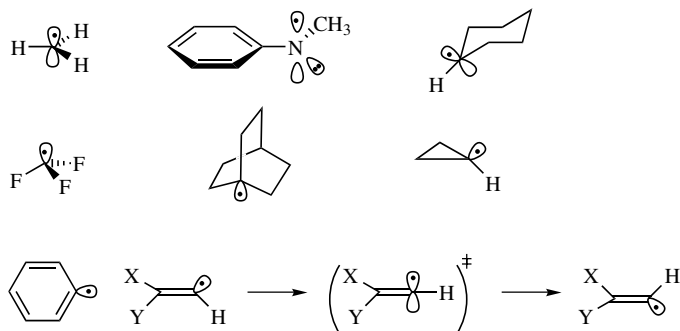
This chapter contains a brief overview of small radical chemistry focusing primarily on carbon-centered radicals and their reactions.
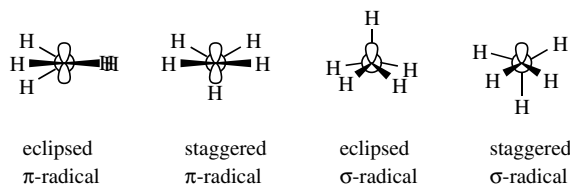
2.1   STRUCTURES OF RADICALS

Most organic compounds are configurationally stable, and one is concerned mainly with dynamic processes that interconvert the conformations of the species. For many radicals, however, configurations interconvert by low-energy pathways. Thus, although most useful reactions of radicals are fast, configurational interconversions as well as conformational interconversions can be faster. Much of the current research in applications of radicals in synthesis is focused on controlling radical structure for diastereoselective reactions.

Radical configurations are described according to whether the odd electron is in a *p* orbital (a π radical) or in a hybrid orbital (a σ radical); examples are shown in Fig. 2.1. A trivalent π radical is planar, and a trivalent σ radical is pyramidal. Each configuration has staggered and eclipsed conformations that interconvert by bond rotation as shown for the ethyl radical in Fig. 2.2. Staggered and eclipsed conformations of a pyramidal radical are similar to those in a hydrocarbon. For a planar radical, the staggered and eclipsed terms refer to the positions of the substituents at the radical center and not to the *p* orbital containing the odd electron.

Figure 2.1   Examples of π (*top* drawings) and σ radicals. The transition state for inversion of the vinyl radical is a π radical.

| eclipsed	staggered	eclipsed	staggered
π-radical	π-radical	σ-radical	σ-radical

Figure 2.2   Possible conformations and configurations for the ethyl radical.

A divalent radical can have either a linear (π-type) or bent (σ-type) configuration. As with the trivalent radical, the difference is that the odd electron is localized either in a p orbital (linear) or in a hybrid orbital (bent). For radicals localized on an sp^2 hybridized atom containing a lone pair, such as nitrogen or oxygen, two low-energy electronic states exist. The odd electron can be in the p orbital (π-type radical) or in an sp^2 hybrid orbital (σ-type radical).

In carbon-centered radicals, the energy difference between planar and pyramidal radical configurations is small. The methyl radical is planar (see Fig. 2.1), but alkyl substitution leads to a slight preference for pyramidalization that increases for the series of primary, secondary, and tertiary radicals as judged by the hyperfine couplings of the ^{13}C nucleus at the radical center. Ultimately, in the *tert*-butyl radical, the deviation from planarity is about 10°, and the barrier for interconversion is about 0.5 kcal/mol.[1]

Substitution of electronegative atoms on a trivalent carbon radical center favors pyramidalization. For example, pyramidalization increases in the series mono-, di-, and trifluoromethyl radicals, and various techniques resulted in estimates that the trifluoromethyl radical is deformed from planarity by 13–18°, close to tetrahedral (deformation of 19°). The effect is a result of the interaction between the semi-occupied molecular orbital (SOMO) containing one electron and the lowest unoccupied molecular orbital (LUMO). In a planar radical, SOMO and LUMO are orthogonal, but they interact in a pyramidal radical. Electronegative substituents increase in the energy level of SOMO by π-donation and decrease the energy level of LUMO by σ withdrawal. As the SOMO and LUMO approach one another in energy, pyramidalization is increasingly favored. Substitution of a π conjugating withdrawing group favors the planar radical structure (Fig. 2.3).

The conformational barriers in acyclic alkyl radicals are diminishingly small, resulting in very fast bond rotations. For a simple single-bond rotation as in the ethyl radical, various measurements give barriers in the range of 0.05–0.5 kcal/mol.[1–3] Heteroatoms and conjugating groups increase the rotational barriers. For example, the barrier to rotation in the methanol radical ($^\bullet$CH$_2$OH) is 4.6 kcal/mol, and that in the acetone radical [$^\bullet$CH$_2$C(=O)CH$_3$] is 9.4 kcal/mol. A state of the art ESR and computational study of a methacrylate-derived radical found a barrier for rotation of 2.9 kcal/mol.[4] The conformational barriers for radicals adjacent to a carbonyl group are high enough that the rate of rotation can be slower than the rates of unimolecular or bimolecular radical reactions, as shown for an α-amide radical,[5] and this potentially has an effect on the stereoselectivity in reactions of these types of

SOMO   LUMO   orthogonal   interacting
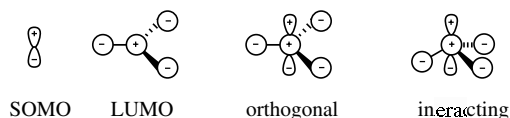
Figure 2.3   SOMO and LUMO orbitals of a trigonal radical center do not interact in a planar radical but do interact when the radical is pyramidal.

radicals. One notes that modern computational methods appear to provide highly reliable conformational barriers for radicals.[6]

The structures of cycloalkyl radicals have been studied by ESR spectroscopy.[7] The cyclohexyl radical has a nearly planar radical center with a low barrier to inversion (3.4 kcal/mol). Even the cyclobutyl radical has an essentially planar radical center, although a pyramidalized structure should have less strain. In the case of the cyclopropyl radical, a pyramidal structure is favored, but the rate of inversion through the planar structure is fast as determined by ESR line broadening studies that gave $k = 1 \times 10^{12}$ s^{-1} at 70°C.[8] Heteroatoms adjacent to the radical center in cyclic radicals result in anomeric effects; in the case of the 2-methyltetrahydropyran-2-yl radical, the preferred structure has the methyl group in an axial position such that the radical orbital overlaps with the oxygen lone pair.[9]

Bridgehead radicals in relatively small bicyclic structures are pyramidal by virtue of the geometry of the molecules. The fact that these radicals are readily generated from bridgehead halides is a reflection of the small energy difference between planar and pyramidal carbon-centered radicals.

Carbon radicals at unsaturated centers are σ-type radicals. That is, they are bent with an sp^2 hybridized carbon atom. This structure is enforced for the phenyl radical. In the case of the vinyl radical, a bent structure is determined by ESR spectroscopy with a low barrier for inversion of 3 kcal/mol ($k = 4 \times 10^{10}$ s^{-1} at 300 K).[10] Computational work on vinyl radicals indicates that sigma substituents give bent structures and pi substituents at the radical center (vinyl, phenyl, formyl) give linear vinyl radicals.[11] Formyl radicals are bent.[12]

Simple nitrogen-centered radials (dialkylaminyl, dialkylaminium) are π-type radicals. Aniline radicals are π-type unless the aromatic ring has electron-withdrawing substituents that favor π donation from nitrogen. The electronic structures of oxygen-centered radicals are quite close in energy.

2.2   RADICAL STABILITIES

2.2.1   Stabilities Evaluated by Hydrogen Atom Bond Dissociation Energies

Knowledge about the stabilities of radicals is important for understanding how readily radical reactions will occur. Hydrogen atom bond dissociation energies (BDEs) can be used to gauge the stability of a particular radical type. The BDE is the energy for homolytic cleavage of a bond at 25°C. Table 2.1 contains a list of BDE values for representative organic compounds. Most of these values are from recently published works.[13–16] For carbon-centered radicals, any type of substitution at the radical center results in increased stability as judged by a reduction in the BDE value for the parent compound. This phenomenon is a feature of the unpaired electron in a semi-occupied molecular orbital (SOMO) and the electron deficient nature of a radical. Any group that provides an orbital that can mix with the SOMO will result in stabilization. In the case of donors, a filled HOMO is close in energy to the semi-occupied MO of the radical (SOMO), and the newly formed orbitals will contain a pair of

**TABLE 2.1   Bond Dissociation Energies for Selected Compounds**[a]

Molecule	BDE	Molecule	BDE
CH_4	104.9 ± 0.1	H H	104.2
CH_3CH_3	101.1 ± 0.4	H_2O	119.30 ± 0.05
$(CH_3)_2CH$ H	98.6 ± 0.4	H_2O_2	88
$(CH_3)_3C$ H	96.5 ± 0.4	CH_3O H	104.2 ± 0.9
c C_3H_6	106	RCO_2 H	ca. 105
H_2C CH_2	111.2 ± 0.8	PhO H	87
Ph H	111.2 ± 0.8	CH_3S H	87.4 ± 0.5
HC CH	132.8 ± 0.7	PhS H	ca. 80 82
H_2C $CHCH_2$ H	88.2 ± 2.1	PhSe H	78 ± 4
$PhCH_2$ H	88.5 ± 1.5	NH_3	108.2 ± 0.3
$HOCH_2$ H	96.06 ± 0.15	Et_3Si H	95.1
$HC(O)CH_2$ H	94.3 ± 2.2	$(Me_3Si)_3Si$ H	87.5
CH_2O	88.04 ± 0.16	Bu_3Ge H	88.6
$CH_3C(O)$ H	89.4 ± 0.3	Bu_3Sn H	78.6
$HOC(O)$ H	>89.5		
$NCCH_3$	94.8 ± 2.1		

[a] Bond dissociation enthalpies at 298 K. Values from Refs. 13 15. PhSeH value from Ref. 16.

electrons in the lower-energy orbital but only a single electron in the higher-energy orbital. In the case of acceptors, the LUMO orbital is close in energy to the SOMO, and a single electron will occupy the lower energy combination orbital. Delocalization of the radical center with π bonds also results in stabilization, and alkyl groups stabilize a radical by interaction of the electron pairs in the σ bonds with the radical center in π-type bonding.

2.2.2   Stability versus Persistence

Despite the stabilization afforded by various groups, most radicals react with one another with diffusion-controlled rates. Some radicals are long-lived, however, and this can be a result of either thermodynamics, sterics that prevent coupling reactions, or both. Examples of some long-lived radicals are shown in Fig. 2.4. The triphenylmethyl (or trityl) radical, the radical identified by Gomberg in 1900 in work that is typically regarded as the beginning of radical chemistry, is stabilized by extensive conjugation. If trityl radicals coupled to give hexaphenylethane, the product would be highly strained, and the actual trityl dimer is the quinoid compound shown in the figure. At equilibrium, enough trityl radical is present to give solutions a yellow color that Gomberg observed. Nitroxyl radicals, represented by 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), are thermodynamically favored in comparison to their dimers because of the very low energy of the O—O bond. Nitroxyl radicals with no hydrogens in the β positions to the nitroxyl are long-lived, and TEMPO is commercially available. Galvinoxyl is another well-known stable radical that is often used to calibrate signal intensities in ESR studies.

trityl radical

TEMPO

galvinoxyl
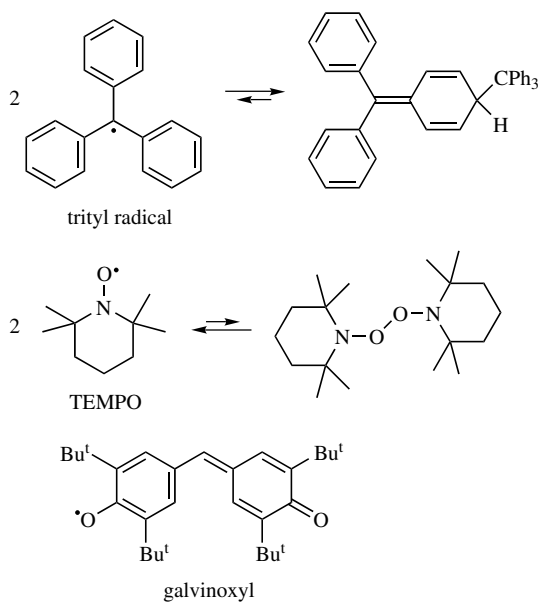
Figure 2.4   Examples of persistent radicals.

2.3   RADICAL REACTIONS
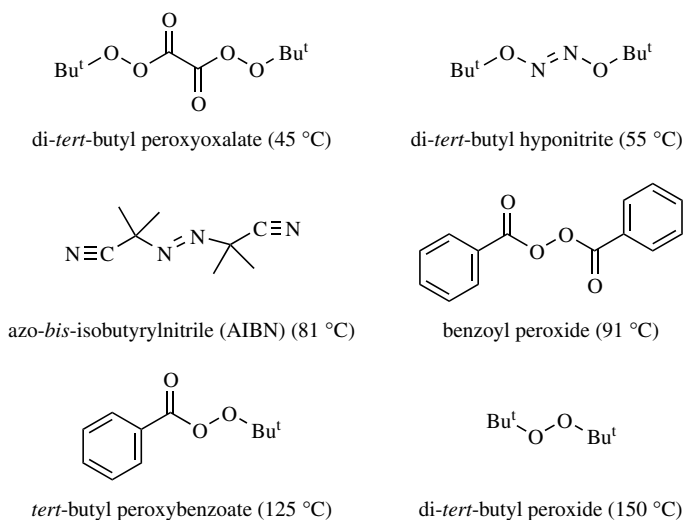
2.3.1   Elementary Radical Reactions

The elementary reactions of small-radical chemistry can be divided into three classes of reactions: those that produce radicals (initiation reactions), those in which a radical reacts to give a radical product (propagation reactions), and those in which radicals are lost (termination reactions). In most synthetic applications of radical chemistry, the propagation steps are the ones that form the desired products, but some useful radical sequence exist wherein the desired products are produced in termination steps as discussed later.

There is an important difference in the nomenclature of reactions in small-radical chemistry and those in polymer radical chemistry where reactions are divided into four elementary groups. Initiation and termination are the same in both, but the propagation reactions of small-radical chemistry are divided into two types of polymer reaction: propagations and transfers. A "propagation" reaction in polymer chemistry is one that increases the chain length of the growing polymer, whereas a "transfer" reaction is one that terminates the polymer chain but does not result in loss of radicals. Examples of polymer transfer reactions are atom and group transfer processes and radical fragmentations.

2.3.2 Initiation Reactions

Various methods can be used to initiate radical reactions, and they can be divided into the broad areas of thermolyses, photolyses, and electron transfer reactions. Most often in organic synthetic sequences, initiation involves a thermolysis reaction of an initiator that contains a weak bond, especially an azo or peroxy compound. Photolysis of many compounds will initiate radical reactions either by homolytic cleavage of a weak bond or by production of an excited state that reacts by electron transfer or atom   ion, but synthetic chemists seldom use this method except in select cases. Electron transfer processes are involved in many reactions of metals with organic substrates, but strong reducing agents will also reduce radicals to anions or organometallic species; therefore, the method is most useful when the reductant or oxidant is not strong enough to intercept the radical rapidly.

Many thermal initiators are available commercially, and these are commonly used in synthetic conversions. In the case of chain reactions, only a small amount of initiator may be required, typically 1 5 mol% relative to substrate. A radical conversion is usually conducted in refluxing solvent (benzene or toluene have been widely used) with the initiator selected to have a half-life of about 1 hour at the reaction temperature. Figure 2.5 shows some of the more common thermal initiators and lists the approximate temperature for decomposition half-lives of 1 h.[17–19] Di-*tert*-butyl peroxide, *tert*-butyl peroxybenzoate, benzoyl peroxide, and AIBN have long shelf lives and are commercially available. The more reactive thermal initiators, di-*tert*-butyl peroxyoxalate[20] and di-*tert*-butyl hyponitrite[21] are usually used soon after preparation. Radical chain reactions are often conducted at temperatures within 10°C of the temperatures shown in Fig. 2.5 for a 1-h half-life of the initiator, but

di-*tert*-butyl peroxyoxalate (45 °C)   di-*tert*-butyl hyponitrite (55 °C)

azo-*bis*-isobutyrylnitrile (AIBN) (81 °C)   benzoyl peroxide (91 °C)

*tert*-butyl peroxybenzoate (125 °C)   di-*tert*-butyl peroxide (150 °C)

Figure 2.5 Common thermal initiators. The temperatures in parentheses are those at which the initiator has a half life of 1 h.

one can operate at higher temperatures by adding the initiator slowly over the course of several hours.

A relatively new thermal initiation procedure can be employed over a wide range of temperatures and has rapidly gained popularity. Admission of a small amount of oxygen and catalytic amounts of Et_3B into a reaction mixture will result in initiation.[22] In fact, adventitious oxygen often is sufficient for initiation such that Et_3B is the only necessary additive. The method has been used at temperatures ranging from -78 to $110°C$, and it appears to be especially attractive when low reaction temperatures are necessary in order to obtain high stereoselectivity in radical functionalization reactions.

Photochemical initiation of radical reactions is possible with a wide range of compounds. The photochemical event either creates a reactive state or cleaves a weak bond homolytically to produce radicals. Photochemical initiation is quite popular in polymer radical chemistry because it is readily controlled and allows the production of commercial formulations with room-temperature stability, and photoinitiators used in polymer chemistry represent a multi-million-dollar business. Many of the commercial initiators are aryl ketones and phosphine oxides that are tuned for specific wavelength initiation. Somewhat ironically, these initiators are not commonly used in small radical chemistry, despite the large amount of photochemical information available.

Photoinduced electron transfer (PET) processes are more common in small-radical chemistry.[23,24] In these reactions, an excited state is produced photochemically that is either a strong oxidant or reductant, and this excited-state species then reacts in an electron transfer reaction with another molecule. For example, chloranil is an oxidant in the ground state with an oxidation potential of 0.32 V versus NHE,[25] but triplet chloranil is a much more powerful oxidant. Irradiation of a stable solution of chloranil and an enol ether in acetonitrile with 355-nm laser light gives the chloranil triplet (lifetime of several microseconds) that oxidizes the enol ether to the corresponding radical cation in a diffusion-controlled process (Fig. 2.6).[26,27] Much of PET chemistry involves reactions of the radical cations and radical anions that are formed in the ET step, but some of these species are capable of fragmenting to give radicals. When that occurs, the PET reaction can result in the same type of initiation as one would have in a homolysis reaction.
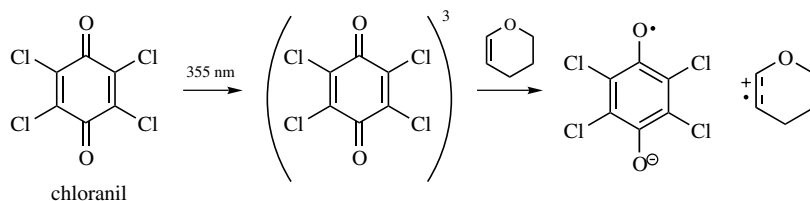

Figure 2.6   An example of photochemically induced electron transfer (PET). Chloranil is excited photochemically to give a relatively long lived triplet state that oxidizes an enol ether to the corresponding radical cation. The chloranil radical anion is the byproduct of the reaction.

Redox initiation of radical reactions can be divided into two types of processes. One type involves either reduction or oxidation of a substrate to give a radical that reacts in one or more radical functionalization steps before a second reduction or oxidation reaction occurs. These types of processes consume two equivalents of reductant or oxidant when chemical redox is involved or are overall two-electron processes when performed electrochemically. They are discussed later in the section on nonchain radical reactions.

The second type of redox initiation also involves nonchain reactions, but the initiator serves as a catalyst. For example, a copper(I) complex will react with an alkyl halide to give a copper(II) complex and an alkyl radical in a process that is not thermodynamically favored [Eq. (2.1)]. The alkyl radical can react in a functionalization reaction, and the newly formed radical product can react with the copper(II) complex to return the thermodynamically favored copper(I) complex and a new, functionalized, alkyl halide. The reaction sequence can be employed in small-radical chemistry in, for example, formation of cyclic product from an acyclic alkene,[28] and it has been incorporated into a powerful ''living radical polymerization'' sequence [atom transfer radical polymerization (ATRP)][29,30] that is discussed in Chapter 11.

$$\text{Ligated Cu(I)} + \text{R}-\text{X} \rightleftarrows \text{ligated Cu(II)X} + \text{R}^{\bullet} \qquad (2.1)$$
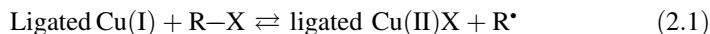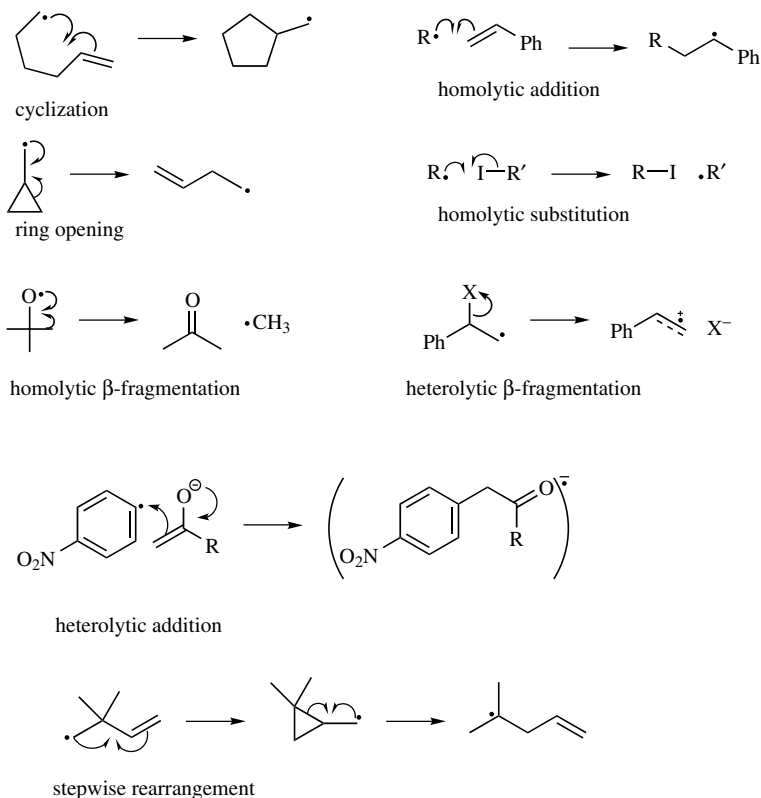
2.3.3 Elementary Propagation Reactions

Radical reactions in nature, in synthesis, and in polymerizations inevitably involve a sequence of reactions. A wide range of unimolecular and bimolecular elementary radical propagation reactions are possible, and some common ones are shown in Fig. 2.7. Note that some reaction types can occur in either a homolytic or heterolytic version, such as for the β-fragmentation reactions shown in the figure. In some cases, differentiation between homolytic and heterolytic pathways might not be obvious, and the pathway might change as a function of solvent polarity. Some concerted radical reactions (migrations and 1,3-eliminations) are implicated from computational work,[31] but they have not been documented experimentally. The concerted reactions result in the same products that would arise from a fragmentation followed by recombination or substitution, respectively, or from the stepwise rearrangement shown in Fig. 2.7, and differentiation between concerted and ion pair or radical pair reactions is subtle.

2.4 RADICAL CHAIN REACTIONS

Most useful radical processes involve a complex series of elementary reactions. In synthetic applications and in polymerizations, these sequences typically constitute chain reactions. The characteristic features of a chain reaction are (1) a series (two or more) of propagation steps exists wherein the radical product in one step is a reactant in another step and (2) the velocities of the propagation steps are fast

cyclization

homolytic addition

ring opening

homolytic substitution

$R-I$ •R′

homolytic β-fragmentation

•CH_3

heterolytic β-fragmentation

heterolytic addition

stepwise rearrangement

Figure 2.7   Some common radical propagation reactions.

relative to the velocity of radical radical reactions that result in termination. The latter property is critically important; if it does not hold, the chain reaction collapses, and the reaction sequence is comprised of initiation and termination steps and may or may not contain propagation reactions. These non-chain reactions are discussed in Section 2.5.

2.4.1   Tin Hydride Radical Chain Reactions

The various components of a radical chain reaction are illustrated in one of the more common types of radical chain reactions, the tin hydride protocol, shown in Fig. 2.8. The method is named after Bu_3SnH, the reagent used almost exclusively in early studies. In this example, initiation is accomplished by thermolysis of AIBN that gives radicals that react with Bu_3SnH. In the propagation sequence, the stannyl radical reacts with an alkyl halide, pseudohalide, or other radical precursor to give Bu_3SnX and a carbon- or heteroatom-centered radical. A radical functionalization
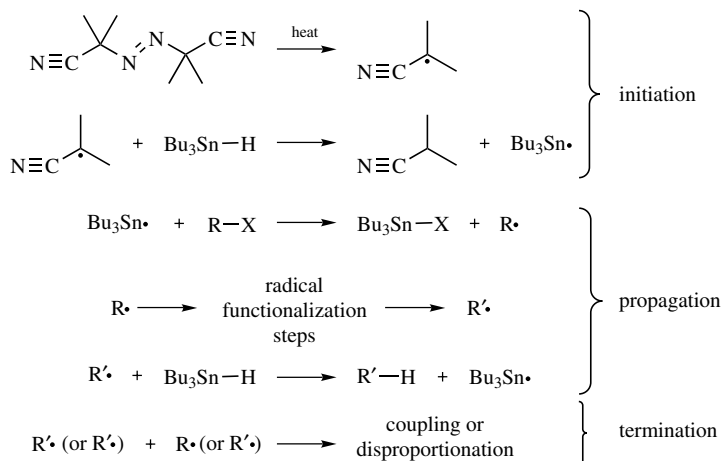
Figure 2.8   Elementary processes in the tin hydride reaction protocol.

reaction or multiple functionalization reactions follow. The final step in the propagation sequence is reaction of a radical with Bu_3SnH to generate another stannyl radical.

Radical radical coupling and disproportionation reactions terminate the chain sequence. In principle, stannyl radicals could be involved in the termination reactions, but the velocities of the termination reactions are controlled by the radical concentrations, and, as discussed later, the stannyl radical usually is present in much smaller concentrations than alkyl radicals.

Many radical chain reactions involve halogen or pseudohalogen transfer steps that give the initial radical from a halide or pseudohalide precursor and hydrogen atom transfer steps that give the final product of the chain reaction. Bu_3SnH provides a nearly ideal combination of high reactivity of the stannane with carbon-centered radicals and high reactivity of the stannyl radical with halide and pseudo-halide precursors, but concerns about the toxicity of tin compounds resulted in a number of alternative H-atom donors that can be used in the "tin hydride" method. The success of a radical chain process is dependent on the velocities of the propagation steps that must be greater than those of the termination steps, and this places a practical limit on the alternatives to tin hydride. For example, germanium- and silicon-centered radicals will react with halides even faster than tin–centered radicals, so germanes and silanes will efficiently replace stannanes for the reactions that produce carbon-centered radicals. Bu_3GeH reacts about 4% as fast as Bu_3SnH with alkyl radicals at room temperature, and trialkylgermanes can be used successfully in chain reactions with alkyl radicals[14] (see Section 2.6.4.1 for rate constants). On the other hand, Et_3SiH reacts nearly four orders of magnitude less rapidly with alkyl radicals than does Bu_3SnH, and simple trialkylsilanes cannot be used for chain reactions with alkyl radicals. The slow reactivity of Et_3SiH with alkyl radicals is in part a
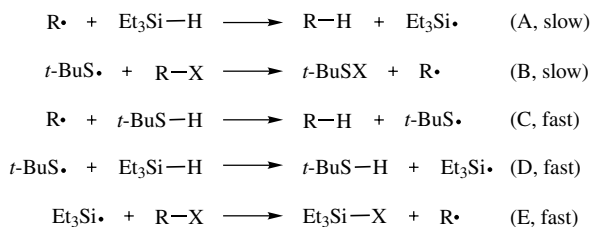
consequence of high Si—H bond energy of this silane (95 kcal/mol), and reduction of the Si—H bond energy by replacing the alkyl groups with thio and silyl groups gives silanes that react fast enough with alkyl radicals to propagate chain reactions.[14] One popular alternative to Bu_3SnH is *tris*-(trimethylsilyl)silane, $(TMS)_3SiH$,[32] which has an Si—H bond energy of 84 kcal/mol and reacts with alkyl radicals about 20% as fast as does Bu_3SnH.

Chain reactions also will fail if the halogen   ion reaction (or other radical generation reaction) is not fast. For example, thiols and selenols react with alkyl radicals faster than Bu_3SnH, but the thiyl and selenyl radicals do not   halogen atoms rapidly from alkyl halides and cannot be used in chain reactions with alkyl halides. There is a modification that will allow the use of thiols and selenols as reducing agents in radical chain reactions with alkyl halides, however. One can successfully use a combination of a silane and a thiol (or a stannane and selenol). For example, when *t*-BuSH and Et_3SiH are used together, an alkyl radical reacts rapidly with the thiol to give a thiyl radical, the thiyl radical reacts rapidly with the silane to give a silyl radical, and the silyl radical rapidly   s halogen from an alkyl halide. Thus, although neither Et_3SiH nor *t*-BuSH would successfully propagate a chain reaction with an alkyl halide, the combination of them would (Fig. 2.9).

A variety of radical precursors can be used in the general tin hydride protocol. Alkyl radicals can be produced from alkyl chloride or, better, alkyl bromides; the highly reactive alkyl iodides could be used but are not necessary. One can substitute the pseudohalogens RSPh and RSePh for alkyl halides where phenyl sulfides react about as rapidly as alkyl chlorides and phenyl selenides react about as rapidly as alkyl bromides. The use of a phenyl sulfide (PhSR) instead of a dialkyl sulfide (RSR′) assures one of the desired regioselectivity of the group transfer reaction due to the "instability" of the phenyl radical. When aryl radicals are desired, aryl iodides can be employed.

2.4.2   Alkylmercuric Halide Protocol

A number of early radical studies were accomplished with alkylmercuric halides as the radical precursors reacting with $NaBH_4$. The relative ease in preparation of the precursors is an advantage of the method, but concerns about the toxicity of mercury

$$R• \;+\; Et_3Si—H \;\longrightarrow\; R—H \;+\; Et_3Si• \qquad (A,\ slow)$$

$$t\text{-BuS}• \;+\; R—X \;\longrightarrow\; t\text{-BuSX} \;+\; R• \qquad (B,\ slow)$$

$$R• \;+\; t\text{-BuS—H} \;\longrightarrow\; R—H \;+\; t\text{-BuS}• \qquad (C,\ fast)$$

$$t\text{-BuS}• \;+\; Et_3Si—H \;\longrightarrow\; t\text{-BuS—H} \;+\; Et_3Si• \qquad (D,\ fast)$$

$$Et_3Si• \;+\; R—X \;\longrightarrow\; Et_3Si—X \;+\; R• \qquad (E,\ fast)$$

Figure 2.9   Sequenced reactions involving a thiol and a silane. When a thiol and silane are present in a mixture with an alkyl halide, the sequence of reactions C E permits an efficient chain reaction.