

Chapter 2

Chain Reactions

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I. Definitions

A. A Free-Radical Reaction

A free radical is an atom or group of atoms containing an unpaired electron. A free-radical reaction then is any chemical reaction in which a species with an unpaired electron is involved at some stage along the reaction pathway. Although a free radical conceivably can be a starting material or a product in a reaction, in practice, free radicals are reaction intermediates in nearly every instance.

Free radicals (or, more simply, radicals) themselves can be separated into different types on the basis of their inherent reactivity. Persistent, stable, and reactive are terms frequently used to describe free radicals.¹ Persistent radicals have kinetic stability; that is, they have an extended lifetime due to shielding from approaching reactant molecules by groups in the vicinity of the radical center. Stable radicals are those for which delocalization of free-electron density leads to a thermodynamic stabilization that significantly decreases radical reactivity. Reactive radicals have only a fleeting existence. They do not have sufficient kinetic or thermodynamic stability to prevent them from reacting rapidly with compounds or radicals present in the reaction mixture.

B. Free-Radical Chain Reactions

Free-radical reactions can be subdivided in a variety of ways. Perhaps the most fundamental subdivision separates these reactions into two groups, those that take place by a chain process and those that do not. The same three stages (radical formation, radical transformation, and radical disappearance) are present in both types of reaction.² Chain reactions proceed through the transformation stage multiple times for each initially formed radical. Nonchain reactions require generation of a new radical for each transformation that takes place. These two types of reaction will be discussed separately. In this chapter the focus will be on chain reactions. Nonchain reactions will be considered in the next chapter (Chapter 3).

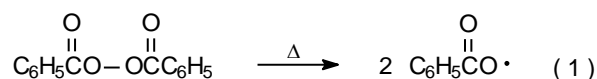
Radical formation, transformation, and disappearance in a chain reaction usually are referred to as the initiation, propagation, and termination phases of the reaction. Some radical chain reactions produce polymers; others do not. A polymerization reaction not only passes repeatedly through a propagation sequence, but each pass increases the length of the chain in the resulting radical (Scheme 1). A nonpolymerization reaction follows this same pattern except that each pass through the propagation sequence does not cause growth of a polymer chain. Whether or not polymerization takes place depends upon the existence of a chain-transfer step. In the reaction shown in Scheme 1, the chain-transfer step stops the radical **1** from proceeding along a polymerization pathway by converting it into the nonradical **2** and, at the same time, creating a new radical ($M\cdot$). This new radical can continue the chain reaction by beginning a new propagation sequence. (Polymerization reactions will not be considered further in this book; rather, discussion from this point on will focus entirely of nonpolymerization reactions.)

II. Basic Stages of a Radical Chain Reaction

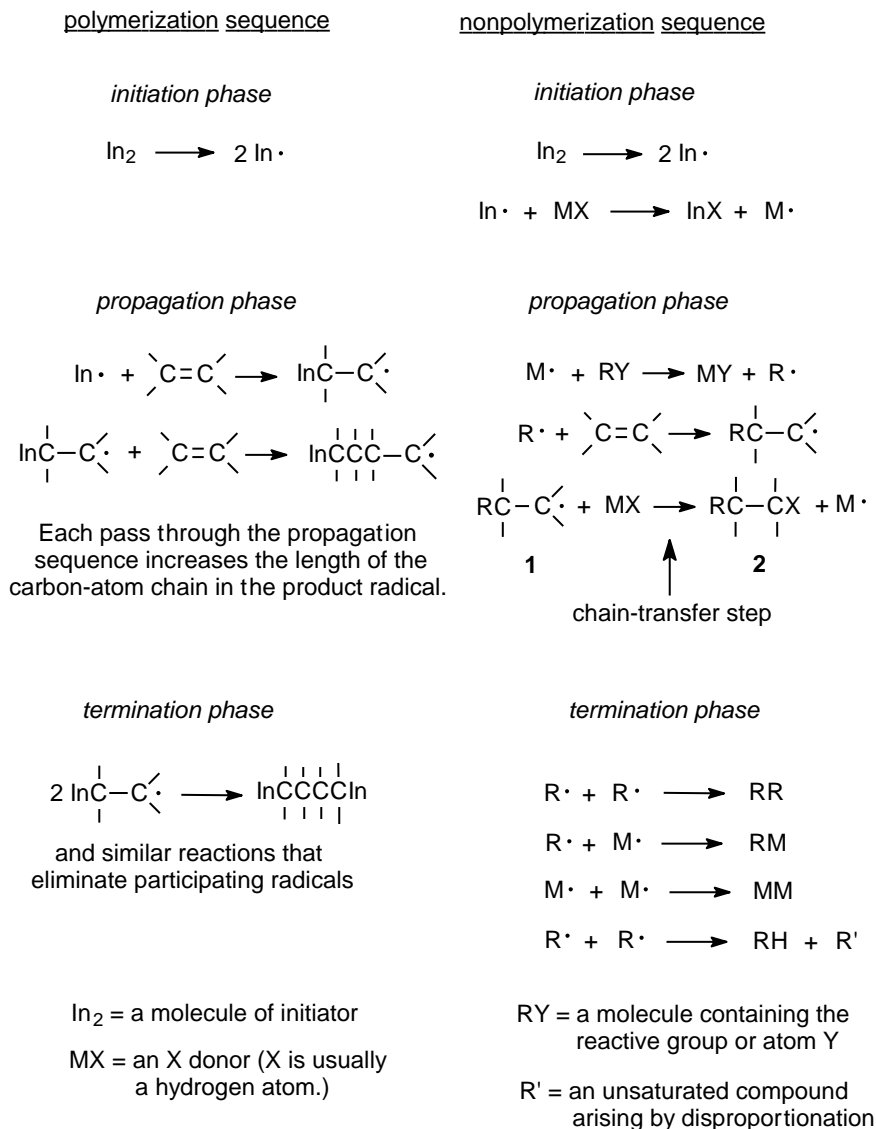
A. The Initiation Phase

1. Thermal Initiation

Radical chain reactions usually occur in solutions maintained at 110 °C or less. Most compounds cannot initiate a reaction under these conditions because most molecules do not undergo bond homolysis rapidly enough at or below 110 °C to provide the supply of radicals needed for a productive chain reaction.³ Compounds that can initiate reaction under these conditions often contain a weak σ -bond (e.g., the O–O bond in benzoyl peroxide) that cleaves thermally to generate a pair of radicals (eq 1).



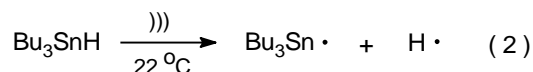
Scheme 1



In addition to simple heating of a reaction mixture, thermal initiation also can be brought about sonochemically. Irradiation of homogeneous liquids with high-intensity ultrasound creates localized, superheated, sonochemical cavities in which radicals are generated by thermal reaction.^{4,5} Sonochemically initiated reactions can be conducted in solutions for which the temperature outside the sonochemical cavities is well below the 80-110 °C that is typical for many radical reactions; for example, sonochemical reaction of tri-*n*-butyltin hydride in a solution held at 22 °C initiates a chain reaction by homolytically cleaving a tin-hydrogen bond (eq 2).⁴

An appropriate initiator should provide a steady supply of radicals during the entire reaction. The needed supply will exist if the initiator has a lifetime comparable to the time required for completion of the reaction being conducted.³ [The lifetime of an initiator is often described in

terms of the amount of time required for 50% of the material to react, that is, its half-life ($t_{1/2}$.)] Continuous formation of radicals is necessary because the time of existence of a typical radical chain is short, usually less than one second; consequently, new chains must be started regularly.³ If the half-life of an initiator is too short to provide the necessary supply of radicals during the entire reaction, either an initiator with a longer half-life can be used, or the initiator can be added to the reaction mixture continuously (or at regular intervals) during the reaction.

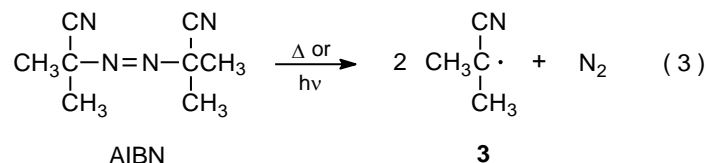


2. Thermal Initiators

a. 2,2'-Azobis(isobutyronitrile)

2,2'-Azobis(isobutyronitrile) (AIBN) is easily the most widely used initiator in radical reactions of carbohydrates. There are compelling reasons for this status. AIBN has a half-life of one hour at 85 °C (five hours at 70 °C);^{3,6,7} consequently, it can continuously supply sufficient initiating radicals at moderate temperatures for reactions requiring several hours to reach completion. Other advantages of AIBN are that it is easily handled, generates good yields of radicals (yields of radicals available for chain initiation are not 100% because some radicals combine before they can escape from the solvent cage), and has a rate of decomposition that is almost independent of the solvent.³

The 2-cyano-2-propyl radical (**3**) generated from AIBN (eq 3) is relatively stable and usually reacts with bonds that are weaker than most C–H bonds; thus, hydrogen-atom abstraction from the solvent or carbohydrate reactant generally is not a complicating factor. Since the 2-cyano-2-propyl radical readily abstracts a hydrogen atom from a compound with a tin–hydrogen bond, AIBN is an excellent initiator for the frequently encountered reactions in which tri-*n*-butyltin hydride is the hydrogen-atom source.³



Another advantage of AIBN is that it does not experience induced decomposition; that is, the kinetics of its reaction are first order, regardless of the solvent or initiator concentration.⁶ (Induced decomposition in this case refers to the more rapid decomposition that sometimes occurs when an initiator undergoes bimolecular reaction in addition to the normal unimolecular one.)

- b. 4,4'-Azobis(4-cyanovaleric Acid) (ACBA); 1,1'-Azobis-(cyclohexanecarbonitrile) (ABCN); 2,2'-Azobis(2,4-dimethyl-4-methoxyvaleronitrile) (V-70); and Di-*tert*-butylhyponitrite (TBHN)

Azo compounds that are known to initiate radical reactions of carbohydrates are shown in Table 1. Even though the vast majority of reactions are initiated by AIBN, each of the other azo compounds listed in Table 1 has a characteristic that is useful in certain situations. The water solu-

Compound	t _{1/2}	Reference
$\begin{array}{c} \text{CN} \quad \text{CN} \\ \quad \\ \text{CH}_3\text{C}-\text{N}=\text{N}-\text{CCH}_3 \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$ <p>AIBN</p>	0.5 h at 85 °C 5 h at 70 °C	3,6,7
$\begin{array}{c} \text{CN} \quad \text{CN} \\ \quad \\ \text{HOOCCH}_2\text{CH}_2\text{C}-\text{N}=\text{N}-\text{CCH}_2\text{CH}_2\text{COOH} \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$ <p>ACVA</p>	10 h at 69 °C	8
$\begin{array}{c} \text{CN} \quad \text{CN} \\ \quad \\ \text{C}-\text{N}=\text{N}-\text{C} \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$ <p>ABCN or ABC</p>	2 h at 100 °C	9
$\begin{array}{c} \text{CH}_3 \quad \text{CN} \quad \text{CN} \quad \text{CH}_3 \\ \quad \quad \quad \\ \text{CH}_3\text{OCCH}_2\text{C}-\text{N}=\text{N}-\text{CCH}_2\text{COCH}_3 \\ \quad \quad \quad \\ \text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3 \end{array}$ <p>V-70</p>	a	10-13
$\begin{array}{c} \text{CN} \quad \text{CN} \\ \quad \\ \text{CH}_3\text{CO}-\text{N}=\text{N}-\text{OCCH}_3 \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$ <p>DTBH</p>	29 min at 65 °C	14

^aA typical reaction is run at room temperature for 12h.

Table 1. Azo compounds used to initiate radical reactions of carbohydrates

ble 4,4'-azobis(4-cyanovaleric acid) (ACBA) initiates reactions run in aqueous solution.¹⁵ 1,1'-Azobis(cyclohexanecarbonitrile) (ABCN or ABC) has a longer half-life than does AIBN and, thus, is better suited for reactions that require higher temperature or extended reaction times.^{16,17} 2,2'-Azobis(2,4-dimethyl-4-methoxyvaleronitrile) (V-70), in contrast, reacts rapidly enough in solution that it initiates reactions run at or near room temperature.¹⁰⁻¹³ Di-*tert*-butyl hyponitrite (TBHN) differs from other azo initiators in that it forms oxygen-centered radicals.¹⁴

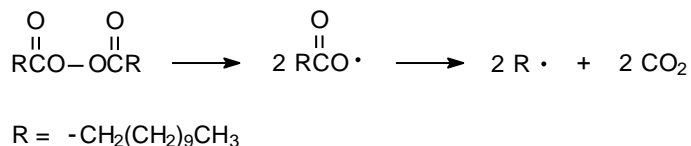
Compound	t _{1/2}	Reference
(CH ₃) ₃ CO—OC(CH ₃) ₃ 4	1 h at 150 °C 10 h at 126 °C	3
$ \begin{array}{c} \text{(CH}_3\text{)}_3\text{CO—O} \quad \text{O—OC(CH}_3\text{)}_3 \\ \quad \quad \quad \diagdown \quad \diagup \\ \quad \quad \quad \text{C} \\ \quad \quad \quad \diagup \quad \diagdown \\ \text{CH}_3 \quad \quad \quad \text{CH}_2\text{CH}_3 \end{array} $ 5	1 h at 125 °C	18
$ \begin{array}{c} \text{O} \quad \quad \quad \text{O} \\ \parallel \quad \quad \parallel \\ \text{CH}_3(\text{CH}_2)_9\text{CH}_2\text{CO—OCCH}_2(\text{CH}_2)_9\text{CH}_3 \end{array} $ 6	1 h at 80 °C	19
$ \begin{array}{c} \text{O} \quad \quad \quad \text{O} \\ \parallel \quad \quad \parallel \\ \text{C}_6\text{H}_5\text{CO—OCC}_6\text{H}_5 \end{array} $ 7	1 h at 95 °C	3

Table 2. Peroxide initiators used in radical reactions of carbohydrates

c. Peroxides

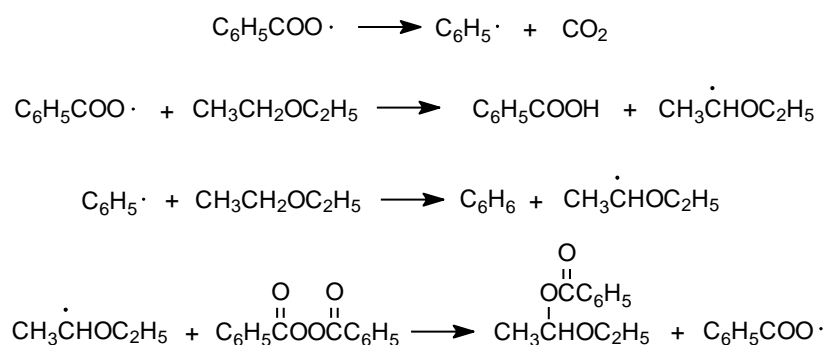
The peroxides shown in Table 2 also are initiators for radical reactions of carbohydrates. These compounds are useful when the 2-cyano-2-propyl radical **3** (eq 3), or any carbon-centered radical generated from other initiators listed in Table 1, does not have the necessary reactivity to cause a chain reaction. Such a situation arises when an initiating radical is required to abstract a hydrogen atom from a carbon–hydrogen bond. The *tert*-butoxy radicals formed from di-*tert*-butyl peroxide (**4**) or 2,2-di-*tert*-butylperoxybutane^{18,20-23} (**5**) are effective at this type of hydrogen-atom abstraction. Sometimes reaction initiation requires a carbon-centered radical that can add to an *O*-thiocarbonyl group. One radical reactive enough to make this addition is CH₃(CH₂)₉CH₂· formed from dilauroyl peroxide (**6**) (Scheme 2).²⁴⁻²⁹ Benzoyl peroxide (**7**) and di-*tert*-butyl peroxide³⁰⁻³² (**4**) also produce radicals that add to an *O*-thiocarbonyl group.

Scheme 2



The ability of radicals formed from peroxides to abstract hydrogen atoms from carbon-hydrogen bonds can be both an advantage and a disadvantage. It is an advantage when such abstraction is necessary for reaction to proceed but a disadvantage when hydrogen-atom abstraction from the carbohydrate or the solvent causes undesired reaction. One undesired reaction is induced decomposition, which can be illustrated by considering the reactions of benzoyl peroxide. At low concentrations in an inert solvent the reaction of benzoyl peroxide follows the first-order kinetics expected for unimolecular reaction,⁶ but at higher concentrations or in the presence of reactive solvents benzoyl peroxide undergoes faster reaction.^{6,33-35} The half-life of this peroxide in ethyl ether in a sealed tube at 80 °C is five minutes rather than the one hour observed in benzene at 95 °C.⁶ The enhanced rate of reaction in ethyl ether is attributed to the induced decomposition that occurs when the radical created by abstraction of a hydrogen atom from the solvent by either $\text{C}_6\text{H}_5\cdot$ or $\text{C}_6\text{H}_5\text{CO}_2\cdot$ reacts with benzoyl peroxide (Scheme 3).⁶

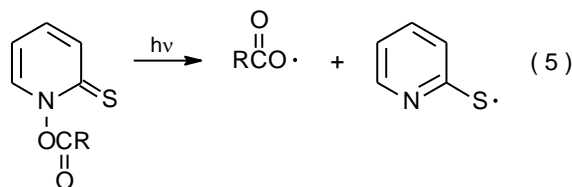
Scheme 3



3. Photochemical Initiation

Photochemical initiation requires a compound to absorb a photon of light and then use this energy to cleave a bond homolytically and, in so doing, create an initiating radical (or radicals). It is desirable for the initiator to absorb visible or long-wavelength ultraviolet (UV) radiation because being able to absorb this type of light minimizes the possibility that another chromophore in a reactant molecule will be excited and undergo an unwanted photochemical reaction. Photo-

chemical initiation is particularly useful for thermally labile substrates because reaction can be conducted at low temperatures.



Carbohydrates that form radicals as a result of light absorption include iodides, bromides, azides, selenides, hypoiodites, and esters of *N*-hydroxy-pyridine-2-thione.³⁶ For hypoiodites (eq 4) and esters of *N*-hydroxypyridine-2-thione (eq 5) photolysis with visible light causes radical formation. Since very few functional groups in carbohydrates react as a result of absorbing visible light, there is little danger that this type of radiation will cause a competing photochemical reaction. For compounds that react with visible light, care must be exercised to protect them from premature reaction due to inadvertent light exposure. Since UV radiation is required for bond breaking in carbohydrate iodides, bromides, azides, and selenides, the possibility for undesired photochemical reaction due to exciting a different chromophore in the substrate is greater when irradiating one of these compounds.

Although radicals form from photolysis of all the compounds mentioned in the previous paragraph, the extent to which a chain reaction takes place depends on both the structure of the substrate and the reaction conditions. In the case of esters of *N*-hydroxypyridine-2-thione, for example, the bond homolysis shown in eq 5 initiates a chain reaction with a quantum yield that ranges from 6 to 35 when $\text{R}=(\text{CH}_2)_{14}\text{CH}_3$ and from 19 to 34 when $\text{R}=\text{C}_6\text{H}_{11}$.³⁷ The range of values for each compound is due to quantum yields being determined under different reaction conditions. (The quantum yield for a reaction is the number of molecules reacted for each photon absorbed; thus, for a radical chain reaction the quantum yield is a measure of the number of propagation cycles produced by each initiating radical.)

Bond homolysis is only one of the possible reactions that can take place when a molecule absorbs a photon of light. Other photochemical reactions (e.g., cycloaddition and geometric isomerization) do not involve radical formation. Reference 36 contains a discussion of both the radical-forming and nonradical-forming photochemical reactions of carbohydrates.

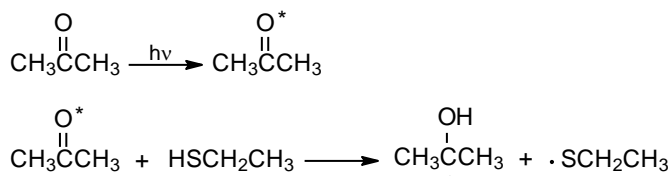
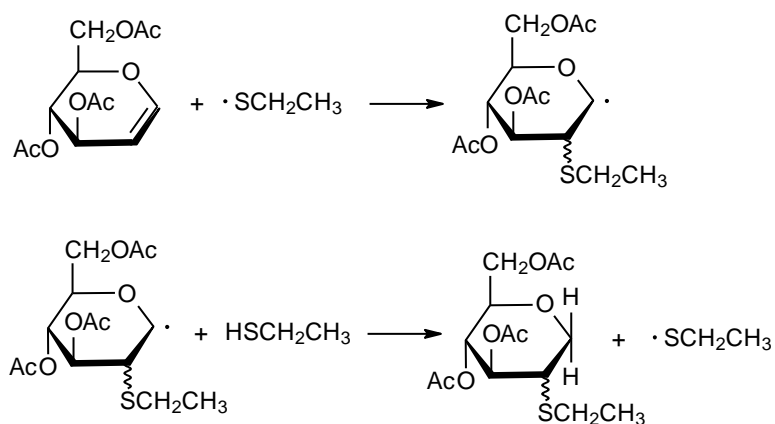
4. Photochemical Initiators

Direct photolysis of carbohydrates is not the only way to initiate their radical reactions photochemically. Irradiation of noncarbohydrates also produces radicals that cause carbohydrate reaction; thus, photolysis of azo compounds, ketones, and hexaalkylditins all generate radicals that initiate chain reactions.

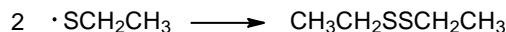
a. 2,2'-Azobis(isobutyronitrile)

2,2'-Azobis(isobutyronitrile) (AIBN) has a maximum absorption at 345 nm in its UV spectrum and fragments when irradiated with light of this wavelength to produce nitrogen and two 2-cyano-2-propyl radicals (eq 3).^{3,7} Because many compounds are transparent to 345-nm light, it is often possible to generate 2-cyano-2-propyl radicals photochemically in a reaction mixture in which AIBN is the only light-absorbing compound. (In contrast to thermal reaction, photolysis of AIBN has the advantage that it can initiate reactions at or below room temperature.)

Scheme 4

initiation*propagation**termination*

radical combination reactions such as

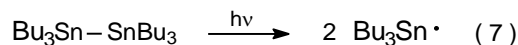
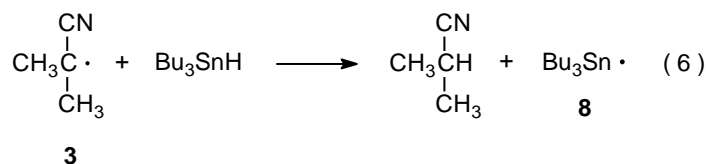


b. Acetone and Benzophenone

A characteristic of ketones, such as acetone and benzophenone, is that absorption of UV radiation produces an excited state (n,π^*) that has considerable radical character on the carbonyl oxygen atom.³⁸ As a result, many excited ketones have reactivity similar to that of alkoxy radicals; in particular, once a photon is absorbed, the excited ketone can abstract a hydrogen atom to begin a

chain reaction.^{38,39} An example of the way in which this type of reaction takes place is shown in Scheme 4, where excited acetone abstracts a hydrogen atom from the S–H bond in ethanethiol to initiate an addition reaction.⁴⁰

Benzophenone has a longer wavelength and more intense (n,π^*) absorption than does acetone; consequently, it is easier to form excited benzophenone without having a carbohydrate reactant absorb the incident light. The presence of the photoproducts benzhydrol and benzpinacol, as well as unreacted benzophenone, can make product purification difficult.⁴¹



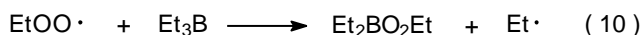
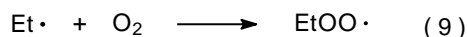
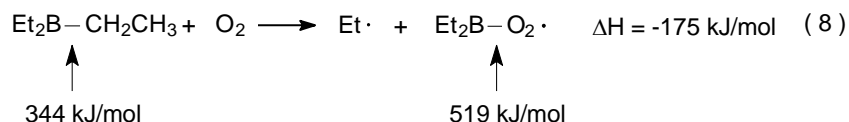
c. Hexaalkylditins

The chain-carrying radical in many reactions of carbohydrates is the tri-*n*-butyltin radical (**8**). This radical usually is generated during the initiation phase of a reaction when the 2-cyano-2-propyl radical **3** abstracts a hydrogen atom from Bu_3SnH (eq 6). Sometimes it is necessary to generate $\text{Bu}_3\text{Sn}\cdot$ without Bu_3SnH being present in the reaction mixture. In such a situation $\text{Bu}_3\text{Sn}\cdot$ can be formed by photolysis of hexabutyltin with ultraviolet light (eq 7).⁴²

5. Chemical Initiation

Thermal and photochemical initiation draw energy for radical formation from heating (vibrational excitation) and photon absorption (electronic excitation), respectively. Chemical initiation is different in that it uses energy stored in bonds to form initiating radicals; for example, triethylboron reacts with molecular oxygen to produce ethyl radicals (eq 8) that then initiate radical reactions.^{43–46} The driving force behind radical formation is the greater strength of the B–O bond [BDE = 519 kJ/mol (124 kcal/mol) in $(\text{EtO})_3\text{B}$] when compared to the B–C bond [BDE = 344 kJ/mol (82.2 kcal/mol) in Et_3B].⁴⁷ The activation energy for this reaction (eq 8) must be exceptionally low because $\text{Et}_3\text{B}-\text{O}_2$ can initiate reactions at temperatures as low as -78°C .^{47,48}

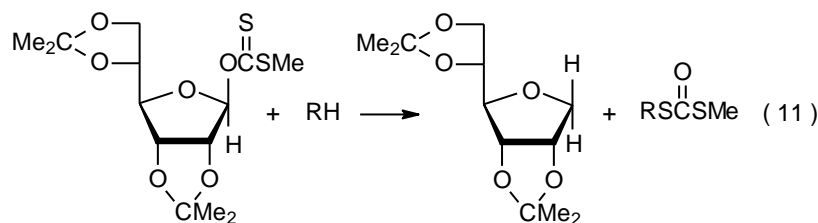
Even though ethyl radicals are generated in a reaction involving molecular oxygen (eq 8), they also can react with oxygen molecules to form peroxy radicals (eq 9). Forming peroxy radicals diverts the ethyl radicals from their role as initiators, but this diversion only temporarily interrupts the initiation process because peroxy radicals react with triethylboron to generate new ethyl radicals (eq 10).⁴⁷ As long as the amount of oxygen added to the system is kept well below the amount of triethylboron present, the ethyl radicals needed to initiate reaction will continue to be produced as oxygen is introduced.



Initiation of a reaction by triethylboron–oxygen shares an important feature with photochemical initiation; namely, both are able to generate radicals well below room temperature. The mild conditions for reactions initiated in this manner can lead to fewer side reactions and higher product yields.⁴⁹ Triethylboron–oxygen initiation can be used in a broad range of situations that include reaction in aqueous solution.⁴⁷

The ability of triethylboron–oxygen to initiate reactions at low temperature indicates that sometimes the sole purpose of heating a reaction mixture is to decompose the initiator. The reaction shown in eq 11, for example, proceeds well at room temperature, when initiated by triethylboron–oxygen. The only apparent reason the reaction must be conducted at higher temperature when AIBN replaces triethylboron–oxygen is to enable fragmentation of the initiator (eq 11).⁵⁰

The hydrogen-atom donor in most radical reactions is either a tin or silicon hydride. The most frequently used tin hydride is Bu_3SnH and the most common silicon hydride is $(\text{Me}_3\text{Si})_3\text{SiH}$. The silicon hydride used in the reaction shown in eq 11 is a less common but effective hydrogen-atom donor.



77 °C, AIBN, EtOAc

86%

25 °C, $\text{Et}_3\text{B}-\text{O}_2$, EtOAc

80%

$\text{R} = (\text{C}_6\text{H}_5)_2\text{Si}(\text{H})\text{Si}(\text{C}_6\text{H}_5)_2$

B. The Propagation Phase

1. General Characteristics

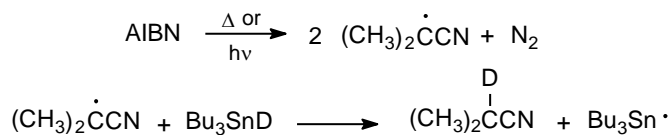
The propagation phase for a chain reaction consists of a group of elementary reactions (also called reaction steps) that are repeated a number of times (Scheme 1). (Elementary reactions are discussed in Chapter 4.) Each repetition represents one reaction cycle, and the number of cycles completed for each initiating radical is the chain length. The final step in a propagation sequence completes the current cycle and generates the radical needed to begin a new cycle. The products from any radical chain reaction are determined by the identity and reactivity of the molecules and radicals participating in the propagation phase.

2. Examples of Propagation Sequences

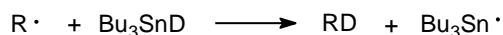
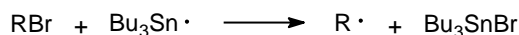
The basic characteristics of a propagation sequence can be seen by examining two specific reactions. One of these is dehalogenation of a D-glucopyranosyl bromide with tri-*n*-butyltin deuteride⁵¹ (Scheme 5), and the other is addition of a D-glucopyranos-1-yl radical to acrylonitrile in the presence of tri-*n*-butyltin hydride (Scheme 6).^{52,53}

Scheme 5

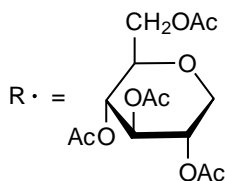
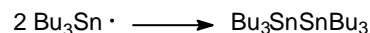
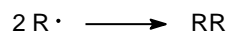
initiation



propagation



termination



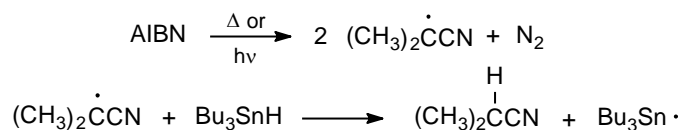
a. Substitution

Reductive dehalogenation with tri-*n*-butyltin deuteride, a substitution reaction with two propagation steps, is a relatively simple chain process (Scheme 5).⁵¹ In the propagation phase for this reaction $\text{R}\cdot$ and $\text{Bu}_3\text{Sn}\cdot$ alternate in carrying the chain forward by each reacting only with a particular type of reactant molecule; that is, $\text{Bu}_3\text{Sn}\cdot$ reacts only with the glucosyl halide (RX), and

the carbohydrate radical ($R\cdot$) reacts exclusively with Bu_3SnD . This discriminating reactivity has been called "disciplined behavior".⁵⁴

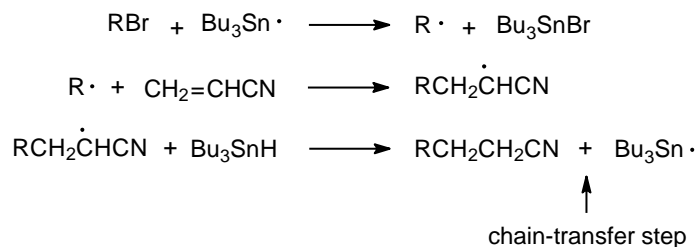
Scheme 6

initiation

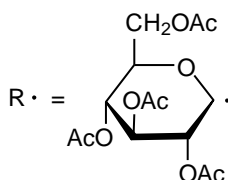
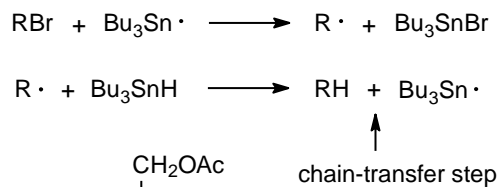


propagation

desired sequence



diverting sequence



b. Addition

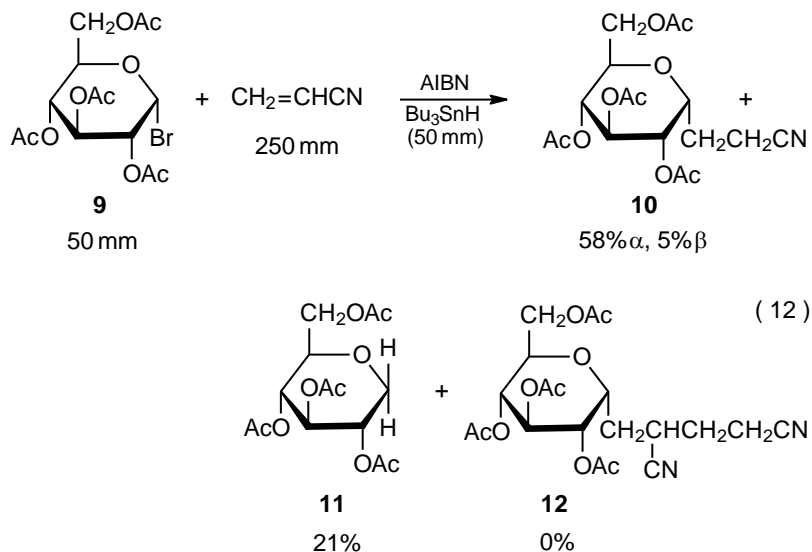
Radical addition to an unsaturated compound is a more complex process than atom substitution because radical addition typically involves at least three propagation steps (Scheme 6, desired sequence). Introducing another step (in this case, addition of $R\cdot$ to $CH_2=CHCN$) to the propagation sequence complicates the sequence not just by the existence of a third elementary reaction but also by the constraints this new reaction places on the entire process. These constraints are discussed in the next several paragraphs.

One requirement for success in the addition process shown in Scheme 6 is that $R\cdot$ must be reactive enough to add to acrylonitrile. Carbon-centered, carbohydrate radicals ($R\cdot$) add rapidly to compounds with electron-deficient multiple bonds but these same radicals add only slowly (too

slowly for observable reaction) to compounds with multiple bonds that are not electron-deficient. The reasons behind different rates of addition of $R\cdot$ to compounds with electron-deficient and electron-rich multiple bonds are discussed in Chapter 7. [If an addition reaction is internal (i.e., a radical cyclization), it sometimes will take place even if the multiple bond is not electron-deficient.]

A second requirement for a successful reaction is that $R\cdot$ exist long enough in solution to add to an unsaturated reactant. One reaction that could prevent this addition from taking place is chain termination ($R\cdot + R\cdot \rightarrow RR$), but chain termination is unlikely to do so because the very low concentration of $R\cdot$ causes the rate of radical combination to be much slower than the rate of addition of $R\cdot$ to a compound with an electron-deficient multiple bond. A more probable reason for $R\cdot$ not adding to an unsaturated compound is that this radical undergoes hydrogen-atom abstraction from tri-*n*-butyltin hydride before addition can occur (Scheme 6, diverting sequence). Such an abstraction diverts reaction away from the desired product. The rate of addition of $R\cdot$ to an unsaturated compound, therefore, must be faster than its rate of hydrogen-atom abstraction from tri-*n*-butyltin hydride in order to keep the chain reaction from being directed into an unwanted propagation sequence (Scheme 6).

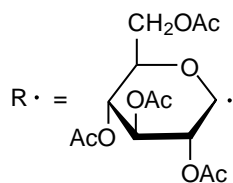
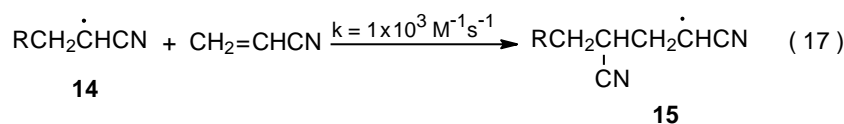
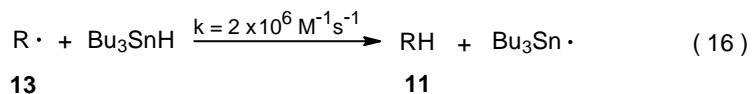
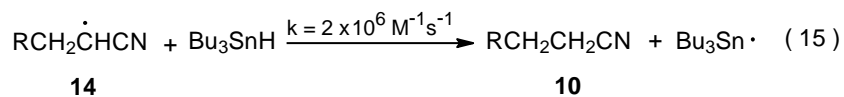
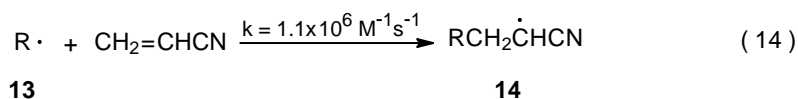
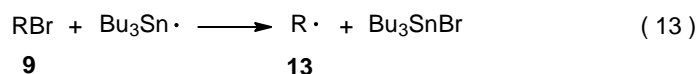
A third constraint placed on the overall addition process by the reaction of $R\cdot$ with acrylonitrile is that the adduct radical must not add to a second molecule of the nitrile before hydrogen-atom abstraction takes place. Although this competing addition sometimes does occur, in most instances hydrogen abstraction is more rapid than a second radical addition.



Another way of describing the constraints placed on the desired sequence in Scheme 6 by an additional propagation step is in terms of chain-transfer reactions. In each propagation sequence the chain-transfer step ends the existing cycle and creates the radical that begins a new cycle. In the

reactions shown in Scheme 6 the third step in the desired sequence and the second step in the diverting sequence are the chain-transfer steps for their respective reactions. Radical addition cannot be successful if the rate of the chain-transfer step in the diverting sequence is greater than the rate of the radical-transforming step (i.e., addition of $R\cdot$ to $CH_2=CHCN$) in the desired sequence. In other words, the addition reaction shown in Scheme 6 will be a minor process if most of the time $R\cdot$ reacts with tri-*n*-butyltin hydride to produce RH (the simple-reduction product) before it adds to acrylonitrile.

Scheme 7



13

References to the rate constants given here, which are for reactions of model compounds, are found in the text. These and many other rate constants are found in Chapter 8.

3. Rate Constants and Reaction Rates

Analysis of the reaction shown in Scheme 6 can be done in a more quantitative manner using the rate constants shown in Scheme 7 and the information given in eq 12.⁵² (The rate con-

stants in Scheme 7 are a few of the many listed in the tables located in Chapter 8.) The first step in the formation of any product in this reaction is bromine-atom abstraction by the tri-*n*-butyltin radical (eq 13). (Equations 13-17 are found in Scheme 7.) After bromine-atom abstraction, the major reaction product (**10**) is formed by a combination of two steps, addition of the D-glucopyranos-1-yl radical **13** to acrylonitrile to give the adduct radical **14** (eq 14) and abstraction by **14** of a hydrogen atom from tri-*n*-butyltin hydride (eq 15). These reaction steps (equations 14 and 15) need to take place in preference to those that produce the side products **11** and **12** (eq 12). Which product will be the major one and which will be the minor ones in this reaction is determined by reactant concentrations and rate constants for the various, possible elementary reactions.

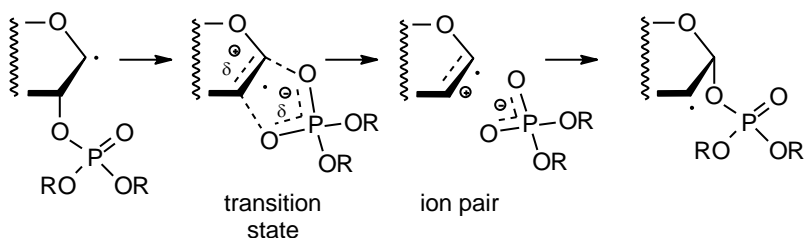
Unfortunately, not all of the rate constant information needed to analyze the reaction shown in eq 12 is available; consequently, in order to proceed it is necessary to estimate some rate constants based upon information from reaction of model radicals. For example, the rate constant for addition of the pyranos-1-yl radical **13** to acrylonitrile (eq 14) is assumed to be similar to that for addition of the model radical $\cdot\text{CH}_2\text{OH}$ to this nitrile.⁵⁵ The rate constant for this reaction (eq 14) is smaller than that for hydrogen-atom abstraction by a typical carbon-centered radical from tri-*n*-butyltin hydride (TBTH) (eq 16);⁵⁶ therefore, if acrylonitrile and TBTH are present in equal amounts, the major reaction product should be compound **11**. The desired reaction (eq 14) will be favored, however, if acrylonitrile is present in much greater amount than TBTH. In the reaction shown in eq 12 the ratio of acrylonitrile to TBTH (5/1) is large enough to make **10** the major product (58%).⁵² The 21% yield of **11**, however, shows that even with an excess of acrylonitrile there still is substantial reaction of the radical **13** with tri-*n*-butyltin hydride (eq 16).

There is a limit to how large the ratio of acrylonitrile to tri-*n*-butyltin hydride can become before adding more nitrile to the reaction mixture is counterproductive. This limit will be reached when reaction of **14** with acrylonitrile (eq 17, $k = 1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$)⁵⁷ competes effectively with reaction of this radical (**14**) with TBTH (eq 15, $k = 2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$).⁵⁶ The difference in rate constants for these two reactions is so great, however, that having acrylonitrile present in fivefold excess is possible without significant formation of the radical **15** (eq 17) and its hydrogen-atom abstraction product **12** (eq 12). The considerable difference in the rate constants for the reactions shown in eq 14 and eq 17 is due primarily to a difference in radical philicity; that is, **13** is more nucleophilic than **14**. Radical philicity and its effect on radical reactivity are discussed in Chapter 7.

4. Solvent Effects

Although solvent selection often plays a decisive role in ionic reactions, strong solvent effects in radical reactions are less common because radical centers are relatively nonpolar and, thus, are not highly solvated.³ A similar statement applies to transition states in radical reactions because most reactions do not develop much, if any, separation of charge at the transition state; hence, stabilization by polar solvents is usually not a significant factor.

Scheme 8

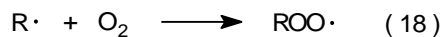


R = an aryl or alkyl group

There are some situations in which solvent effects are significant in radical reactions.⁵⁸ One of these occurs during phosphatoxy group migration.⁵⁹ The rate determining step in this reaction involves formation of a polarized transition state on its way to becoming an ion pair (Scheme 8); consequently, reaction is faster in solvents that stabilize charge separation. Acyloxy and phosphatoxy group migrations are similar in many ways, including more rapid reaction in polar solvents.

C. The Termination Phase

Any process that stops the participation of a radical in a propagation sequence terminates the reaction chain. In typical chain reactions, such as those described in Schemes 1, 4, 5, and 6, radical combination and disproportionation are terminating steps. Chain termination in this way is limited primarily by how rapidly radicals diffuse through a solution.^{60,61} Successful chain reactions have concentrations of radicals low enough (approximately 1×10^{-7} M)^{57,62} to prevent even diffusion controlled processes from competing effectively with chain propagation. Because low radical concentrations make chain-terminating reactions less competitive, adding only a limited amount of an initiator with an appropriate half-life to a reaction mixture generates the small but steady supply of radicals required to maintain reaction and avoid premature chain termination.



Chain termination can occur when a participating radical is transformed into a radical that is not involved in the reaction sequence.⁶³ A common way for this to happen is to have a carbon-centered radical ($R\cdot$) combine with a molecule of oxygen to give a peroxy radical ($ROO\cdot$) (eq 18). Formation of $ROO\cdot$ would terminate propagation sequences such as those shown in Schemes 5 and 6 because a peroxy radical is not a participant in either sequence. (Forming a peroxy radical by reaction with oxygen not only terminates a desired propagation sequence, but it also creates a reactive radical that is capable of becoming part of a different reaction sequence.) Because reaction of carbon-centered radicals with molecular oxygen occurs at or near diffusion control ($k = 10^9$ - 10^{10}

$M^{-1}s^{-1}$),⁶⁴ minimizing chain termination by oxygen, requires radical reactions to be conducted in an inert atmosphere such as that provided by argon or nitrogen.

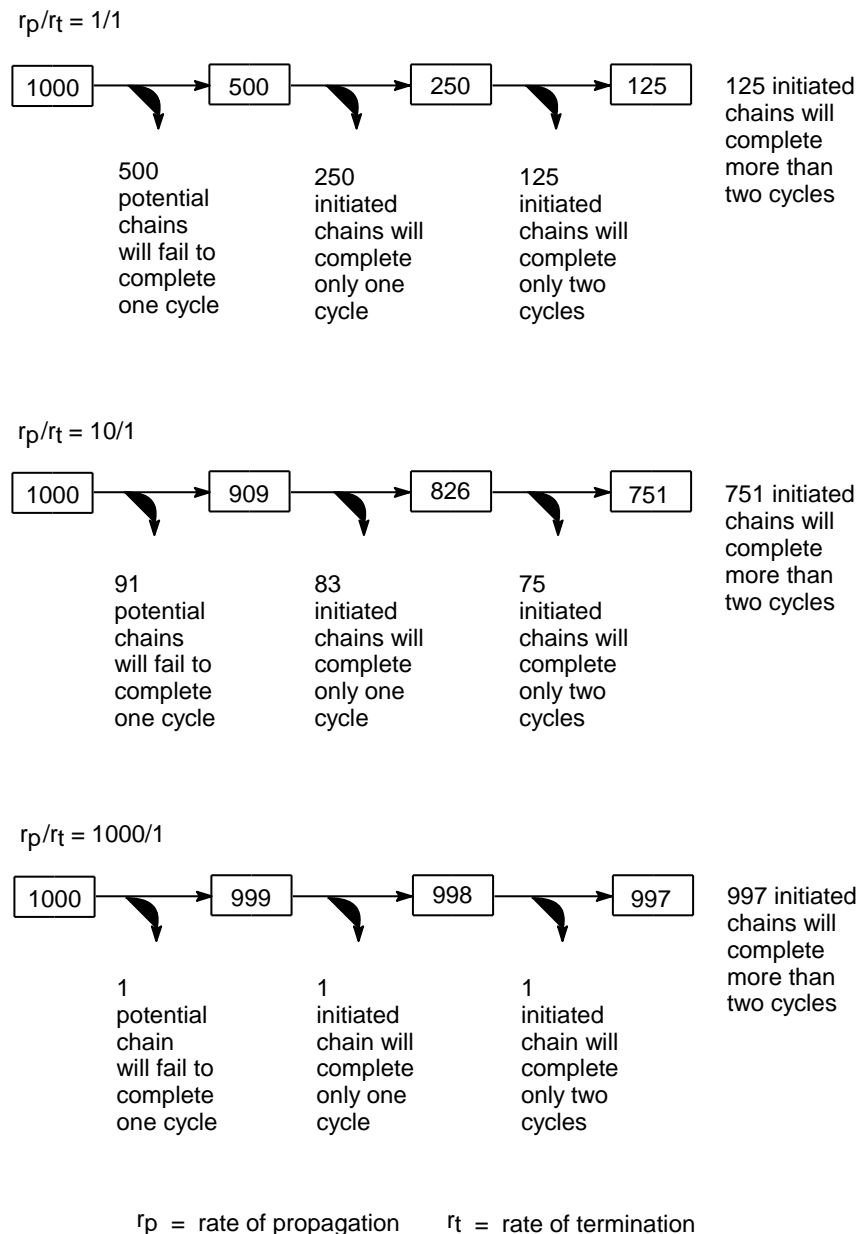


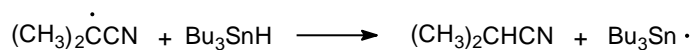
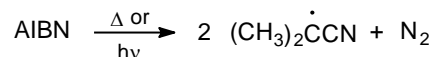
Figure 1. Comparison of the propagation cycles completed by 1000 radicals when $r_p/r_t = 1/1$, $10/1$, and $1000/1$.

Even when a reaction is conducted in an inert atmosphere, it is nearly impossible to eliminate all traces of oxygen from a reaction mixture. A small amount of oxygen can cause initial reaction chains to have short lengths. Once the oxygen concentration falls to a low enough level that

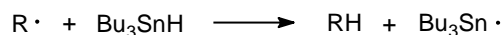
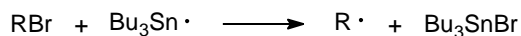
premature chain termination is no longer significant, reaction can proceed without noticeable inhibition by oxygen.

Scheme 9

initiation



propagation



termination



III. Reaction Efficiency

Reaction efficiency is a relative concept. Reference to efficiency can take the form of a statement that one reaction is more efficient than another or that a reaction is an efficient process. Establishing a dividing line between efficient and inefficient reactions involves an arbitrary decision; nevertheless, it is sometimes helpful in discussing chain reactions to use the term efficiency and to associate a numerical value with it. Choosing chain length to measure efficiency can provide this number; thus, one way to define an efficient reaction is as one that has a chain length greater than 100.⁶⁵

The efficiency of a chain reaction is determined by its relative rates of propagation (r_p) and termination (r_t). A reaction becomes more efficient as the ratio r_p/r_t increases; thus, the chain length in a reaction differs significantly when r_p/r_t is 10/1 as opposed to when it is equal to 1/1 (Figure 1). When r_p/r_t is 1/1, only 12.5% of the initiating radicals begin a chain destined to have a length greater than 2, but if the ratio of r_p to r_t is raised to 10/1, more than 75% of the initiating radicals produce chains with lengths greater than 2 (Figure 1). Even when r_p/r_t is 10/1, the reaction would not be described as an efficient one because a chain length of 100 in such a reaction would be a rare event. If, on the other hand, r_p/r_t is equal to 1000/1, nearly every initiated chain will complete two cycles (Figure 1) and most chains will have a length greater than 100; thus, the re-

action is an efficient one. One desirable characteristic of a reaction with a long chain length is that converting all the starting material into product requires only a small amount of initiator.

It is informative to consider some actual numbers for rates of propagation (r_p) and termination (r_t) reactions to better appreciate how these rates determine chain length. One way to do this is to analyze a typical reaction such as the dehalogenation process shown in Scheme 9. Since the rate determining propagation step in this type of reaction is hydrogen-atom abstraction by $R\cdot$ from Bu_3SnH ,^{66,67} the rate of propagation (k_p) is given by eq 19. A typical value for the rate constant (k_p) for this reaction is $2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.⁵⁶ Since combination of two $R\cdot$ radicals is assumed to be the only significant termination process, the rate of termination is given by eq 20. The rate constant for termination (k_t) will depend upon how rapidly these radicals come together in solution, that is, upon their rate of diffusion. The rate constant for diffusion is $1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ in benzene,⁶⁸ a common solvent for such reactions. A typical radical concentration in a chain reaction is less than $1 \times 10^{-7} \text{ M}$.^{57,62} A normal concentration for a hydrogen-atom donor is one molar. Based upon these numbers and the assumptions made about this reaction, dehalogenation with tri-*n*-butyltin hydride as the hydrogen-atom donor would be quite efficient because r_p/r_t would be approximately 2000 (eq 21).

$$r_p = k_p [R\cdot] [Bu_3SnH] \quad (19) \quad r_t = k_t [R\cdot] [R\cdot] \quad (20)$$

$$\frac{r_p}{r_t} = \frac{k_p [Bu_3SnH]}{k_t [R\cdot]} = \frac{(2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1})(1\text{M})}{(1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1})(1 \times 10^{-7}\text{M})} = 2 \times 10^3 \quad (21)$$

Although discussion of chain reactions naturally focuses on how to increase efficiency, it is informative to examine the other end of the efficiency spectrum to determine the problems associated with inefficient reactions. As reactions become less efficient, more chains must be started in order for reaction to reach completion; consequently, more initiator must be added to the reaction mixture to compensate for the decrease in the average chain length. Increasing the initiator concentration increases the possibility of side reactions involving the initiator and radicals present in solution. As efficiency drops, chain termination products become more abundant. When this happens, product purification sometimes is more difficult. There are clear disadvantages to inefficient reactions.

A guideline for deciding when a chain reaction becomes too inefficient to be synthetically useful can be formulated in terms of rates of propagation and termination reactions.⁵⁷ A criterion for usefulness is that the rate of propagation for a reaction (eq 19) should be greater than its rate of termination (eq 20).⁵⁷ (This means that the first possibility pictured in Figure 1 would be just on the “wrong side” of the line for synthetic usefulness.) This dividing line is a reasonable one because

any reaction in which an undesired product is formed at a faster rate than the desired product ($r_t > r_p$) is unlikely to be effective in synthesis.

Using the guideline that r_p/r_t should be greater than unity in a synthetically useful reaction sets a lower limit on the rate constant for propagation (k_p).⁵⁷ This limit is based on the following assumptions: (a) chain termination is a diffusion controlled process for which the rate constant (k_t) is between 1×10^9 and $1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$;⁶⁸ (b) the radical concentration in a typical reaction is approximately $1 \times 10^{-7} \text{ M}$;^{57,62} and (c) the concentration of the hydrogen-atom donor Bu_3SnH is 1 M.

$$\frac{r_p}{r_t} = \frac{k_p [\text{Bu}_3\text{SnH}]}{k_t [\text{R}\cdot]} = \frac{k_p [1 \text{ M}]}{[1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}] [1 \times 10^{-7} \text{ M}]} \quad (22)$$

$$\text{If } \frac{r_p}{r_t} > 1, \text{ then } k_p > 1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1} \quad (23)$$

Based on these assumptions, the rate constant for propagation (k_p) for a synthetically useful reaction should be greater than $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ (eq 22 and eq 23). This limiting value for k_p would hold for any reaction that satisfies the assumptions (a)-(c).

IV. Summary

Free-radical processes can be divided into chain and nonchain reactions. Chain reactions consist of initiation, propagation, and termination phases. A similar set of reactions (i.e., radical formation, transformation of one radical into another, and radical disappearance) also occurs in nonchain processes. The difference in these two types of reaction is that in a chain reaction the transformation of one radical into another also creates the radical needed to start the transformation process anew, but for nonchain reactions each radical formed causes only one "trip" through the transformation cycle. The most widely used initiator in chain reaction is 2,2'-azobis(isobutyronitrile), a compound that provides the continuous supply of radicals needed to sustain a typical reaction; that is, a reaction that takes place over a period of several hours at 80-110 °C. Peroxides also are thermal initiators, but they are less commonly used because they produce reactive radicals that can cause undesired side reactions. Triethylboron-oxygen, ultrasound, and light all initiate radical reactions and have the added advantage that they can be used in reactions that are conducted at or below room temperature.

At the core of a chain reaction is the propagation phase, the part of the reaction where reactant molecules are converted into products. Each propagation sequence consists of a group of elementary reactions. Successful propagation depends upon the ability of each participating radical to react selectively with only one type of molecule present in the reaction mixture.

The final phase in a chain reaction is termination. Chain reactions are terminated by any process, such as radical combination, that removes a participating radical from the propagation

sequence. Reaction efficiency is a measure of how long a typical chain reaction continues before termination takes place. An efficient reaction is generally regarded as one with a chain length greater than 100.

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