RADICAL REACTIONS OF CARBOHYDRATES I: STRUCTURE AND REACTIVITY OF CARBOHYDRATE RADICALS

Roger W. Binkley and Edith R. Binkley

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Introduction: Free-Radical Reactions in Carbohydrate Chemistry

I. The Emergence of Free-Radical Reactions

The success of free-radical reactions in chemical synthesis is one of the remarkable developments in chemistry during the past several decades. Investigation and application of these reactions continues unabated at present and shows no sign of decreasing in the future. To appreciate the rapid rise of free-radical reactions to their position of prominence in the synthesis of organic compounds, it is only necessary to compare the wealth of information in existence today with the modest amount of material that was available prior to the 1970s. This comparison is easily done by consulting some of the many books and review articles describing the development of various aspects of free-radical chemistry during the past several decades.[1-102] (Free-radical polymer formation has a different history. Considerable information on this topic existed prior to the 1970s.)

Once extensive investigation began, synthetic, free-radical chemistry matured so rapidly that by 1993 it was possible to state with confidence that “radical reactions, even with highly complex and heavily substituted substrates, can be conducted in a highly selective and efficient manner."[23] Assessments such as this, which continue to be reinforced as additional discoveries are made, leave little doubt about the importance of radical reactions; yet, chemists saw these processes much differently earlier in the 1900s. In reflecting on these earlier times, the pioneering, free-radical chemist C. Walling noted that most chemists considered radical reactions to be "messy, unpredictable, unpromising and essentially mysterious".[7]

What caused such a dramatic change in attitude toward radical reactions? Undoubtedly there were a number of reasons, but several are particularly noteworthy. One of these is the discovery of radical-based reactions for such synthetically important transformations as extending carbon-atom chains, creating new ring systems, and altering substitution patterns. Another decisive factor is the sophistication, based largely on careful measurement of rate constants, that researchers developed in adjusting reaction conditions to favor specific pathways. Also influential is the information discovered about ways to conduct radical reactions under mild conditions. All of these factors participated in changing attitudes toward free-radical reactions to the point that these reactions became recognized as powerful synthetic tools and considered to be valuable compliments to their ionic counterparts.[103]

II. The Role of Free-Radical Reactions in Carbohydrate Synthesis

The characteristics of free-radical reactions are well suited for transformation of multifunctional compounds such as carbohydrates. The presence of many functional groups in a compound can open a variety of easily activated reaction pathways; consequently, any mild reaction that accomplishes a desired structural change in the face of many possible changes is greatly prized. The high levels of selectivity and mild conditions characteristic of many radical reactions make these processes particularly attractive for carbohydrate synthesis.

III. Chain Reaction: A Natural Pathway for Free-Radicals

Free radicals in solution tend to combine with each other at rates that are close to the highest possible, that is, rates approaching those at which reactants diffuse through a solution.[104] Rapid radical combination dictates that to observe other radical reactions, a low concentration of radical intermediates must be maintained. The problem of avoiding radical combination and, at the same time, promoting other radical reactions finds a natural solution in the use of chain reactions. Efficient chain reactions are processes in which each of a small number of radicals starts a sequence of reactions that is repeated many times before a reaction such as radical combination terminates the chain. The match between the need to maintain low radical concentration and the benefit that low concentration brings to chain reactions naturally leads to many of the most useful, free-radical reactions being chain processes. It is reasonable (perhaps mandatory), therefore, to begin describing free-radical chemistry with a detailed discussion of chain reactions. Such a discussion is the focus of the next chapter.

Preface

Structure and Reactivity of Carbohydrate Radicals is the first Volume in the series *Radical Reactions of Carbohydrates*. Volume I contains eleven chapters that describe the basic chemistry of carbohydrate radicals. The first of these chapters briefly outlines the emergence of radical reactions in organic chemistry and links these reactions to carbohydrates. The next two chapters introduce radical chain (Chapter 2) and nonchain (Chapter 3) reactions. Chapter 4 catalogs and illustrates elementary radical reactions of carbohydrates, and Chapter 5 shows how these reactions are combined into sequential processes. Once a foundation has been established by the first five chapters, discussion turns to how radical structure and conformation (Chapter 6), radical philicity (Chapter 7), and reaction rates (Chapter 8) affect radical reactivity. The final chapters build on the information from earlier ones to explain how the more complex phenomena of chemoselectivity (Chapter 9), regioselectivity (Chapter 10), and stereoselectivity (Chapter 11) are applied to understanding radical reactions of carbohydrates.

This book is directed toward a broad range of scientists. It provides the information needed for an individual to start with a basic understanding of organic chemistry and reach the current level of understanding of the radical chemistry important in the study of carbohydrates. It also serves as a resource for experienced researchers who may wish to review some aspect of the field and, at the same time, find references to the primary literature. Other scientists who may find this book useful are persons whose primary interest is in radical chemistry but who recognize the expanded understanding of radicals that comes from studying reactions of carbohydrates, that is, reactions of polyfunctional molecules that differ in stereochemistry in a systematic way.

A look ahead to Volume II in this series finds *Radical Reactions in Carbohydrate Synthesis*, a book containing twenty-four chapters that describe and analyze radical reactions as they are used in carbohydrate chemistry. Each of the first nineteen chapters in Volume II is devoted to discussion of the radical reactions of a particular type of carbohydrate derivative. The remaining chapters describe how transition-metal complexes are used either to generate carbohydrate radicals or form radicals that react with carbohydrates. Taken together the twenty-four chapters in Volume II provide a complete picture of radical reactions involving carbohydrates.

About the Authors

Roger and Edie Binkley are retired and live in Oberlin, Ohio. One of their activities is to write about carbohydrate chemistry. Their first joint effort was the book *Carbohydrate Photochemistry.* Roger is presently an Emeritus Professor of Chemistry at Cleveland State University and an Affiliate Scholar at Oberlin College. Edie has an undergraduate degree in chemistry and spent many years teaching the Cleveland Heights-University Heights school system.

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CHAPTER OVERVIEW

2: Chain Reactions

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.

Topic hierarchy

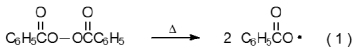
I. Definitions

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).



(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]

(2)

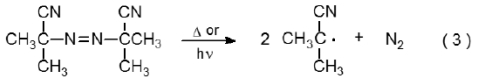
An appropriate initiator should provide a steady supply of radicals during the entire reaction. The needed supply will exist if the initiator has a lifetime comparable to the time required for completion of the reaction being conducted.[3] [The lifetime of an initiator is often described in terms of the amount of time required for 50% of the material to react, that is, its half-life ($t_{½}$).] 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]



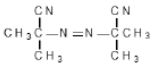
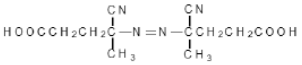
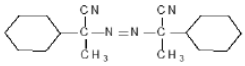
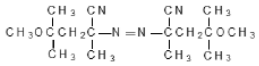
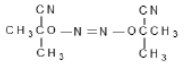
(3)

AIBN **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 soluble 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 termperature.[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
 AIBN	0.5 h at 85 °C 5 h at 70 °C	3,6,7
 ACVA	10 h at 69 °C	8
 ABCN or ABC	2 h at 100 °C	9
 V-70	a	10-13
 DTBH	29 min at 65 °C	14

[a] A typical reaction is run at room temperatrue for 12h.

Table 1. Azo compounds used to initiate 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 $CH_3(CH_2)_9CH_2\cdot$ formed from dilauroyl peroxide (**6**) (Scheme 2).[24–29] Benzoyl peroxide (**7**) and di-*tert*-butyl peroxide[30–32] (**4**) also produce radicals that add to an *O*-thiocarbonyl group.

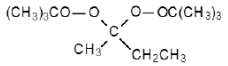
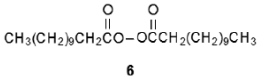
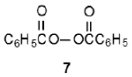
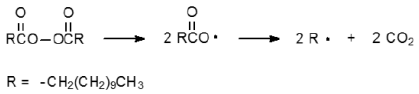
Compound	$t_{1/2}$	Reference
4	1 h at 150 °C 10 h at 126 °C	3
 **5**	1 h at 125 °C	18
 **6**	1 h at 80 °C	19
 **7**	1 h at 95 °C	3

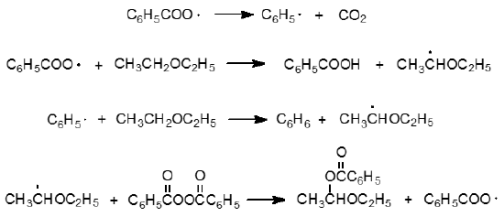
Table 2. Peroxide initiators used in radical reactions of carbohydrates

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 $C_6H_5\cdot$ or $C_6H_5CO_2\cdot$ reacts with benzoyl peroxide (Scheme 3).[6]

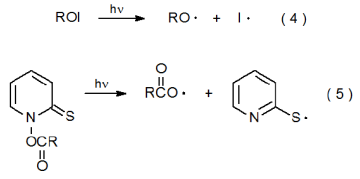
Scheme 3



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 ultra-violet (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. Photochemical 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 R=$(CH_2)_{14}CH_3$ and from 19 to 34 when R=C_6H_{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.

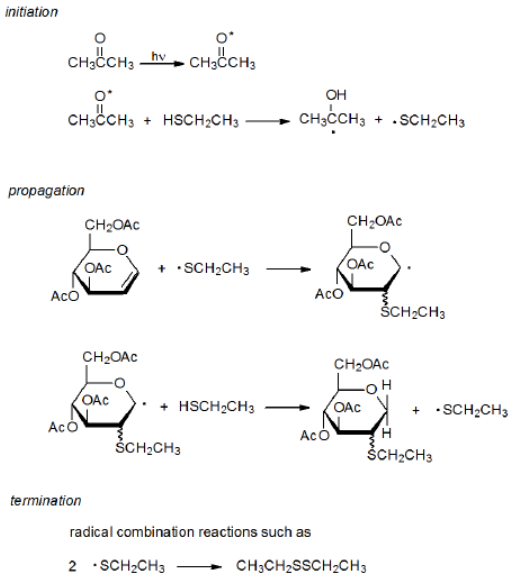
a. 2,2'-Azobis(isobutyronitrile)

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.)

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]

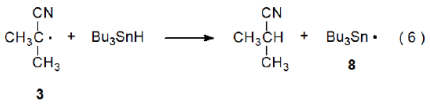
Scheme 4

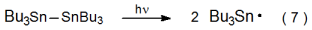


Benzophenone has a longer wavelength and more intense (n,π*) absorption than does acetone; consequently, it is easier to form excited benzophenone without having a carbohydrate reactant absorb the incident light. The presence of the photoproducts benzhydrol and benzpinacol, as well as unreacted benzophenone,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

c. Hexaalkylditins

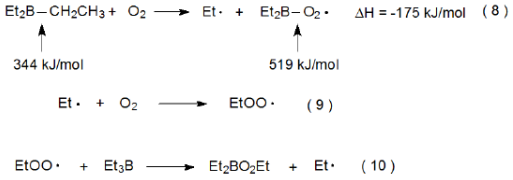
The chain-carrying radical in many reactions of carbohydrates is the tri-*n*-butyltin radical (**8**). This radical usually is generated during the initiation phase of a reaction when the 2-cyano-2-propyl radical **3** abstracts a hydrogen atom from Bu_3SnH (eq 6). Sometimes it is necessary to generate $Bu_3Sn\cdot$ without Bu_3SnH being present in the reaction mixture. In such a situation $Bu_3Sn\cdot$ can be formed by photolysis of hexabutylditin with ultraviolet light (eq 7).[42]





5. Chemical Initiation

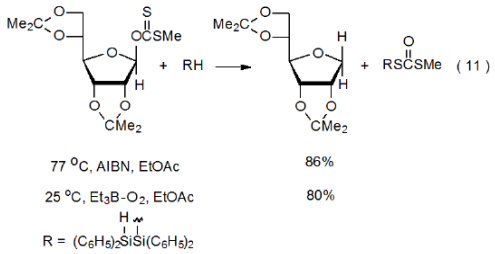
Thermal and photochemical initiation draw energy for radical formation from heating (vibrational excitation) and photon absorption (electronic excitation), respectively. Chemical initiation is different in that it uses energy stored in bonds to form initiating radicals; for example, triethylboron reacts 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 $(EtO)_3B$] 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 $Et_3B–O_2$ 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 $(Me_3Si)_3SiH$. The silicon hydride used in the reaction shown in eq 11 is a less common but effective hydrogen-atom donor.

B. The Propagation Phase

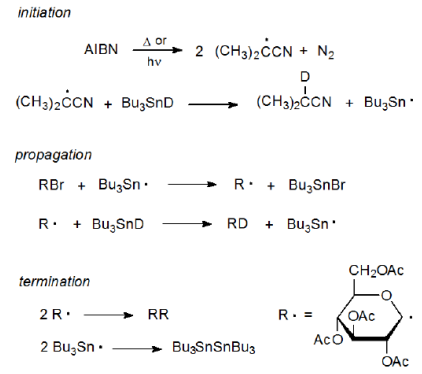
1. General Characteristics

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.

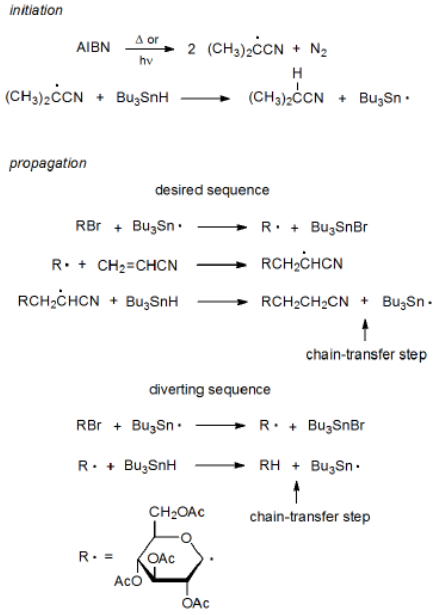
2. Examples of Propagation Sequences

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 deuteride[51] (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



Scheme 6



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 R· and Bu_3Sn· alternate in carrying the chain forward by each reacting only with a particular type of reactant molecule; that is, Bu_3Sn· reacts only with the glucosyl halide (RX), and the carbohydrate radical (R·) reacts exclusively with Bu_3SnD. This discriminating reactivity has been called "disciplined behavior".[54]

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· 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· must be reactive enough to add to acrylonitrile. Carbon-centered, carbohydrate radicals (R·) 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· 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.]

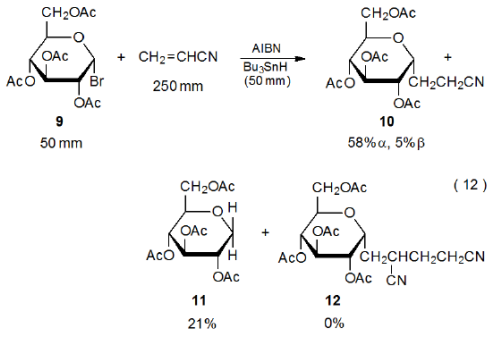
A second requirement for a successful reaction is that R· exist long enough in solution to add to an unsaturated reactant. One reaction that could prevent this addition from taking place is chain termination (R· + R· → RR), but chain termination is unlikely to do so because the very low concentration of R· causes the rate of radical combination to be much slower than the rate of addition of R· to a compound with an electron-deficient multiple bond. A more probable reason for R· 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· 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· 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-atom abstraction is more rapid than a second radical addition.

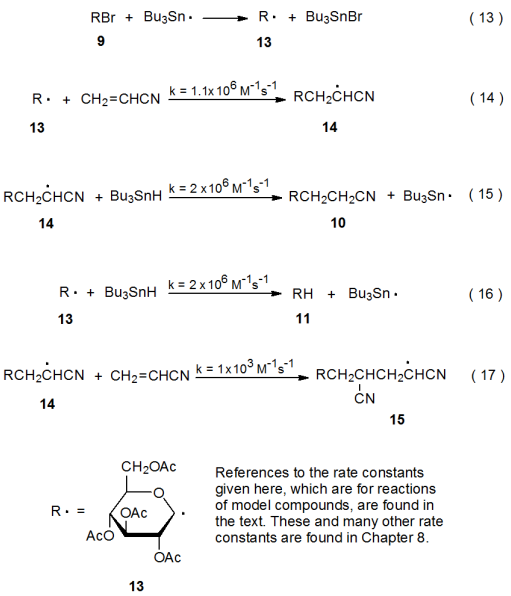
Another way of describing the constraints placed on the desired sequence in Scheme 6 by an additional propagation step is in terms of chain-transfer reactions. In each propagation sequence the chain-transfer step ends the existing cycle and creates the radical that begins a new cycle. In the reactions 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· 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· reacts with tri-*n*-butyltin hydride to produce RH (the simple-reduction product) before it adds to acrylonitrile.

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 constants 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.



Scheme 7



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 ·CH_2OH 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).

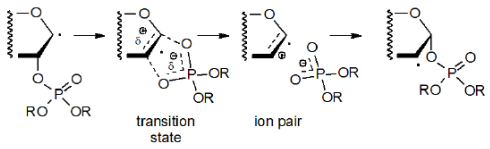
There is a limit to how large the ratio of acrylonitrile to tri-*n*-butyltin hydride can become before adding more nitrile to the reaction mixture is counterproductive. This limit will be reached when reaction of **14** with acrylonitrile (eq 17, k = 1 x 10^3 M^{-1} s^{-1})[57] competes effectively with reaction of this radical (**14**) with TBTH (eq 15, k = 2 x 10^6 M^{-1} 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.

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.

Scheme 8



R = an aryl or alkyl group

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 x 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·) combine with a molecule of oxygen to give a peroxy radical (ROO·) (eq 18). Formation of ROO· 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.

$$R\cdot + O_2 \longrightarrow ROO\cdot \quad (18)$$

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.

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 reaction 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.

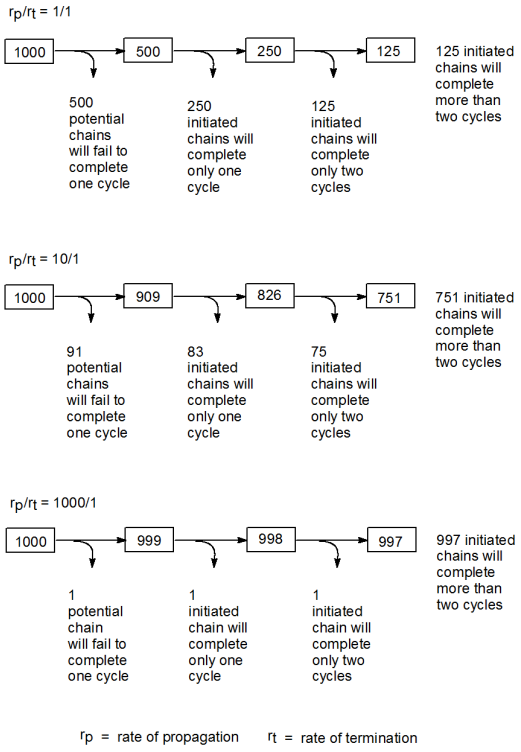
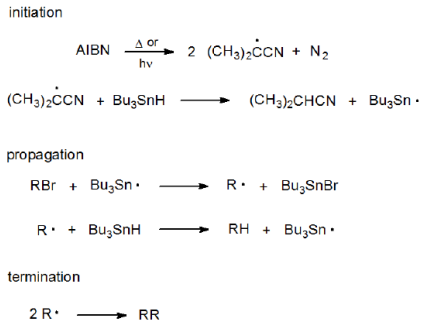


Figure 1. Comparison of the propagation cycles completed by 1000 radicals when r_p/r_t = 1/1, 10/1, and 1000/1.

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· 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 2×10^6 M^{-1} s^{-1}.[56] Since combination of two R· 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 1×10^{10} M^{-1} s^{-1} in benzene,[68] a common solvent for such reactions. A typical radical concentration in a chain reaction is less than 1×10^{-7} 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).

Scheme 9



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

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

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 1×10^{10} M^{-1} s^{-1};[68] (b) the radical concentration in a typical reaction is approximately 1×10^{-7} M;[57,62] and (c) the concentration of the hydrogen-atom donor Bu_3SnH is 1 M. Based on these assumptions, the rate constant for propagation (k_p) for a synthetically useful reaction should be greater than 1×10^2 M^{-1} s^{-1} (eq 22 and eq 23). This limiting value for k_p would hold for any reaction that satisfies the assumptions (a)-(c).

$$\frac{r_p}{r_t} = \frac{k_p[Bu_3SnH]}{k_t[R\cdot]} = \frac{k_p[1\ M]}{[1 \times 10^9\ M^{-1}s^{-1}]\ [1 \times 10^{-7}\ M]} \quad (22)$$

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

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 ^{o}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.

CHAPTER OVERVIEW

3: Nonchain Reactions

Although many radical reactions in carbohydrate chemistry are chain processes, nonchain reactions also play a significant role in the chemistry of these compounds. As mentioned at the beginning of Chapter 2, chain and nonchain reactions each involve radical formation, transformation, and disappearance. The difference is that for chain reactions the transformation cycle typically is repeated many times for each initiating radical, but for nonchain reactions each radical formed causes transformation to take place only once. The radicals that participate in nonchain reactions sometimes are formed by bond homolysis but more often are produced by electron transfer. Bond homolysis is usually a photochemical reaction. Electron transfer typically involves transition-metal-generated radicals.

Topic hierarchy

II: Transition-Metal-Generated Radicals

Reactions of radicals generated from transition-metal complexes can be divided into two types based on the direction of electron flow. In some of these reactions the transition metal accepts an electron during radical formation (oxidative electron transfer) and in others it donates an electron during this process (reductive electron transfer). The compounds that most often participate in oxidative electron transfer are manganese(III) acetate [$Mn(OAc)_3$] and ammonium cerium(IV) nitrate [$(NH_4)_2Ce(NO_3)_6$], while those frequently involved in reductive electron transfer are bis(cyclopentadienyl)titanium(III) chloride (Cp_2TiCl), and samarium(II) iodide (SmI_2). Carbohydrates that are bonded to a cobalt-containing complex by a C–Co bond form radicals by oxidative electron transfer and then frequently reform a C–Co bond by reductive electron transfer.

Coenzyme B_{12} (**5**, Figure 1) is one of a group of biologically active molecules that have similar structures.[7] Each member of this group has a cobalt atom surrounded by a macrocyclic ligand (a corrin ring) that bears various substituents. In addition to the corrin ring the cobalt atom in each of these compounds also is coordinated with a ligand that contains a phosphate group, a sugar moiety, and a nitrogenous base. Compounds related to **5** differ from each other in the structure of the R group attached to cobalt. R represents the 5'-deoxyadenosyl group in coenzyme B_{12} (**5**), but for related compounds R can be as structurally simple as a methyl or hydroxyl group.[7]

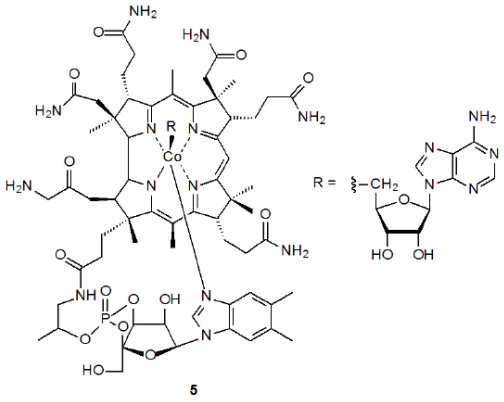
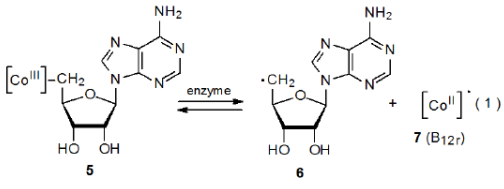


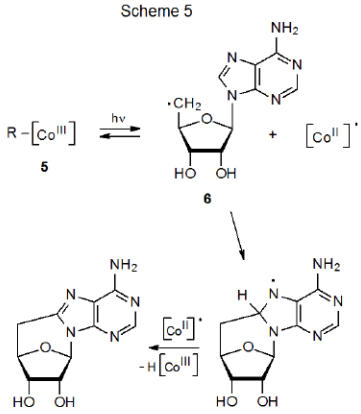
Figure 1. The structure of coenzyme B_{12} (5'-adenosylcobalamin)

The original stimulus for study of carbon–cobalt bond homolysis as a pathway for forming carbon-centered radicals came from investigation of the reactions of coenzyme B_{12} (**5**).[8–10] In biological systems enzyme-induced homolysis of the carbon–cobalt bond in **5** produces the 5'-deoxyadenosyl radical **6** and the cobalt-centered radical **7** (B_{12r}, eq 1).[8–10] In experiments outside biological settings the 5'-deoxyadenosyl radical (**6**) is produced from coenzyme B_{12} (**5**) by photolysis with visible light.[11] When photolysis is conducted in the absence of an effective hydrogen-atom donor or other radical trap, cyclization follows homolysis of the carbon–cobalt bond (Scheme 5).[8-10,12]



[Co^III] or [Co^II] = coenzyme B_{12} (Figure 1) without the adenosyl group but with cobalt in different oxidation states

Scheme 5



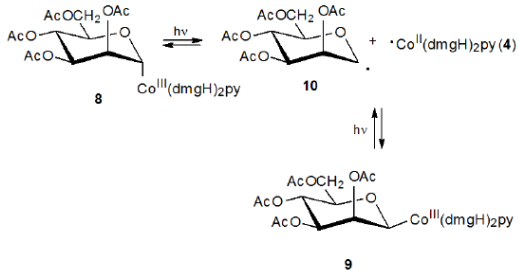
$R-[Co^{III}]$ = coenzyme B_{12} (see Figure 1)

$[Co^{II}]^{\cdot}$ = coenzyme B_{12} without the adenosyl group

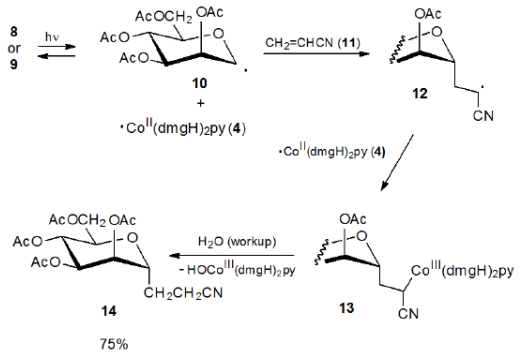
b. Cobaloxime Complexes

The discovery that carbon–cobalt bond homolysis in coenzyme B_{12} (**5**) produced the carbon-centered radical **6** (eq 1), led to investigation of simpler molecules that could model this behavior. Cobaloximes are one of several types of compounds found to be effective choices for this role.[13–16] Carbohydrate cobaloximes **8** and **9** produce radicals **10** and **4**, which recombine in the absence of radical traps (Scheme 6).[13] In the presence of compounds that react with radicals, **10** and **4** undergo characteristic radical reactions; thus, the D-mannopyranos-1-yl radical **10** adds to acrylonitrile (**11**) to give the adduct radical **12**, which then combines with ·Co(dmgH)$_2$py (**4**) to form the addition product **13** (Scheme 7).[13]

Scheme 6



Scheme 7



A necessary condition for the reaction shown in Scheme 7 is that **4** [Co(dmgH)$_2$py] be stable enough to remain unchanged while the addition of **10** to **11** is taking place. The needed stability of **4** derives from protection of its radical center by the attached ligands; thus, **4** can be viewed as a persistent radical.

c. The Persistent-Radical Effect

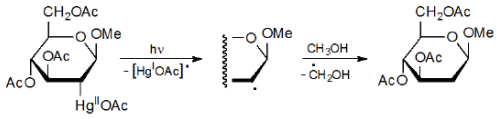
Persistent radicals, such as ·Co(dmgH)$_2$py (**4**), are responsible for a type of reactivity known as the persistent-radical effect.[17–19] This effect causes a reaction that generates a persistent radical (R_1·) and a transient radical (R_2·) in equal amounts to give a higher yield of the cross-coupling product (R_1R_2) than would be expected from random radical coupling. The explanation for greater cross-coupling product formation begins with the recognition that although persistent and transient radicals are formed in equal amounts, this equality is short lived. Due to the reactive nature of transient radicals their concentration decreases more rapidly in the early stages of a reaction than does the concentration of persistent radicals. (Transient radicals combine, disproportionate, and undergo other reactions much more rapidly than persistent radicals.) The rapidly developed, higher concentration of persistent radicals in the early stages of reaction means that any newly formed, transient radical is more likely to encounter and combine with a persistent radical than with another transient one; in other words, the cross-coupling product R_1R_2 becomes the major coupling product.

An example of the persistent radical effect is shown in the reaction given in Scheme 4, where carbon–cobalt bond homolysis in **1** or **2** produces the persistent radical **4** and the transient radical **3**. Even with the extended heating or photolysis needed to reach equilibrium, there was no evidence of formation of a coupling product other than the cross-coupling products **1** and **2**. The persistent radical effect also is operative in the addition reaction shown in Scheme 7. In this case the transient radical **12**, produced by addition of **10** to acrylonitrile (**11**) , and the persistent radical **4** combine to form the only radical-coupling product isolated.

2. Carbon-Mercury Bond Homolysis

There are similarities in reactivity among compounds with C–Co and C–Hg bonds. Both bonds are strong enough to exist in stable structures at room temperature but both readily cleave upon photolysis. The result in each case is formation of a metal-centered and a carbon-centered radical. Carbon-centered radicals produced by carbon–mercury bond homolysis undergo typical radical reactions, such as the hydrogen-atom abstraction shown in Scheme 8.[20]

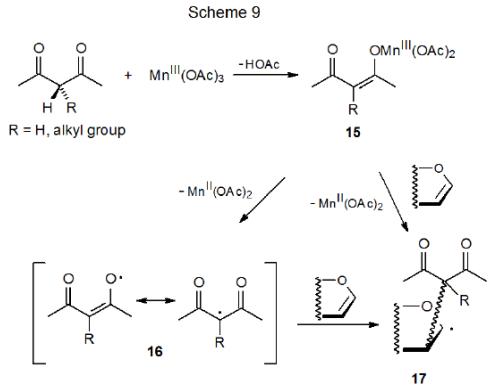
Scheme 8



3. Manganese(III) Acetate [Mn(OAc)$_3$] Reactions

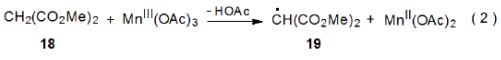
Carbon-centered radicals can be generated by reaction of manganese(III) acetate with CH-acidic compounds such as the β-diketone shown in Scheme 9.[21–24] The first step in this process is formation of the enolate **15**.[23] In the presence of an unsaturated compound two mechanisms for reaction of **15** are considered to be possible. In the first of these electron transfer forms manganese(II) acetate and the resonance-stabilized radical **16**, which then adds to an unsaturated compound. A second possible pathway for addition is a concerted process in which the enolate **15** reacts directly with the unsaturated compound to produce the adduct radical **17** (Scheme 9).[23] Reaction by either of these pathways is believed to take place by inner-sphere electron transfer.

Scheme 9

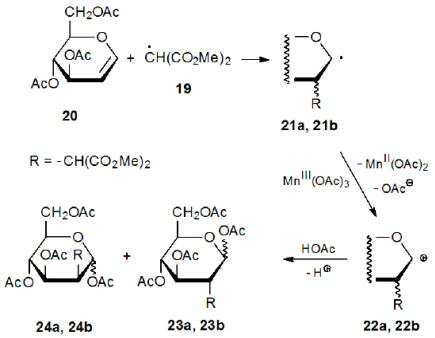


Since radical centers with two, attached carbonyl groups are electrophilic, radicals such as **16** (Scheme 9) add most easily to unsaturated compounds with electron-rich multiple bonds.[22] This is the point at which carbohydrates typically become involved in reactions begun by manganese(III) acetate because glycals have electron-rich π systems that are attractive targets for addition of

electrophilic radicals; for example, the radical **19**, formed by reaction of dimethylmalonate (**18**) with manganese(III) acetate (eq 2), adds to the tri-*O*-acetyl-D-glucal **20** to produce the stereoisomeric radicals **21a** and **21b** (Scheme 10).[25,26] This addition, which occurs regioselectively at C-2, is followed by oxidation of the resulting radicals with a second molecule of manganese(III) acetate to give the corresponding cations **22a** and **22b**. These cations react with the solvent (acetic acid) to yield the final products (**23a**, **23b**, **24a**, and **24b**). Manganese(III) acetate, therefore, is involved in both the formation and disappearance of the radicals in this reaction. (Electrophilic radicals and other aspects of radical philicity are discussed in Chapter 7.)



Scheme 10



Manganese(III) acetate has a more complicated structure than the formula $Mn(OAc)_3$ indicates. It is an oxo-centered trimer of three manganese ions held together by six bridging acetates.[27–29] Three representations for this structure are shown in Figure 2. It is often convenient in discussing reactions of this compound to use the abbreviated formula $Mn(OAc)_3$.

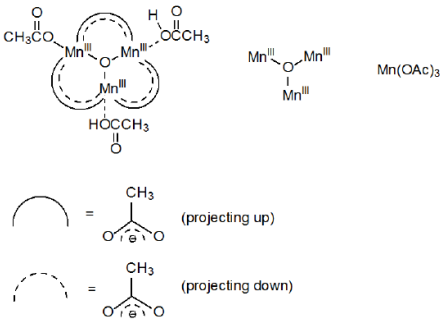
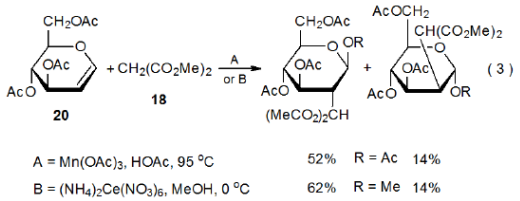


Figure 2. Three representations for maganese(III) acetate

4. Ammonium Cerium(IV) Nitrate $[(NH_4)_2Ce(NO_3)_6]$ Reactions

Reaction of CH-acidic compounds with ammonium cerium(IV) nitrate generates electrophilic, resonance-stabilized radicals in a manner similar to reaction with manganese(III) acetate.[30,31] As mentioned in the previous section, these radicals add readily to the electron-rich double bonds such those found in glycals (eq 3).[30] Oxidation of CH-acidic compounds with ammonium cerium(IV) nitrate to produce electrophilic radicals has the advantage, when compared to reactions with manganese(III) acetate, of being able to be conducted at or below room temperature. [The reactions of manganese(III) acetate and ammonium cerium(IV) nitrate are discussed further in Chapter 21 of Volume II.]



III. Photochemically Generated Radicals

Although, as described in Chapter 2, photolysis sometimes initiates chain reactions, it also can produce radicals that undergo nonchain reactions. In a photochemically initiated chain reaction the number of photons that must be absorbed to cause complete reaction typically is far smaller than the number of molecules reacted. (A radical formed by absorption of one photon can begin a chain that produces many product molecules.) In a nonchain reaction the number of photons absorbed typically must be at least equal to the number of molecules reacted. Actually, it is rare that each, absorbed photon causes a reaction to take place because reaction is only one of the ways an excited molecule dissipates its energy; consequently, for complete reaction to occur in a non-chain process the number of photons absorbed often greatly exceeds the number of molecules reacted.

Although cleavage of weak carbon–metal bonds (e.g., carbon–cobalt bonds) tends to occur readily upon photolysis, photochemical processes do not require a reactant to have a weak bond in order for bond homolysis to take place. When ultraviolet light is absorbed by a compound, enough energy is present in the excited system to break even strong bonds.

IV. Thermally Generated Radicals

Heating of carbohydrates has a limited role in causing useful radical reactions. Few carbohydrates or their derivatives have bonds weak enough to generate radicals at temperatures that avoid general structural decomposition. As described earlier in this chapter, a carbohydrate derivative with a carbon–cobalt or oxygen-iodine bond can generate radicals by thermal reaction, but even for such compounds radical formation usually takes place photochemically.

V. Summary

Transition-metal-generated radicals are involved in most nonchain, radical reactions of carbohydrates. In some of these reactions the transition metal accepts an electron, and in others it is an electron donor. The carbohydrate radicals thus produced undergo typical radical reactions, such as addition to a double bond and hydrogen-atom abstraction. Manganese(III) acetate and ammonium cerium(IV) nitrate both react with CH-acidic compounds, such as those with β-dicarbonyl substituents, to produce electrophilic radicals that add readily to electron-rich double bonds (e.g., those present in glycals). Bis(cyclopentadienyl)titanium chloride (Cp_2TiCl) reacts with glycosyl halides to produce pyranos-1-yl radicals. In the absence of a radical trap these radicals generate anomeric mixtures of glycosyl titanium compounds that undergo β-elimination to form glycals. Radical intermediates also are produced when Cp_2TiCl causes reductive opening of epoxide rings. The samarium(II) iodide–hexamethylphosphoramide (SmI_2–HMPA) complex often serves as an electron donor in radical-forming reactions where a carbohydrate sulfone or halide is the electron acceptor.

Organocobalt and organomercury compounds generate radicals by carbon–cobalt and carbon–mercury bond homolysis, respectively. These compounds form carbon-centered radicals by both thermal and photochemical reaction. Carbon–cobalt bonds also undergo enzymatic cleavage, but in nonbiological settings photochemical bond homolysis is most common.

Photolysis of a variety of carbohydrates produces radicals that participate in nonchain reactions. Excited carbonyl compounds generate radicals by hydrogen-atom abstraction and by C–C bond fragmentation. Oxygen–iodine bonds cleave homolytically upon photolysis to produce highly reactive, alkoxy radicals.

CHAPTER OVERVIEW

4: Elementary Reactions

Radical reactions are composed of sequences of elementary reactions. An elementary radical reaction is one that does not produce an intermediate. Most elementary, radical reactions consist of transformation of one radical into another, but those that create radicals from nonradicals or cause radicals to disappear also qualify. Where radicals are concerned, an elementary reaction either creates a radical from a nonradical, transforms one radical into another, or causes a radical to disappear.

Topic hierarchy

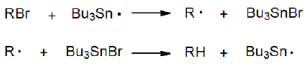
I. Introduction

An elementary reaction is one that has no intermediates. Every reaction that forms an intermediate actually is a combination of two or more elementary reactions. Where radicals are concerned, an elementary reaction either creates a radical from a nonradical, transforms one radical into another, or causes a radical to disappear.[1,2]

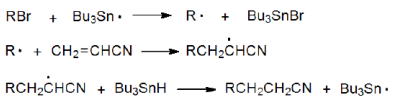
For chain reactions the propagation phase always contains at least two elementary reactions (Scheme 1). Nonchain reactions are similar in that they also contain at least two elementary reactions (Scheme 2). The elementary reactions upon which the free-radical chemistry of carbohydrates is based are listed in a general form in Table 1.[1,2] Specific examples are given in the discussion of each reaction that takes place in this chapter. In describing these reactions the term "carbohydrate radical" (CARB·) refers to a radical centered on one of the atoms, usually carbon, in a carbohydrate.

Scheme 1

simple reduction: two elementary reactions

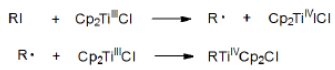


radical addition: three elementary reactions



Scheme 2

two elementary reactions: both electron-transfer



three elementary reactions: two electron transfer and one cyclization

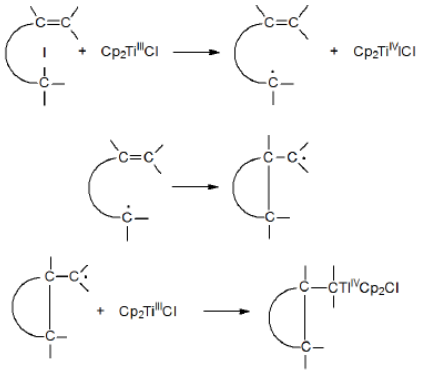
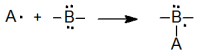
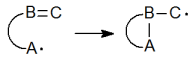
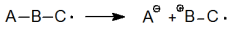
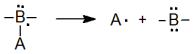
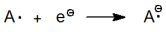
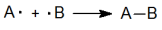
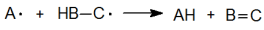
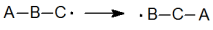


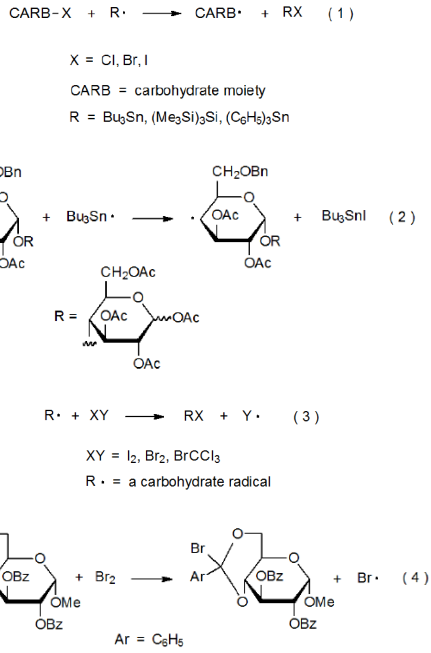
Table 1. Elementary Radical Reactions

Reaction Description	Reaction Equation
atom abstraction (B is a single atom.)	
group abstraction (B is a group of atoms.)	
addition to a compound with a multiple bond	
addition that produces a hypervalent atom	
cyclization (internal addition)	
homolytic β-fragmentation	
heterolytic β-fragmentation	
α-fragmentation	
bond homolysis	
electron capture by a radical	
electron donation by a radical	
radical combination	
disproportionation	
migration	

II. Atom Abstraction

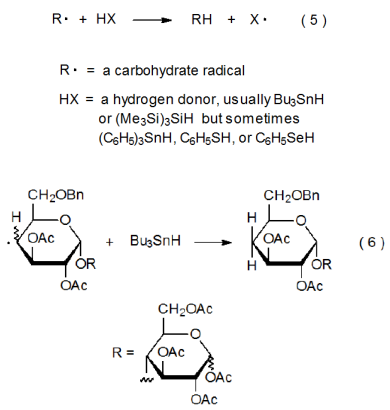
A. Halogen-Atom Abstraction

Halogen-atom abstraction can take place both in forming a halogenated carbohydrate and in removing a halogen atom from such a compound. When abstraction is from a halogenated carbohydrate, it produces a carbohydrate radical (eq 1). The abstracting radical typically is tin-centered or silicon-centered. In the reaction shown in eq 2, for example, a carbohydrate radical forms when a tin-centered abstracts an iodine atom from a deoxyiodo sugar.[3] Abstraction that generates a halogenated carbohydrate takes place when I_2, Br_2, or another halogen donor reacts with a carbohydrate radical (eq 3). Equation 4 describes a reaction of this type.[4]



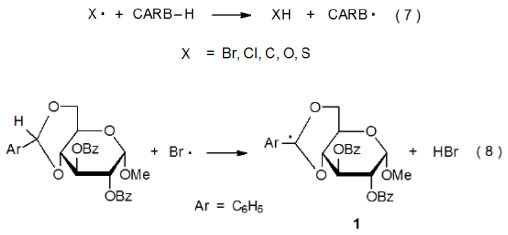
B. Hydrogen-Atom Abstraction

Hydrogen-atom abstraction is an elementary reaction that permeates the free-radical chemistry of carbohydrates. Because it is the final propagation step in many chain reactions, hydrogen-atom abstraction often converts a carbon-centered radical into a stable product. The hydrogen-atom donor in such reactions usually is a tin or silicon hydride, but sometimes a thiol or selenol serves in this role (eq 5). The final step in the simple reduction shown in eq 6 is a typical, hydrogen-atom-abstraction reaction.[3]

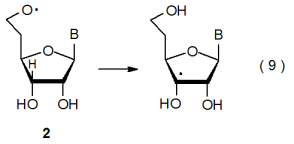


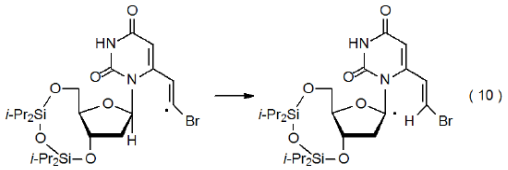
Carbohydrates also can serve as hydrogen atom donors (eq 7). A radical centered on a bromine, chlorine, or oxygen atom (and, sometimes, on a sulfur or carbon atom) is able to abstract a hydrogen atom from a carbohydrate in an elementary reaction that can be highly regioselective. For intermolecular reactions this selectivity is due to radicals preferentially abstracting the hydrogen

atoms that produce the most stable carbon-centered radicals. In the reaction shown in eq 8, for example, the bromine atom abstracts only the hydrogen atom that produces the highly resonance-stabilized radical **1**.[4]



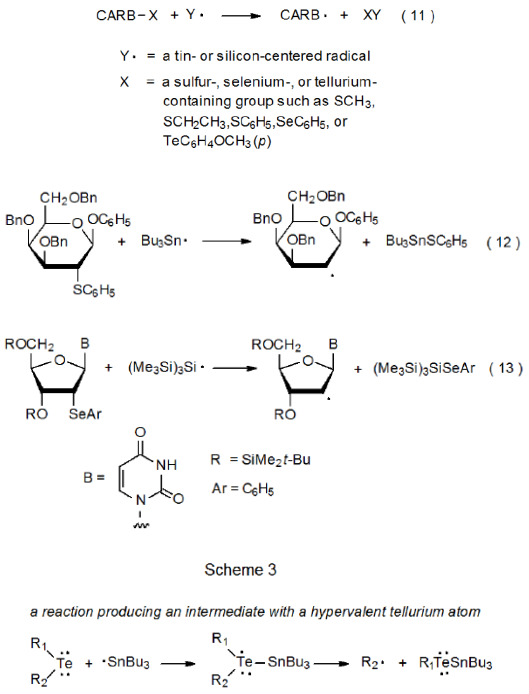
If a radical is centered on an oxygen or carbon atom in a carbohydrate, internal abstraction becomes a possibility. Such abstraction is regioselective not only because a more stable radical is being produced but also because the radical center is able easily to come within bonding distance of a limited number of hydrogen atoms (sometimes only one). In the reaction shown in eq 9, the only hydrogen atom abstracted is the one that is 1,6-related to the radical center.[5] Although an oxygen-centered radical (e.g., **2** in eq 9) is reactive enough to abstract a hydrogen atom from any carbon-hydrogen bond in a carbohydrate,[6] only the most reactive carbon-centered radicals (e.g., primary and vinylic ones) are capable of such reaction (eq 10).[7]





III. Group Abstraction

Group abstraction is possible when a group is attached to a carbon atom in a carbohydrate by a bond to a sulfur, selenium, or tellurium atom (eq 11). The abstracting radical in nearly every instance is tin-centered (eq 12)[8] or silicon-centered (eq 13).[9] Although group abstraction reactions can be elementary ones, they cease to be so if an intermediate with a hypervalent atom forms (Scheme 3). (Generating a hypervalent atom causes abstraction to become a combination of radical addition and α-fragmentation.) Only rarely is a hypervalent atom believed to be involved if a sulfur or selenium atom provides the link to the carbohydrate framework.[10,11] (An example of a noncarbohydrate, selenide reaction that appears to involve a hypervalent selenium atom is described in Chapter 8, Section III.B.) Where the connection is to a tellurium atom, computational investigations indicate that a radical with a hypervalent atom is likely form.[10]



Scheme 3

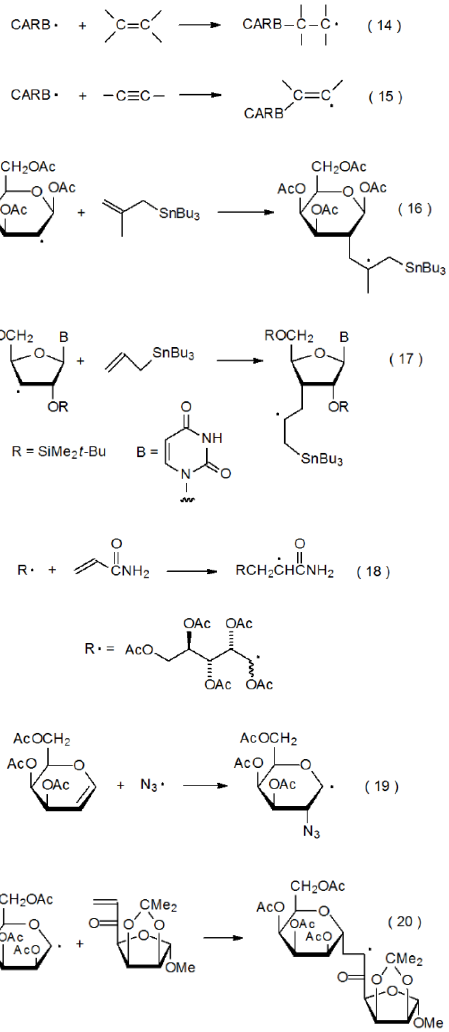
a reaction producing an intermediate with a hypervalent tellurium atom

IV. Radical Addition

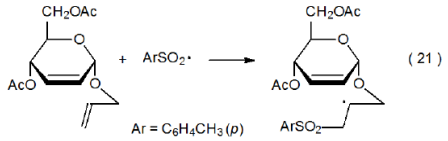
A. Intermolecular Reaction

1. Addition to a Multiple Bond

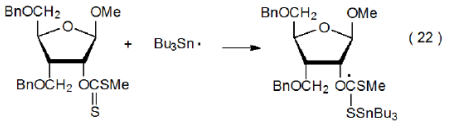
Addition of a carbon-centered radical to a multiple bond in an unsaturated compound is an elementary reaction that forms a new carbon–carbon bond (eq 14 and eq 15). One way for this to happen is for a radical centered on one of the carbon atoms in a pyranoid or furanoid ring to add to an unsaturated noncarbohydrate. Examples of this type of addition are found in the reactions shown in eq 16,[12] where a radical is centered on C-2 in a pyranoid ring, and eq 17,[13] where the radical center is on C-3' in a furanoid ring. It is also possible to have the radical center located on a carbon atom that is in an open-chain structure (eq 18).[14] Addition can involve a noncarbohydrate radical or a carbohydrate radical adding to an unsaturated carbohydrate (eq 19[15] and eq 20[16], respectively). When the radical and the compound to which it is adding are both carbohydrates, reaction creates complex structures quickly (eq 20).



Heteroatoms play a role in radical addition when a radical centered on a nitrogen, phosphorous, silicon, sulfur, or tin atom adds to an unsaturated carbohydrate; for example, a nitrogen-centered radical is involved in the reaction shown in eq 19,[15] and the adding radical in the reaction pictured in eq 21 is sulfur-centered.[17] Radicals also add to unsaturated carbohydrates in which the multiple bond contains one or two heteroatoms. An example of this type of reaction is given in eq 22, where addition is to a carbon–sulfur double bond.[18] Similar radical addition reactions occur with carbohydrates containing carbon–oxygen, carbon–nitrogen, and nitrogen–oxygen multiple bonds.



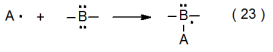
(21)



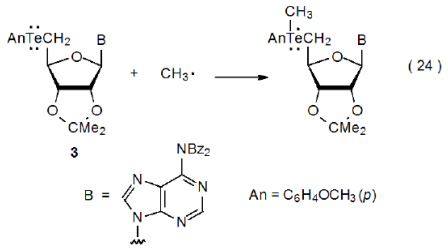
(22)

2. Addition That Forms a Radical with a Hypervalent Atom

Although most addition reactions consist of a radical adding to a multiple bond, reaction that does not involve a double or triple bond also can take place. This happens when addition produces a radical in which an atom has an expanded octet (eq 23). Such a reaction is thought to take place when a telluride, such as **3**, reacts with a methyl radical (eq 24).[19]



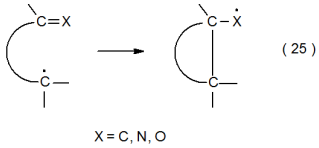
(23)



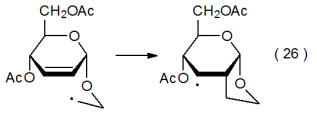
(24)

B. Intramolecular Reaction (Radical Cyclization)

Radical cyclization (eq 25) is an intramolecular version of radical addition that merits special mention due to the synthetic importance of new ring formation. Five- and six-membered rings are created most often, but larger rings also can be produced. A typical radical cyclization reaction is shown in eq 26.[20]



(25)

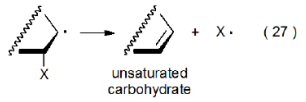


(26)

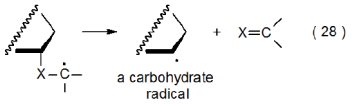
V. Fragmentation Reactions

A. β-Fragmentation

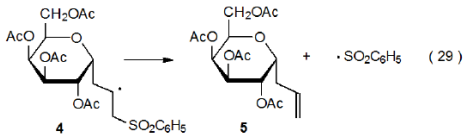
Homolytic β-fragmentation of a radical is an elementary reaction that cleaves a bond to one of the atoms adjacent to a radical center. (Other names for β-fragmentation are β-cleavage and β-scission.) This type of reaction sometimes produces an unsaturated carbohydrate by expelling a noncarbohydrate radical (eq 27), and other times it gives a carbohydrate radical and an unsaturated noncarbohydrate (eq 28). Equation 29 illustrates the first of these possibilities with a reaction in which the radical **4** fragments to give $C_6H_5SO_2\cdot$ and the unsaturated carbohydrate **5**.[21] Being able to form a stabilized radical such as $C_6H_5SO_2\cdot$ is an essential factor in this reaction.



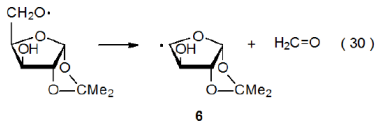
X = Cl, Br, -S(=O)C_6H_5, -SC(=O)SCH_3, -CH_2C(=O)C_6H_5, -SCH_3, N_3

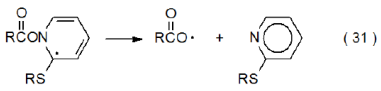


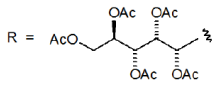
X = O, N

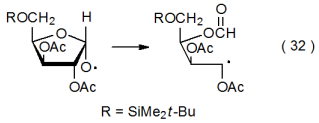


A β-fragmentation reaction producing a carbohydrate radical and an unsaturated noncarbohydrate is one driven by formation of a compound with a thermodynamically stabilized multiple bond (usually a carbon–oxygen double bond) and a radical that also is stabilized (usually by an oxygen atom attached to the radical center). The reaction shown in eq 30 fits this pattern because it produces formaldehyde and the oxygen stabilized radical **6**.[22] Forming an aromatic ring is another way for providing a substantial driving force for β-fragmentation (eq 31).[23] A further option for β-fragmentation is ring opening, a possibility that presents itself when a radical is centered on an atom attached to the ring (eq 32).[24]





R = 

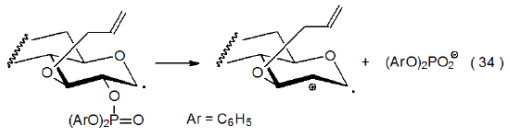


R = $SiMe_2t$-Bu

B. Heterolytic β-Fragmentation

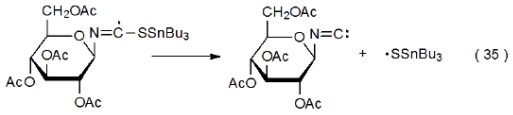
When a radical is centered on a carbon atom that has an effective nucleofuge attached to a neighboring carbon atom, the possibility exists for formation of a radical cation (eq 33). The bond from the neighboring carbon atom to the leaving group needs to be one that does not cleave homolytically with ease; otherwise, β-fragmentation producing ionic intermediates could be preempted by homolytic fragmentation. Heterolytic β-fragmentation occurs in the reaction shown in eq 34.[25]

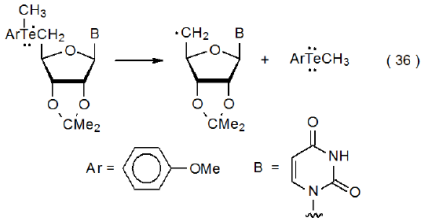
X = $SO_2C_6H_4CH_3$ (*p*), SO_2CH_3, P(=O)(OC_6H_5)$_2$



C. α-Fragmentation

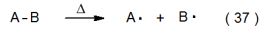
α-Fragmentation is an elementary reaction in which a bond attached to a radical center cleaves homolytically. This reaction is rare because it requires the energy-demanding step of bond breaking without the energetic compensation of bond formation. One situation in which α-fragmentation takes place is in the formation of the isonitrile and stabilized, sulfur-centered radical shown in eq 35.[26] A second occurs in the fragmentation of the hypervalent radical shown in eq 36.[19]



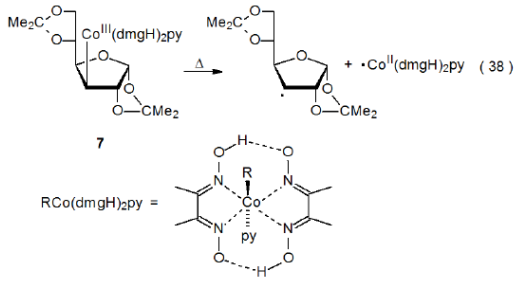


D. Bond Homolysis

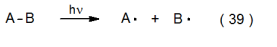
Bond homolysis either produces a pair of radicals (eq 37), or if the bond being broken is part of a ring system, a diradical. Thermal reaction cleaves the weakest bond in a molecule; thus, when the cobaloxime **7** is heated, the carbon–cobalt bond, one of the weakest covalent bonds known, breaks homolytically at temperatures well below those necessary for cleavage of other bonds in the molecule (eq 38).[27] This bond homolysis involves electron transfer with cobalt acting as the electron acceptor.



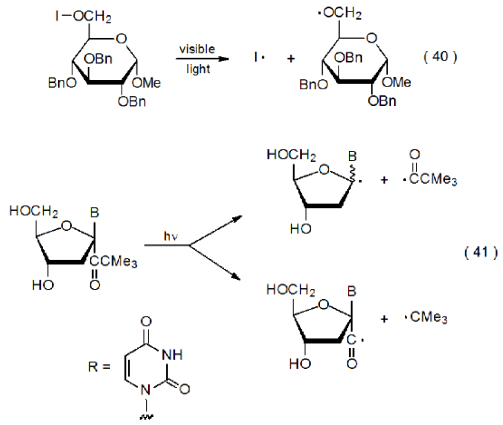
A-B = C-Co, C-Hg, O-I



Photochemical reaction offers a range of possibilities for bond homolysis (eq 39). Success depends both upon a compound being able to absorb the incident light and on this light supplying sufficient energy for bond breaking. Absorption of visible light provides the energy needed to cleave weaker covalent bonds, such as the iodine–oxygen bond in the reaction shown in eq 40.[28] UV radiation is energetic enough to break stronger bonds, such as the carbon–carbon bonds in the reactions pictured in eq 41.[29]



A-B = C-C, C-I, C-Br, C-Cl, C-Co, C-Hg, O-I



Unlike thermal reaction, bond breaking during a photochemical process does not necessarily cleave the weakest bond in a molecule. Selectivity in bond breaking during photolysis results from a combination of factors that control the reactivity of electronically excited molecules. In the reaction shown in eq 41, for instance, excitation energy is quickly localized in the keto group in the substrate. This localization leads to one of the characteristic reactions of an excited aldehyde or ketone, namely, breaking the bond between the carbonyl carbon atom and one of its attached carbon atoms.[30]

VI. Electron Transfer

A. Reactions of Carbohydrate Radicals

Transition-metal complexes can act as electron transfer agents when reacting with carbohydrate radicals (eq 42 and 43). In the reaction shown in eq 44, titanium donates an electron during formation of the carbon-titanium bond between titanocene(III) chloride (Cp_2TiCl) and the pyranos-l-yl radical **8**.[31,32] In the reaction shown in eq 45, ammonium cerium nitrate [$(NH_4)_2Ce(NO_3)_6$] accepts an electron from the pyranos-1-yl radical **9** to convert it into the corresponding cation.[33,34] Other compounds that serve as electron donors in reactions with carbohydrate radicals are SmI_2, $Cr(EDTA)^{2-}$, $[Ru(bpy)_3]^{2+}$, and $Co(dmgH)_2py$. (The structures of the ligands in these compounds are pictured in Figure 1). In addition to $(NH_4)_2Ce(NO_3)_6$, $Mn(OAc)_3$ also acts as an electron acceptor in reactions with carbohydrate radicals.

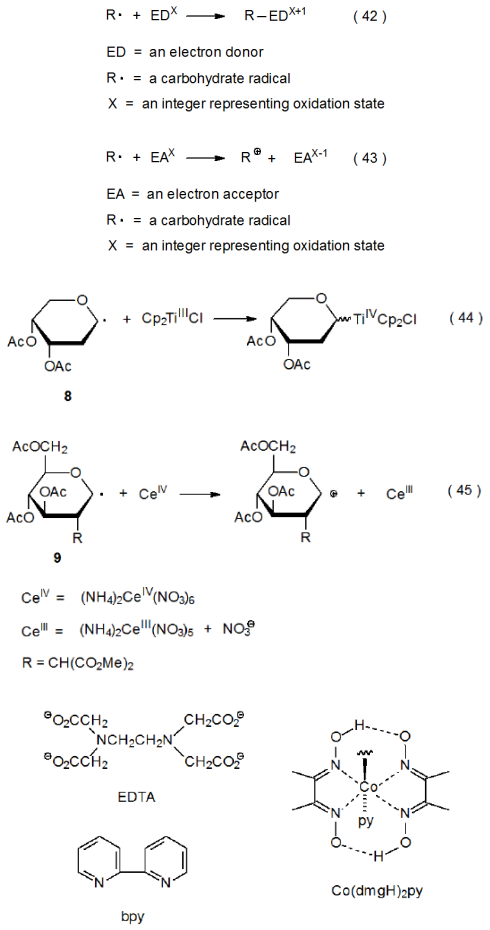
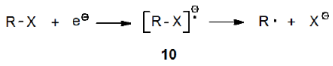


Figure 1. Ligand structures in electron donors

B. Formation of Carbohydrate Radicals

When an electron is transferred to a carbohydrate chloride, bromide, iodide, or sulfone, the resulting radical anion reacts to form a carbohydrate radical (Scheme 4). The two electron donors participating in most of these reactions are SmI_2 (eq 46)[35] and Cp_2TiCl (eq 47),[36] but other transition-metal complexes [e.g., $Cr(EDTA)^{2-}$] are able to function in this capacity. Although the radical anion **10** is pictured in Scheme 4 as a discrete intermediate, in some instances cleavage of the RX bond may be simultaneous with electron transfer.

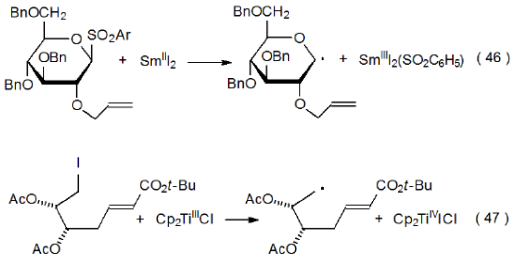
Scheme 4



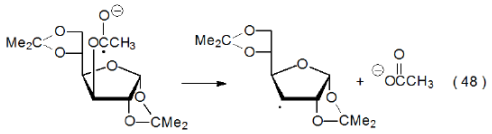
10

R-X = a carbohydrate chloride, bromide, iodide, or sulfone

$e^{\ominus}$ = an electron supplied by an electron donor



Solvated electrons, which are more reactive as electron donors than transition-metal complexes, combine with esterified carbohydrates to produce radical anions. These radical anions then expel carboxylate anions to form carbohydrate radicals (eq 48).[37]



Reaction of an aldehyde or ketone with samarium(II) iodide produces a samarium ketyl (eq 49),[38] an intermediate considered to be a hybrid of structures **11**-**13** (Figure 2). These ketyls exhibit reactivity characteristic of carbon-centered radicals.

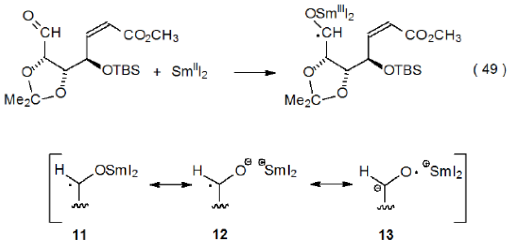
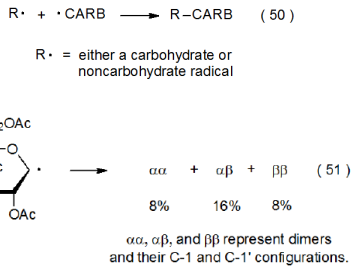


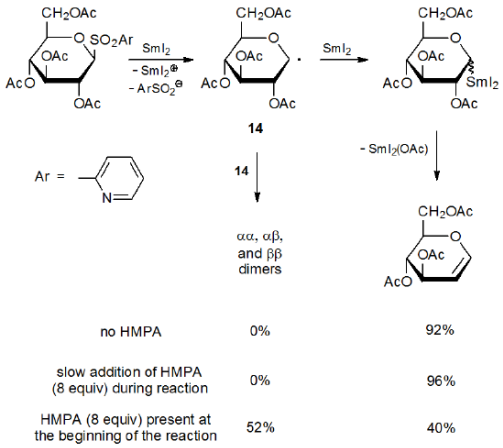
Figure 2. Resonance contributors for samarium ketyls

VII. Radical Combination

Radical combination involving carbohydrates takes place either by reaction between two carbohydrate radicals or between a carbohydrate and a noncarbohydrate radical (eq 50). Successful radical combination requires that the rates of competing reactions (e.g., hydrogen-atom abstraction and radical addition) be reduced to the point that radicals exist long enough in solution to combine. Under most conditions the lifetimes of typical carbohydrate radicals are too short for two of them to diffuse through solution and react. If conditions are selected to minimize competing reactions, pyranos-1-yl radicals, which are among the most stable carbohydrate radicals, exist in solution long enough to come into contact with each other and thus form dimers, although in low yield (eq 51).[39] If conditions are chosen that produce large numbers of radicals in a short period of time, radical concentration can be raised to the point where substantial combination takes place (Scheme 5).[40]

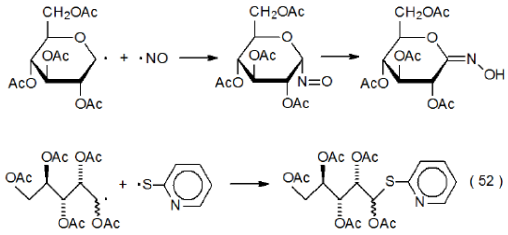


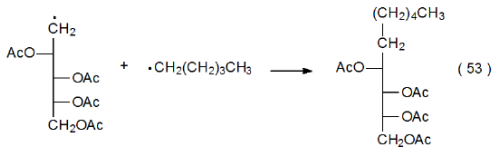
Scheme 5



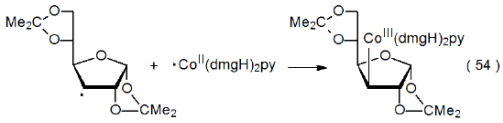
The noncarbohydrate radicals taking part in radical combination have a range of possible structures. The basic requirement in most instances is that the noncarbohydrate radical be sufficiently stable that its concentration in solution builds to the point that it will combine quickly with the more reactive carbohydrate radicals as they are produced. [Radicals with considerable stability are described as being either persistent or stable (Chapter 2, Section I). The presence of such radicals provides the basis for the "persistent radical effect" discussed in Chapter 3 (Section II.B.1.c.).] Noncarbohydrate participants in radical combination range from stable compounds, such as nitric oxide (Scheme 6),[41] to resonance-stabilized radicals, such as the 2-pyridylthiyl radical (eq 52).[23] Electrolysis is different from most reactions because it can produce locally high enough concentrations of radicals to allow even reactive ones to combine (eq 53).[42]

Scheme 6



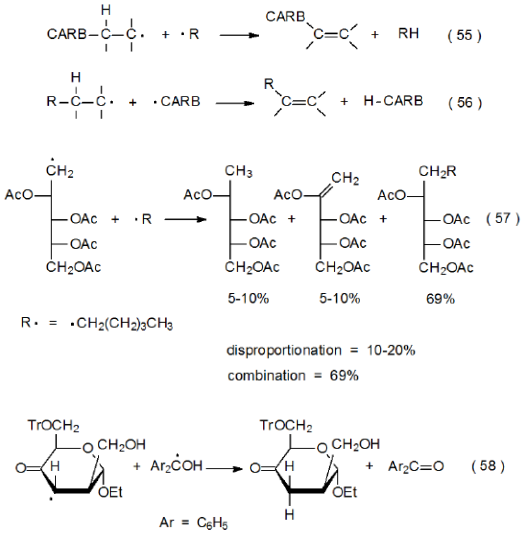


Some electron-transfer reactions between carbohydrate radicals and transition-metal complexes have a similarity to radical combination. In the reaction shown in eq 54, for instance, a change in oxidation states accompanies the combination between the carbohydrate radical and the cobalt complex.[27]



VIII. Disproportionation

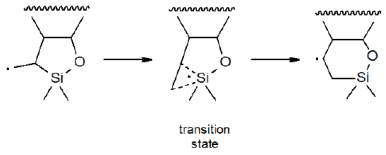
Disproportionation involving carbohydrate radicals (eq 55 and eq 56) is similar to radical combination in that most such radicals do not exist long enough in solution to come into contact with each other before another reaction takes place. As mentioned in the previous section, one situation in which two radicals can interact is when locally high concentrations are created by electrolysis; thus, when the radicals shown in eq 57 come within bonding distance, both disproportionation (10%-20%) and radical combination (69%) take place.[42] In contrast, disproportionation is the exclusive process in the reaction shown in eq 58 because there is considerable thermodynamic gain from forming a highly resonance-stabilized ketone while avoiding the hindrance inherent in the combination of sterically demanding radicals.[43]



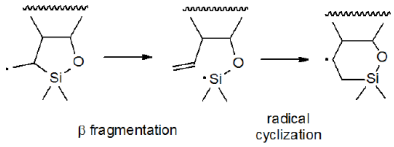
IX. Group Migration

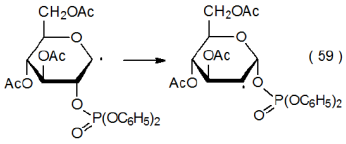
Acyl, silyl, phosphatoxy, phenyl, and cyano groups all are capable of undergoing group migration. Because in most reactions these groups are stable substituents and often act as protecting groups, migration is an event that depends not only on reaction conditions but also on the substrate having a particular type of structure. Sometimes it is unclear whether group migration is an elementary reaction or a combination of elementary reactions. The silyl group migration pictured in Scheme 7 is thought to be an elementary reaction, but it is possible that this process consists of a pair of reactions, β-fragmentation and radical cyclization (Scheme 8).[44] The group migration shown in eq 59[45] appeared at first to be an elementary reaction, but extensive investigation has shown that it consisted of heterolytic fragmentation followed by ionic recombination (Scheme 9).[46–48]

Scheme 7

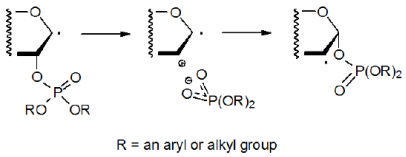


Scheme 8





Scheme 9



X. Summary

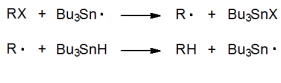
Radical reactions are composed of sequences of elementary reactions. An elementary radical reaction is one that does not produce an intermediate. Most elementary, radical reactions consist of transformation of one radical into another, but those that create radicals from nonradicals or cause radicals to disappear also qualify. Elementary reactions are listed in a general form in Table 1. Examples of carbohydrates that undergo each type of reaction are discussed.

CHAPTER OVERVIEW

5: Sequential Reactions

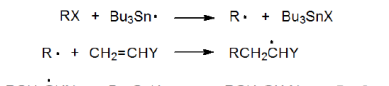
The propagation phase in a chain reaction is composed of a sequence of elementary reactions. The simple reduction pictured in Scheme 1 consists of two such reactions, and the radical addition shown in Scheme 2 has three elementary reactions in its propagation phase. Even though the overall reaction in each case (Schemes 1 and 2) consists of two or more elementary reactions occurring in sequence, neither overall reaction is described as a sequential one because to merit this designation, radical formation from the substrate and radical conversion to the product are not included.[1] With these beginning and ending steps removed, the reactions shown in Schemes 1 and 2 do not qualify as sequential. [Cascade, domino, and tandem are other names used to describe sequential reactions.]

Scheme 1



R· = carbohydrate radical
X = reactive substituent

Scheme 2



R· = carbohydrate radical X = reactive substituent
Y = an electron-withdrawing group

Elementary radical reactions readily occur in sequence because most produce a new radical poised for further reaction.[1,2] Since all participants in a sequential reaction, including the intermediate radicals, are present in the reaction mixture at the same time, achieving the selectivity necessary to have each radical react in the desired manner at the correct time is a challenging task, one that is critical to the success of the overall process. This selectivity is controlled by the rates of the various, possible propagation steps.

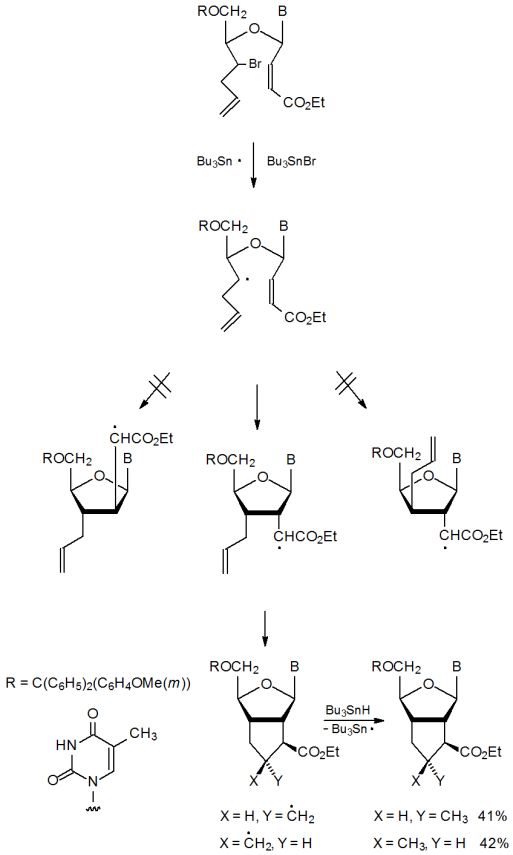
Successful, sequential reactions have several common characteristics. Propagation steps are faster than termination steps. Intermediate radicals react rapidly with the correct nonradicals, but avoid reaction with the solvent and initiator. The final radical, but not the intermediate ones, is converted into a stable product.

Topic hierarchy

II. Advantages and Disadvantages of Sequential Reactions

When two or more reactions occur in sequence, there is a savings in time, effort, and chemicals, compared to performing each reaction individually; therefore, sequential reactions can increase synthetic efficiency and provide a positive environmental impact by reducing chemical use.[3–5] An example of this efficiency is seen in the process pictured in Scheme 3, where two new rings form in a single reaction.[6] There is a price to be paid for this efficiency. It comes in the form of the additional effort that usually is necessary in preparing the starting materials and establishing the reaction conditions so that each step in this more complicated process proceeds in the desired direction.[4,5] Not only may more synthetic work be required in substrate preparation, but controlling product regio- and stereochemistry also may be more challenging in a process where multiple structural changes occur in a single reaction.

Scheme 3



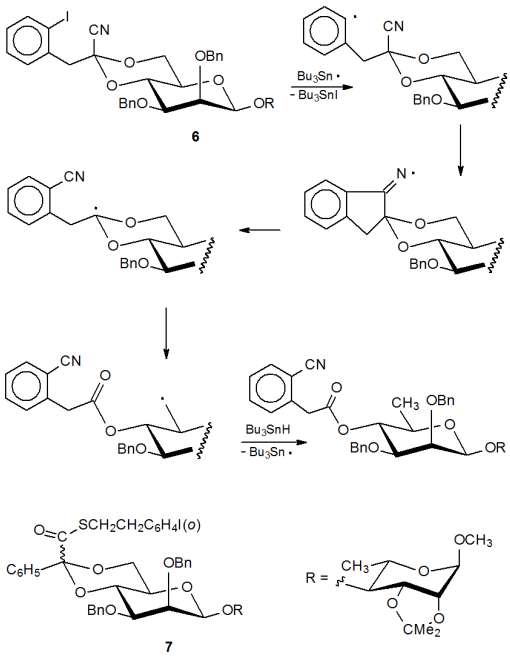
III. Two-Step Sequential Reactions

When planning a sequential reaction, it is natural to gravitate toward elementary reactions that are rapid and occur in a highly predictable fashion; also, because a more complex structure is often the target in a synthetic reaction, forming a carbon–carbon bond is usually one of the goals of a sequential process. Since internal addition of a radical to a multiple bond often is both rapid and predictable and usually involves new carbon–carbon bond formation, many sequential reactions include at least one radical cyclization step; some contain more. Cyclization-cyclization, the first sequential reaction to be discussed, involves forming of two rings.

IV. Three-Step Sequential Reactions

Three-step sequential reactions often consist primarily of combinations of cyclization and β-fragmentation steps.[56,73–82] One group of such reactions involves ring opening of cyclic acetals.[73–77] Since these reactions contain more fragmentation than cyclization, they tend to produce less complicated structures (e.g., compounds with fewer rings). In the reaction shown in Scheme 12, for example, internal radical addition to a cyano group creates a nitrogen-centered radical. This cyclization then is followed by successive β-fragmentation steps. Together these elementary reactions cause acetal ring opening.[73]

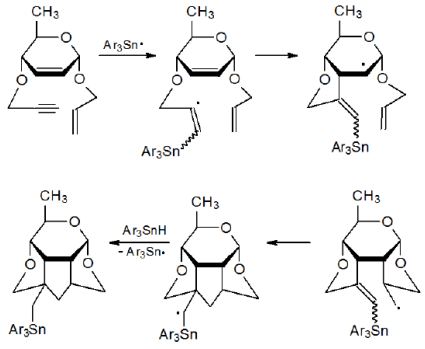
Scheme 12



Balancing the advantage gained against additional effort needed to prepare the starting materials and adjust the reaction conditions is always a consideration when conducting a sequential reaction. Such consideration motivated the preparation of the acetal **6** (Scheme 12),[73–75] when the effort necessary to synthesize **7**, the first acetal used in this type of reaction, significantly offset the advantage derived from the sequential process.[73,76,77]

The synthetic potential of three-step sequential reactions changes when there is more cyclization than fragmentation. When such a change occurs, reactions can be used to build more complex structures.[78–81] Specifically, the process shown in Scheme 13, which contains only cyclization steps, generates three new rings in a single reaction.[81]

Scheme 13



V. Related Reactions

Parallel reactions and sequences of reactions cause multiple structural changes to occur in molecules under a single set of conditions. These reactions are different from sequential reactions, however, in that neither parallel reactions nor sequences of reactions are a series of conversions of one radical into another; rather, they each consist of two or more distinct, complete reactions taking place under a single set of conditions.

VI. Summary

Elementary radical reactions readily occur in sequence because many of these reactions produce new radicals ready for further reaction. Such reactions provide an opportunity for multiple structural change under a single set of reaction conditions; consequently, these reactions, when properly chosen, represent an increase in synthetic efficiency. Two-step sequential reactions often involve radical cyclization in combination with radical addition, β-fragmentation, or hydrogen-atom abstraction. Three-step reactions usually consist of a combination of cyclization and β-fragmentation steps.

CHAPTER OVERVIEW

6: Radical Structure

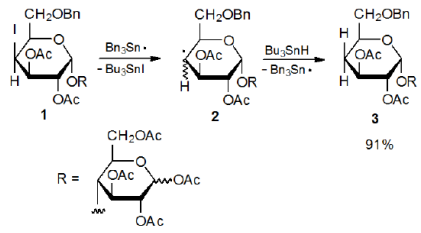
Establishing the structure of a free radical is a prerequisite for understanding its reactivity. Structural determination for a radical requires the same type of information needed to establish the structure of any reactive intermediate or stable molecule. The process begins by identifying the constituent atoms and their connectivity. Since radicals normally are generated from known compounds, connectivity information usually comes directly from the substrate structure. The configuration at ever carbon atom, except the one where the radical is centered, ordinarily is unchanged from that in the substrate. With this basic, structural information in hand, one can turn to investigating the remaining unknowns, that is, radical-center configuration and radical conformation. Although reactive intermediates, such as radicals, present special problems in structural determination due to their transient nature, the basic information needed is the same for both intermediates and stable molecules.

Topic hierarchy

II. Structural Formulas

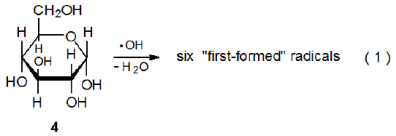
The structural formula for a radical often, but not always, can be deduced from a combination of different types of information. This information includes the structure of the radical precursor, the method of radical formation, and the identity of the reaction products. For example, in the reaction shown in Scheme l the structure of the deoxyiodo sugar **1**, the known reactivity of alkyl iodides with the tri-*n*-butyltin radical, and the structure of the product **3** together provide enough information to assign the basic structural formula **2** to the intermediate radical.[1] At this point, the configuration at the radical center in **2** and the conformation of this radical remain to be determined. The way in which radical configuration and conformation are assigned is discussed in Sections III and IV, respectively, in this chapter.

Scheme 1



The same type of information that effectively establishes the structure of the radical **2** (Scheme 1) is insufficient for determining the structures of the radicals produced by hydrogen-atom abstraction from simple sugars. Due to the large number of hydrogen atoms present in even simple sugars, knowing the structure of the starting material has limited value in establishing the identity of any particular intermediate radical. Product structures also are of limited usefulness due to the large number of compounds generated by hydrogen-atom abstraction (at least twenty-five from D-glucose[2]), and the probability that molecular rearrangement has occurred during formation of some of these products.[2,3] Proposing structures for the radicals generated by hydrogen-atom abstraction from even a simple sugar, such as D-glucose, can involve a good deal of speculation, but such speculation can be reduced by using electron spin resonance (ESR) to observe radicals directly.

It is possible to identify six, first-formed radicals in the ESR spectrum of the mixture produced by reaction of α-D-glucopyranose (**4**) with the hydroxyl radical (eq 1).[3] These six radicals are the ones generated by hydrogen-atom abstraction from of the six carbon atoms present in **4**. (Hydrogen-atom abstraction from the oxygen atoms is too slow to be competitive.) Identification of first-formed radicals is possible because when the structure of the radical precursor is combined with information from its ESR spectrum, the combination provides a basis for assigning a structural formula to each radical.



Whenever a radical reaction is encountered for the first time, the structure of any intermediate radical is naturally a topic of primary interest. Once the basic structure of a radical has been established, the unknowns that usually remain are the configuration at a radical center and conformation of the radical. Establishing this configuration and determining radical conformation often involve both experimental findings and molecular-orbital calculations.

III. Radical-Center Configuration

A. Planar and Pyramidal Structures

The configuration of a radical defines the location in space of the atoms directly attached to the radical center. When three such atoms are bonded to the carbon atom upon which a radical is centered, the configuration is either planar or pyramidal.[4] A planar configuration is one in which the atoms directly attached to the radical center and the center itself all exist in the same plane (Figure 1). For pyramidal radicals the plane defined by these directly attached atoms no longer includes the central atom (Figure 1).

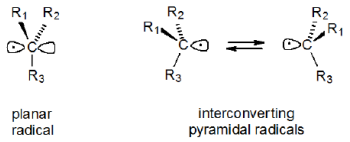


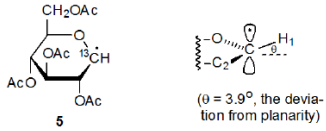
Figure 1. Possible configurations for carbon-centered radicals

Nearly every carbon-centered radical has a pyramidal configuration at the radical center, but these radicals vary widely in how close their configurations are to being planar.[5] A terminology has arisen that is designed to indicate approximate radical configuration. If a radical center has a nearly planar arrangement of attached atoms, the radical is described as being π-type.[6] (Since in a π-type radical the orbital in which the electron is centered is close to being a *p* orbital, this orbital is often referred to as being *p*-type.) If a radical has a decidedly pyramidal configuration (i.e., one approaching that corresponding to sp^3 hybridization), the radical is described as being σ-type.

Pyramidal, carbon-centered radicals with no electronegative substituents attached to the radical center tend to have a small distortion from planarity;[5] that is, they usually are considered to be π-type radicals. (It is worth noting that the magnitude of the angle of distortion can be deceptive. The relatively small 6.2° distortion from planarity reported for the ethyl radical means that this radical is actually about 1/3 of the way to being sp^3 hybridized.[7]) The distortion from planar arrangement increases as electron-withdrawing substituents replace other groups attached to the radical center. The change in configuration that accompanies replacement of the hydrogen atoms in the methyl radical by fluorine atoms provides a clear example of the effect of electronegative substituents on radical geometry.[5,8,9] The methyl radical is either planar, or nearly so,[10] but progressive replacement of hydrogen atoms with fluorine atoms produces pyramidal radicals with structures increasingly further from planarity until the trifluoromethyl radical is reached, in which case the F–C–F bond angles are similar to those found in tetrahedral structures.[11]

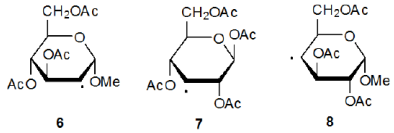
B. Configurational Determination from α-^{13}C Hyperfine Coupling Constants

Information about radical configuration can be obtained from analysis of α-^{13}C hyperfine coupling constants. These coupling constants, obtained from the ESR spectra of ^{13}C-enriched radicals, provide a sensitive measure of the hybridization at a radical center.[12,13] The configuration of a pyranos-1-yl radical is naturally of considerable interest due to the unique role of the anomeric carbon atom in carbohydrate chemistry. The α-^{13}C hyperfine coupling constants, obtained from the ESR spectrum of the ^{13}C-enriched D-glucopyranos-1-yl radical **5**, show the deviation from planarity for this radical to be 3.9° (Figure 2).[6,14] Since an sp^3-hybridized σ radical would have a deviation 19.5°, the D-glucopyranos-1-yl radical **5** is considered to be π-type.[6] Radicals centered at C-2 (**6**), C-3 (**7**), and C-4 (**8**) in pyranoid rings also have π-type configurations.[15]



5

Figure 2. The D-glucopyranos-1-yl radical **5** and its configuration at C-1



6 **7** **8**

Since organic radicals with no electronegative substituents attached to the radical center have π-type configurations, finding that radicals **6**-**8** have this type of configuration is not surprising. Because radical centers with electronegative atoms attached become

more pyramidal, it is surprising to discover that the radical **5**, which has an oxygen atom bonded to the radical center, also has a π-type configuration. To understand why this configuration is adopted, it is helpful to analyze of the stability of **5** as determined by frontier-orbital interactions.

C. Theoretical Explanation of Observed Configurations

1. Frontier-Orbital Interactions

Frontier-orbital interactions are based on an approximate, quantum-mechanical method that assumes that all interactions between occupied orbitals in a bimolecular reaction can be neglected and that the only interactions that need to be considered are between the highest occupied molecular orbital (HOMO) of one reactant and the lowest unoccupied molecular orbital (LUMO) of the other. A small energy difference between the HOMO and the LUMO (the frontier orbitals) translates into a large stabilizing interaction. In radical reactions the singly occupied molecular orbital (SOMO) can be either an HOMO or a LUMO.[16] Although frontier-orbital interactions are intended to be applied to bimolecular reactions, they can be used for understanding radical structure. In making such an application the radical is formally split into two fragments and fragment recombination is treated as a bimolecular reaction.[16] This approach, which has enjoyed widespread application and success in explaining radical structure,[17] will be used to rationalize the π-type configuration at C-1 adopted by the D-glucopyranos-1-yl radical **5** (Figure 2).

2. p_c /p_o Orbital Interaction

Experimental and theoretical studies show that the two unshared pairs of electrons on an oxygen atom in a pyranoid ring, do not have the same energy.[18,19] The higher energy pair exists in a *p*-type orbital while the lower energy pair is in a hybrid orbital that has considerable *s* character. As pictured in Figure 3, stabilization should result from interaction of the electrons in a *p*-type orbital on a ring oxygen atom (p_o) with the electron in the singly occupied, *p*-type orbital on an adjacent carbon atom (p_c). The increase in energy of the electron in the singly occupied molecular orbital (SOMO) is more than offset by the combined decrease in energy of the two electrons in the doubly occupied orbital. Because a nonparallel alignment of orbitals would exist in a pyranos-1-yl radical with a σ-type configuration, stabilizing orbital interaction for such a radical would be less than that for a radical with a π-type configuration, thus, there is a gain in radical stabilization to be had from having a *p*-type orbital at C-1 even though this atom has an electronegative oxygen atom attached.

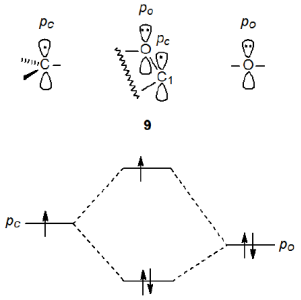


Figure 3. Change in energy levels from p_o/p_c orbital interaction

IV. Radical Conformation

Conformations of a molecule are usually viewed as arrangements of atoms that differ only by rotation about one or more single bonds. This view needs to be expanded where radicals are concerned because in some instances radicals with pyramidal configurations change from one conformation to another by inversion of configuration at the radical center. Consider the case of the ethyl radical (Figure 4). This radical is reported to have a pyramidal configuration with a 6.2° distortion from planarity and an extremely low (0.15 kcal/mol) energy barrier between conformations.[20–22] For the ethyl radical bond rotation and inversion of configuration both can contribute to conversion of one conformation into another (Figure 4).[20]

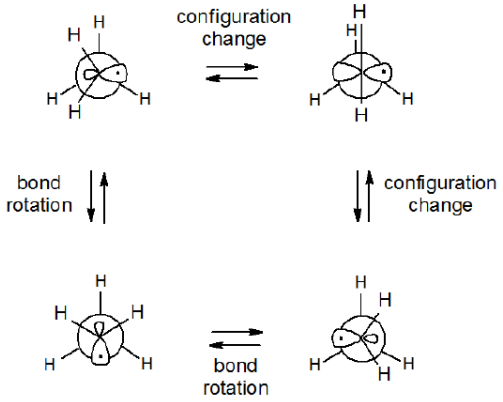


Figure 4. Interconversion of ethyl radical conformations by bond rotation and change of configuration

The intriguing complications associated with changes in conformation of alkyl radicals are not a major focus for conformational analysis of carbohydrates. The primary objective where carbohydrate radicals are concerned is to determine why a particular conformation is preferred and then to understand how conformation influences reactivity. ESR spectroscopy is an essential tool in achieving these objectives because it enables direct observation of radicals and, in so doing, provides valuable information about their conformation.

V. Quasi-Anomeric Radical Stabilization

Radicals centered at various carbon atoms in a pyranoid ring can be divided, on the basis of their stability, into two groups. The first group includes the pyranos-1-yl and pyranos-5-yl radicals, intermediates that are stable enough to be generated and observed in toluene or tetrahydrofuran. The second group, pyranosyl radicals centered at C-2, C-3, and C-4, cannot be observed in toluene or tetrahydrofuran because they abstract hydrogen atoms from these solvents too rapidly.[15] Since only the pyranos-1-yl and pyranos-5-yl radicals are capable of experiencing stabilization from the quasi-anomeric effect (Figure 8), the special stability of these radicals provides further support for the existence of quasi-anomeric stabilization.

VI. Summary

Determining the structure of a radical is essential to understanding its reactivity. The process begins by establishing the structural formula for the radical, that is, by identifying the constituent atoms, their connectivity, and elements of stereochemistry. Remaining unknown at this point typically are radical-center configuration and radical conformation.

The structural formula of a radical often can be determined reliably from knowledge of the structure of the radical precursor, the method of radical formation, and the reaction products. In instances where this information is insufficient, direct observation of the radical by ESR spectroscopy sometimes is possible and can provide the additional information needed to establish a structural formula.

The configuration at a radical center defines the location in space of the atoms directly attached to this central atom. Nearly every carbon-centered radical has a pyramidal configuration, but these radicals vary widely in how close their configurations are to being planar. If a radical is nearly planar, it is described as being π-type. If, on the other hand, a radical is much more pyramidal, it is considered to be a σ-type radical. Information about radical structure is obtained from molecular-orbital calculations and from observation of α-^{13}C hyperfine coupling constants (determined from ESR spectra of the ^{13}C-enriched radicals).

A conformation of a radical is one of the arrangements of atoms that can be formed by rotation about one or more single bonds. Pyranos-1-yl radicals have been extensively studied and some have been found to favor unexpected conformations. Perhaps most striking among these is the 2,3,4,6-tetra-*O*-acetyl-D-glucopyranos-1-yl radical, which exists in a distorted $B_{2,5}$ boat conformation.

Information about radical conformations is derived from both experimental and theoretical studies. Experimental information comes from analysis of ESR spectra. Study of pyranos-1-yl radicals has led to the identification of the quasi-anomeric effect as a general, controlling influence in determining conformations in many radicals. Understanding of radical conformation comes both from simple and complex applications of molecular-orbital theory. Frontier-orbital interactions offer a simple, theoretical means for rationalizing radical conformation. The far more sophisticated ab initio molecular-orbital calculations also provide understanding of the reasons for a radical adopting a particular conformation.

CHAPTER OVERVIEW

7: Radical Philicity

CHAPTER OVERVIEW

Front Matter

7: Radical Philicity

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I. Introduction

A. The Evans-Polanyi Relation

For many radical reactions there is a simple relation between the energy of activation for the reaction and its enthalpy. This relation, which is referred to by several, similar names[1–3] (Evans-Polanyi being a common one), is given in eq 1. Equation 1 expresses in a quantitative fashion the notion that in a group of closely related reactions the enthalpy for a particular reaction should be related to its energy of activation; specifically, energies of activation should decrease in a linear fashion as reactions become more exothermic.

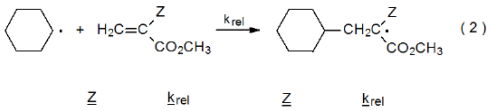
$$E_a = \text{constant} + \alpha H_r \quad (1)$$

E_a = activation energy
H_r = reaction enthalpy

Once the two constants in eq 1 have been determined, it is possible to predict the energy of activation for reaction of any member of the group from knowledge of the reaction enthalpy. The numerical value of the constant α represents the fraction of the overall enthalpy change that exists at the transition state. The value of α can be viewed as a measure of how far a reaction has proceeded along the reaction coordinate when the transition state is reached. The later a transition state occurs in a reaction the closer α will be to unity.

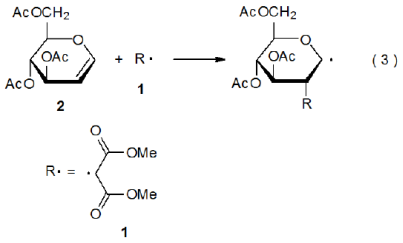
B. Nucleophilic and Electrophilic Radicals

Although radicals are neutral species, they often exhibit behavior characteristic of either nucleophilic or electrophilic intermediates.[4,5] This behavior facilitates certain types of reaction; for example, in the addition reactions shown in eq 2, the carbon-centered, cyclohexyl radical behaves as a nucleophile by adding more rapidly to compounds with more electron-deficient double bonds than to ones in which the double bonds are less electron-deficient.[6] In contrast, the malonyl radical **1** can be viewed as electrophilic because it adds to electron-rich double bonds such as that in the D-glucal **2** (eq 3).[7] A good beginning point for discussing radical philicity is examining some hydrogen-abstraction reactions.



(2)

Z	k_{rel}	Z	k_{rel}
CN	1940	H	6
CO_2CH_3	940	CH_3	5
Cl	75	CH_3O	1



(3)

II. Bond Polarities, Bond-Dissociation Energies, and Rate Constants for Hydrogen-Abstraction Reactions

Bond polarities, bond-dissociation energies, and rate constants for abstraction of hydrogen atoms bonded to tin, silicon, sulfur, selenium, and carbon all are given in Table 1. Based on Pauling's electronegativity values, hydrogen has a small negative charge when bonded to tin or silicon and a small positive charge when bonded to sulfur, selenium, or carbon. The information in Table 2 shows that for each type of bond, the rate constant for hydrogen-atom abstraction by simple primary, secondary, and tertiary, carbon-centered radicals is nearly the same.

	$\overset{\delta\oplus}{H}-\overset{\delta\ominus}{Sn}$	$\overset{\delta\oplus}{H}-\overset{\delta\ominus}{Si}$	$\overset{\delta\oplus}{H}-\overset{\delta\ominus}{S}$	$\overset{\delta\oplus}{H}-\overset{\delta\ominus}{Se}$	$\overset{\delta\oplus}{H}-\overset{\delta\ominus}{C}$
Pauling's electro-negativity values	2.1 1.8	2.1 1.8	2.1 2.5	2.1 2.4	2.1 2.5
bond energies (kcal/mol)[8]	78.0 (Bu_3SnH)	95.0 (Me_3SiH)	88.6 (Me_3CSH)	78 (C_6H_5SeH)	95 (Me_3CH)
		83.7 ($(Me_3Si)_3SiH$)	83.5 (C_6H_5SH)		
rate constants ($M^{-1}s^{-1}$)	2×10^6 (Bu_3SnH)	7.0×10^3 (Et_3SiH)	8.0×10^6 (Me_3CSH)	2.1×10^9 (C_6H_5SeH)	---
		3×10^5 ($(Me_3Si)_3SiH$)	1×10^8 (C_6H_5SH)		

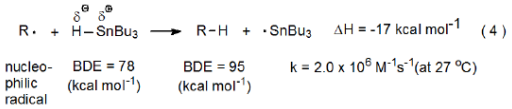
(References to these rate constants are found in Table 2.)

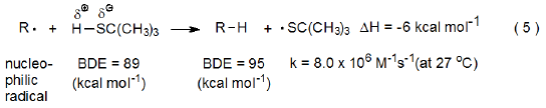
Table 1. Bond polarities, bond dissociation energies, and rate constants for hydrogen abstraction

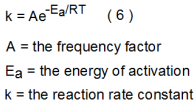
abstracting radical	hydrogen donor	reaction rate, $M^{-1}s^{-1}$	temp	ref
ethyl	Bu_3SnH	2.4×10^6	27 °C	9
iso-propyl	Bu_3SnH	1.5×10^6	27 °C	9
tert-butyl	Bu_3SnH	1.8×10^6	27 °C	9
general rate constant for abstraction by alkyl radicals	Bu_3SnH	2×10^6		
primary	Et_3SiH	7.0×10^3	50 °C	10
primary	$(Me_3Si)_3SiH$	3.8×10^5	25 °C	11
secondary	$(Me_3Si)_3SiH$	1.4×10^5	25 °C	11
tertiary	$(Me_3Si)_3SiH$	2.6×10^5	25 °C	11
general rate constant for abstraction by alkyl radicals	$(Me_3Si)_3SiH$	3×10^5		
primary	Me_3CSH	8.0×10^6	25 °C	12
ethyl	C_6H_5SH	1.36×10^8	25 °C	13
iso-propyl	C_6H_5SH	1.05×10^8	25 °C	13
tert-butyl	C_6H_5SH	1.47×10^8	25 °C	13
general rate constant for abstraction by alkyl radicals	C_6H_5SH	1×10^8		
primary	C_6H_5SeH	2.1×10^9	25 °C	14, 15

Table 2. Rate constants for hydrogen abstraction by simple, carbon-centered radicals from common hydrogen-atom donors

When the bond dissociation energies in Table 1 are used to calculate reaction enthalpies, they show that the reaction in eq 4 is more exothermic than that in eq 5. If the Evans-Polanyi relation is obeyed, the first reaction (eq 4) should have a lower energy of activation than the second (eq 5), but the opposite appears to be true. The rate constants for these reactions, when related to activation energies through the Arrhenius equation (eq 6), show that, unless the frequency factors for these two reactions are quite different, the reaction given in eq 4 actually has a higher energy of activation. Clearly, something in addition to reaction enthalpies must have a significant role in determining energies of activation for these two reactions.







The identification of a likely candidate for this additional factor can be made by returning to the reactions pictured in equations 2 and 3 and recalling that these reactions show some carbon-centered radicals to be nucleophilic and others electrophilic. If one assumes that the *tert*-butyl radical is similar in its philicity to the nucleophilic cyclohexyl radical, then in the reaction in eq 5 there is a polarity match between the nucleophilic radical and the electron-deficient hydrogen atom being abstracted. Since a similar match does not exist in the slower reaction (eq 4), radical philicity becomes a prime candidate for the factor that joins with reaction enthalpy in explaining the rate constants for hydrogen-abstraction reactions.

III. Determining Radical Philicity

Since radical philicity appears to have an important role in radical reactivity, it is valuable to be able to determine easily whether a particular radical is electrophilic or nucleophilic. A procedure that accomplishes this task would be especially useful if it could be implemented simply by inspecting the structure of the radical in question. Fortunately, two such procedures exist. One is based on atom electronegativity[16] and the other on cation and anion stability.[17] More sophisticated techniques for determining radical philicity also are known. One of these, principal component analysis,[18,19] extracts information about nucleophilicity and electrophilicity of radicals from experimentally determined rate constants. A second, based on ab initio molecular orbital calculations, determines radical philicity from the extent and direction of charge transfer between a radical and an alkene at the transition state for an addition reaction.[3,20–23] These different approaches to determining radical philicity are described in the next four sections.

IV. Explaining Radical Philicity

A. Valence Bond Theory

One way to explain the existence of radical philicity begins with the addition reaction shown in eq 7. The transition-state structure in this reaction can be represented as a hybrid of valance-bond structures. If there is no separation of charge, the transition state can be represented by the contributors **3** and **4** shown in Figure 1. Unequal electron distribution at the transition state can be taken into account by including additional resonance contributors. If in the transition state there is a transfer of electron density from R· to the C–C double bond, this transfer can be represented by adding contributors **5** and **6** (Figure 2). If electron transfer is in the other direction, resonance contributors **7** and **8** (but not **5** and **6**) make a significant contribution to the transition state structure (Figure 2).

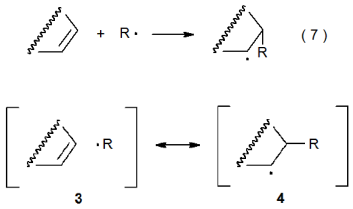


Figure 1. Valence-bond contributors to a nonpolar transition state for radical addition

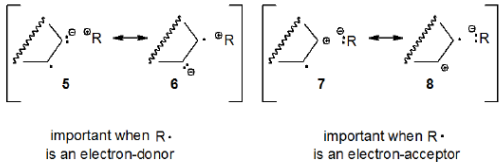
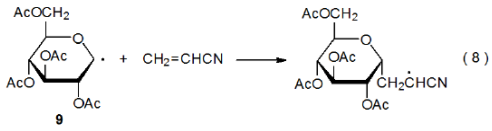


Figure 2. Significant valence-bond contributors when a transition state is polar

1. Nucleophilic Radicals

To illustrate the way in which valance bond theory explains radical nucleophilicity, it is instructive to examine the reaction shown in eq 8. In this reaction the D-glucopyranos-1-yl radical **9** is considered to be nucleophilic because it adds to the electron-deficient double bond in acrylonitrile.[24] The valence-bond structures **10**-**14** (Figure 3) all potentially contribute to the transition-state structure in this reaction. Structures **10** and **11** are major contributors that have no separation of charge. Structures **12** and **13** are minor but significant contributors, minor because they involve separation of charge but significant because they stabilize either negative charge (**12**) or positive and negative (**13**) charges effectively. Structure **14** is not significant because it has charge-separation and the charges are not effectively stabilized. Since structures **12** and **13** make a greater contribution than does **14** to the transition state in this reaction (eq 8), the radical **9** becomes a net electron-donor at the transition state and, thus, is considered to be nucleophilic.



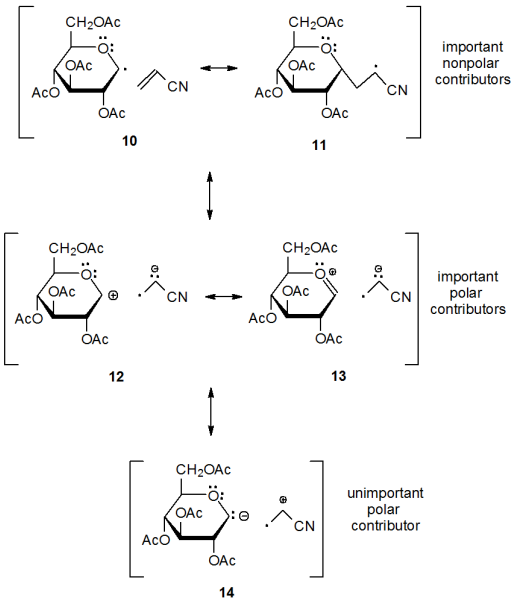


Figure 3. Resonance contributors to the transition-state for addition of a pyranos-1-yl radical to acrylonitrile

2. Electrophilic Radicals

If a radical center has a sufficiently strongly electron-withdrawing substituent (or substituents) attached, the inherently nucleophilic character of a carbon-centered radical is reduced to the point that the radical becomes electrophilic.[18] For example, the malonyl radical **1**, which has two electron-withdrawing groups attached to the radical center, is considered to be electrophilic because it adds to the electron-rich double bond in the D-glucal **2** (eq 3).[7] The electrophilicity of **1** can be understood primarily in terms of the importance to the transition-state structure of the charge-transfer contributor **15**, a structure in which the electron-withdrawing methoxycarbonyl groups stabilize the negative charge and the ring oxygen atom stabilizes the positive charge (Figure 4). Together these stabilizing interactions increase the contribution at the transition state from a structure in which the radical **1** is acting as an electrophile by accepting electron density from the D-glucal **2**. The resonance structure **16** is not an important contributor at the transition state because within **16** there is a destabilizing shift of electron density away from a radical center that contains electron-withdrawing, methoxycarbonyl substituents.

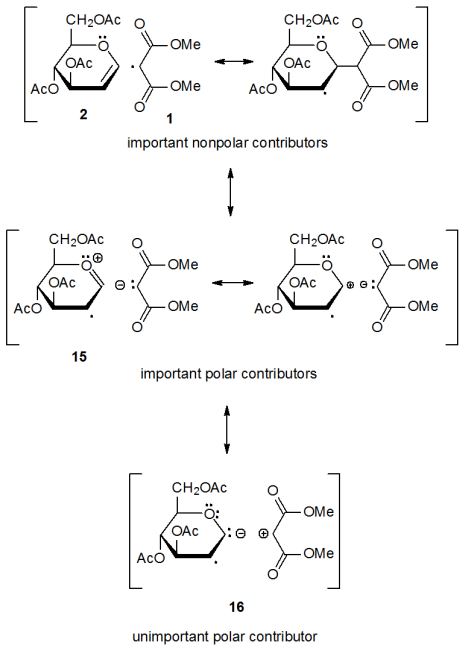


Figure 4. Polar resonance contributors to the transition state during addition of the malonyl radical **1** to the D-glucal **2**

3. Ambiphilic Radicals

Inherent in defining radical philicity in terms of electron-transfer is the idea that the philicity of a radical is a function of the reaction in question. This means that instead of describing a radical as nucleophilic, it should be described as nucleophilic in a particular reaction. It is fair to say, however, that radicals that are moderately or strongly electrophilic or nucleophilic in one reaction are likely to have the same philicity in all reactions, but radicals that are weakly nucleophilic or electrophilic in one reaction are better candidates for a philicity change in a different reaction. Radicals that are nucleophilic in one reaction but electrophilic in another are classified as ambiphilic.

B. Molecular Orbital Theory: Frontier-Orbital Interactions

When a transition-state structure for a reaction resembles the structure of the starting materials, frontier-orbital interactions provide qualitative information about energy changes taking place at the transition state. (Since frontier orbitals are based on the structures of the starting materials, the further the transition state is along the reaction pathway the less reliable frontier-orbital interactions will be in predicting or rationalizing reactivity.) According to Hammond's postulate,[25] an exothermic reaction should have an early transition state with a structure resembling that of the starting materials; therefore, such a reaction should be suitable for analysis by frontier-orbital interactions. A reaction involving addition of a carbon-centered radical to a carbon–carbon double bond is a prime candidate for this type of analysis because such a reaction replaces a π bond with a more stable σ bond, a change that should produce a decidedly exothermic reaction.[1,3,6,26]

1. Nucleophilic Radicals

A beginning point for explaining radical nucleophilicity in terms of frontier-orbital interactions is found in Figure 5, which pictures the singly occupied molecular orbital (SOMO) in the radical **17** interacting with both the π* (LUMO) and the π (HOMO) orbitals of the alkene **18**. Identifying the most important interaction is critical to determining the nucleophilicity of the adding radical. When the SOMO of **17** interacts with the alkene **18**, the greater interaction is with the π* orbital of the alkene (Figure 5).[6] Convincing evidence supporting this position comes from plotting calculated HOMO and LUMO energies of substituted alkenes against the natural logarithm of the relative rate constants (ln k_{rel}) for addition of a carbon-centered radical (the *tert*-butyl radical was used) to these alkenes.[27] A linear correlation exists between ln k_{rel} and LUMO energies, but no such correlation exists between ln k_{rel} and HOMO energies. The correlation with LUMO energies then is consistent with the dominant frontier-orbital interaction being between the SOMO of the radical **17** and the π* orbital of the alkene **18** (Figure 5).

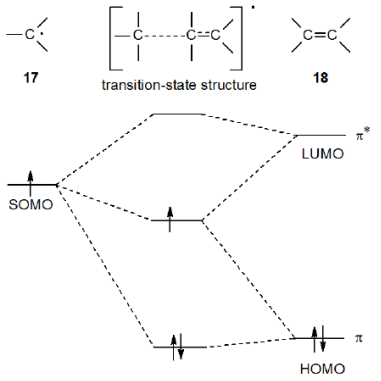


Figure 5. Frontier-orbital interactions for addition of an unsubstituted, carbon-centered radical to a compound with a carbon-carbon double bond

The next step in understanding how frontier-orbital interactions can explain radical nucleophilicity involves the addition of the radical **17** to the alkene **19**, a compound in which the double bond contains the electron-withdrawing substituent Z (Figure 6). When Z replaces one of the hydrogen atoms attached to a doubly bonded carbon atom, the π* orbital is stabilized and the associated energy level moves closer to that of the SOMO of **17**.[28] This change in energy level position increases the interaction between the SOMO and the π* orbital (Figure 6). Greater interaction translates into a lower transition-state barrier for reaction; therefore, the radical **17** will add more rapidly to the alkene containing the electron-withdrawing Z group than to an unsubstituted alkene. This preferential reaction with electron-deficient alkenes makes the radical **17** nucleophilic.

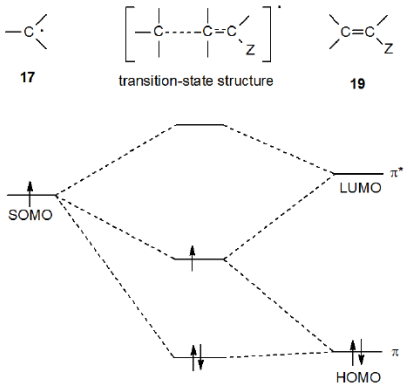


Figure 6. Frontier-orbital interactions for addition of a carbon-centered radical to a compound with an electron-deficient double bond

It is possible to increase the nucleophilicity of a carbon-centered radical still further if its SOMO energy level moves even closer to that of the π* orbital of an alkene. This type of change occurs when an oxygen atom is attached directly to the radical center because interaction between the *p*-type orbital on the carbon atom and the *p*-type orbital on the adjacent oxygen atom raises the SOMO energy level in the resulting radical (**20**) (Figure 7). This higher energy level places the SOMO closer energetically to the π* orbital of the reactant alkene. Such a change further increases orbital interaction and in so doing causes greater transition-state stabilization. The enhanced reactivity, due to the presence of the attached oxygen atom, means that the radical **20** will be even more nucleophilic than **17**; thus, this oxygen-substituted radical (**20**) is considered to be strongly nucleophilic.

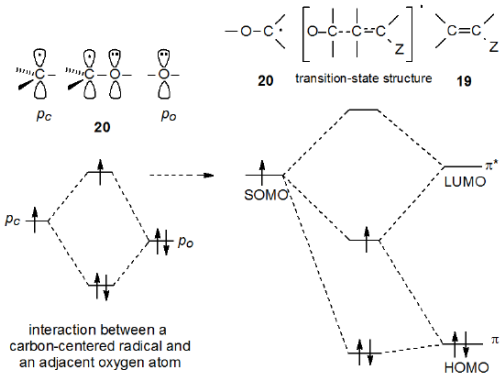


Figure 7. Frontier-orbital interaction for addition of an oxygen-substituted radical to a compound with an electron-deficient double bond

There is an additional way of viewing the frontier-orbital interaction between an alkene and a carbon-centered radical. Understanding this alternative view begins by recalling that the major, frontier-orbital interaction between a carbon-centered radical and an unsaturated compound is between the SOMO of the radical and the π* orbital (LUMO) of the alkene (Figures 5-7). Since SOMO-LUMO interaction is the most important and since any electron donation at the transition state resulting from this interaction must involve electron transfer from the SOMO (the LUMO has no electrons to transfer), the radical is acting as an electron donor and, therefore, is behaving as a nucleophile.[29]

2. Electrophilic Radicals

If a hydrogen atom attached to a carbon-centered radical is replaced by an electron-withdrawing substituent (e.g., a cyano or carbonyl group), the resulting radical becomes more electrophilic.[6,18,30,31] Additional substitution of this type further increases radical electrophilicity (Figure 8). The electron-withdrawing group causes the energy level associated with the singly occupied molecular orbital of the substituted radical to move to a position lower in energy; that is, the radical becomes more stable.[6,32] When the energy level of an SOMO in a carbon-centered radical becomes sufficiently low, the major, frontier-orbital interaction with an alkene changes; that is, the primary interaction is no longer with the π* orbital of the alkene but rather with its π orbital (Figure 9). When this change occurs, the primary shift in electron density at the transition state is away from the filled HOMO toward the partially filled SOMO; thus, the radical is electrophilic.

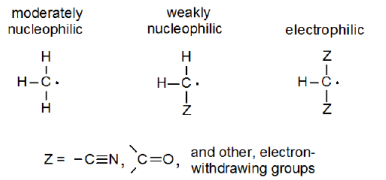


Figure 8. Replacement of the hydrogen atoms in the methyl radical with electron-withdrawing substituents

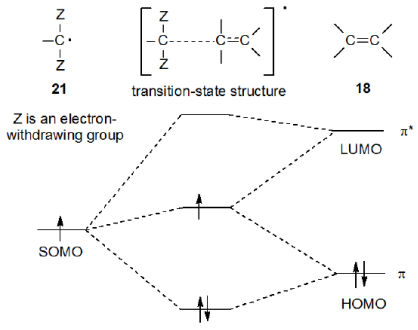


Figure 9. Frontier-orbital interactions for addition of an electron-deficient, carbon-centered radical to an unsaturated compound

Figure 10 pictures the frontier-orbital interaction of the radical **21** with an alkene that has an electron-donating substituent. Since the HOMO for the substituted alkene (Figure 10) is higher in energy than the HOMO of the unsubstituted alkene (Figure 9),[28] transition-state stabilization from SOMO-HOMO interaction will be greater for reaction involving the substituted alkene (Figure 10). Due to this greater stabilization, the radical **21** reacts more rapidly with the more electron-rich alkene, a behavior expected from an electrophilic intermediate.

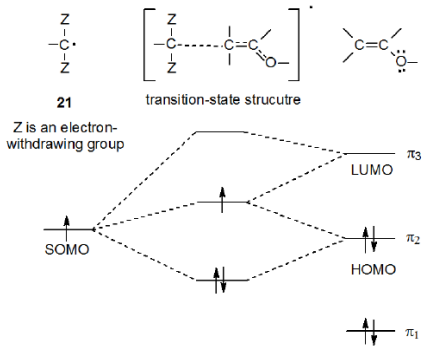


Figure 10. Frontier-orbital interactions for addition of an electron-deficient, carbon-centered radical to a compound with an oxygen-substituted double bond

C. Balancing Polar and Enthalpy Effects

The discussion at the beginning of this chapter focused on groups of similar reactions that obey the Evans-Polanyi relation, that is, reactions in which the energies of activation can be determined from reaction enthalpies using eq 1. Attention then turned to reactions where this simple relation (eq 1) does not hold. The energies of activation for reactions that do not obey the Evans-Polanyi relation are influenced by polar effects operative at the transition state. Since some reactions are more subject to enthalpy effects and others to polar effects, the question naturally arises as to what the balance is between these two. Principal component analysis answers this question with the finding that “the dominant factors influencing radical addition reactions are polar effects alone for strongly nucleophilic or strongly electrophilic radicals...and enthalpy effects alone for weakly nucleophilic or weakly electrophilic radicals”.[18] For moderately nucleophilic or moderately electrophilic radicals both polar and enthalpy effects are important.[18]

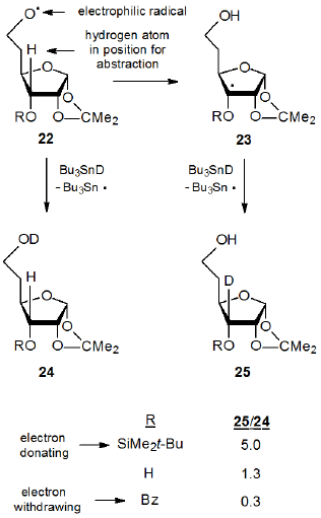
V. Examples of Radical Philicity in Reactions of Carbohydrates

A. Hydrogen-atom abstraction

The reactions shown in equations 4 and 5 illustrate the importance of radical philicity in hydrogen-abstraction reactions by showing that the nucleophilic radical R· abstracts the electron-deficient hydrogen atom attached to sulfur (eq 5) more rapidly than the electron-rich hydrogen atom bonded to tin (eq 4).[33–35] The differences in rate constants and enthalpies for these two reactions underscore the fact that radical philicity affects the stability of the transition-state structure in a reaction but not the overall energy changes due to bond breaking and bond formation.

Comparing the three reactions pictured in Scheme 1 draws attention to the effect of radical philicity on hydrogen-atom abstraction from carbohydrates. In each of these reactions the oxygen-centered radical **22** either abstracts a deuterium atom from Bu_3SnD to give the deuterated alcohol **24**, or it reacts internally with H-3 to generate the carbon-centered radical **23**.[36] After the radical **23** forms, it then abstracts a deuterium atom for Bu_3SnD to give the second reaction product (**25**). The relative amounts of products **24** and **25** provide a measure of external (deuterium) versus internal (hydrogen) abstraction. As H-3 becomes less electron rich, internal reaction (**22**→**23**) becomes less competitive. External abstraction (**22**→**24**), on the other hand, should not be noticeably affected by changes in substituents at C-3. If, as expected, the transition states for the internal hydrogen-abstraction reactions shown in Scheme 1 are early, these reactions support the idea that polarity matching has a critical role in determining the favored reaction pathway for the radical **22**.

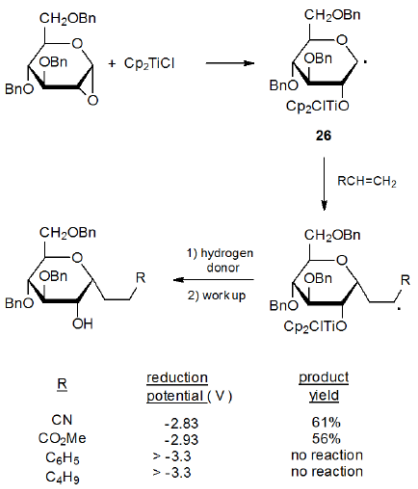
Scheme 1



B. Radical Addition

Pyranos-1-yl radicals add readily to electron-deficient, carbon-carbon double bonds but are much less reactive toward double bonds lacking electron-withdrawing substituents.[37,38] A group of reactions that illustrates this difference in reactivity is found in Scheme 2.[37] The ability of the pyranos-1-yl radical **26** to add to the unsaturated compounds shown in Scheme 2 correlates with the reduction potentials of these compounds; that is, addition to compounds with less negative reduction potentials occurs more rapidly than addition to compounds with more negative reduction potentials.[37]

Scheme 2



R	reduction potential (V)	product yield
CN	-2.83	61%
CO_2Me	-2.93	56%
C_6H_5	> -3.3	no reaction
C_4H_9	> -3.3	no reaction

Since the reduction potential in a substituted alkene is a measure of the ease of introducing an electron into a π* orbital, this potential becomes an indicator of energy-level positioning. When comparing two reduction potentials, the less negative one has a lower energy level for the π* orbital. Because this lower energy level causes the π* orbital (LUMO) to interact more effectively with the SOMO of the adding radical, transition-state stabilization due to frontier-orbital interaction increases as the reduction potential for the substituted alkene becomes less negative (Figure 11).

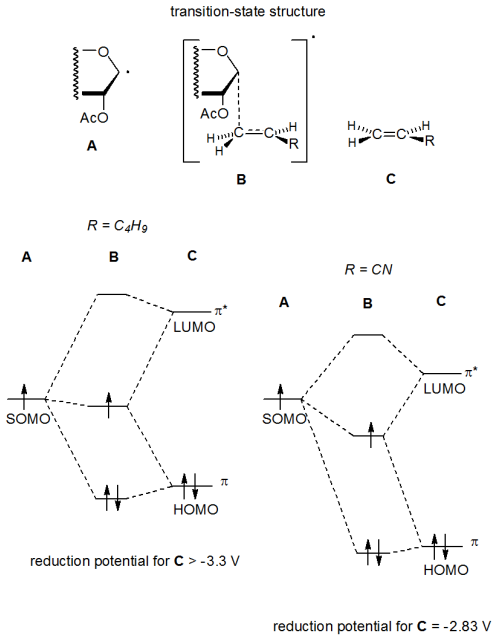
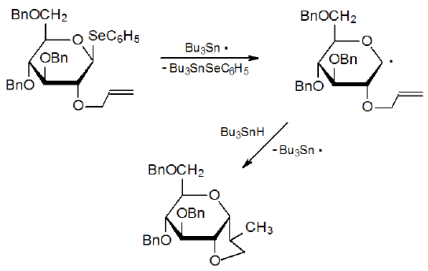


Figure 11. Reaction of a nucleophilic radical with substituted alkenes

Although the addition of a nucleophilic radical to a π bond that is not electron-deficient is too slow to be observed in the reactions shown in Scheme 2, the situation changes when reactions become intramolecular. For π bonds that are 1,5- or 1,6-related to a radical center, intramolecular addition can take place even if the π bond is not decidedly electron-deficient (Scheme 3).[39] As far as overall reaction rate is concerned, forced, close proximity of the radical center to the π bond can compensate for a small transition-state stabilization caused by a large separation in energy levels of interacting, frontier orbitals.

Scheme 3



C. Polarity-Reversal Catalysis

The philicity of radicals involved in hydrogen-abstraction reactions provides the basis for a phenomenon known as polarity-reversal catalysis.[4,33–35,40] This type of catalysis, which is responsible for the effect that thiols have on the reactions of carbohydrate acetals and ethers, is discussed in Section III of Chapter 5 in Volume II.

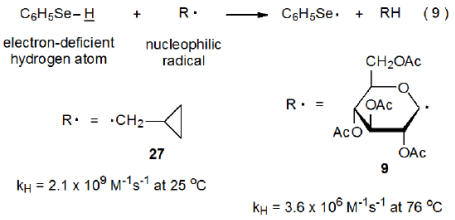
VI. Rate Constants for Hydrogen-atom abstraction by Carbohydrate Radicals

A. Extrapolating Results From Model Radicals

Radical philicity first was encountered in this chapter in the reactions of simple organic compounds (Section I.B). The assumption was that information about the reactivity of these compounds could be extrapolated to more complex ones, specifically, carbohydrates. Experimental data supported the validity of this assumption by providing examples of reactions of carbohydrate radicals that qualitatively paralleled those of simpler radicals. For instance, the reactions in eq 2 showed the cyclohexyl radical (a carbohydrate model) to be nucleophilic because it added more rapidly to electron-deficient multiple bonds than to electron-rich ones.[6] A similar, nucleophilic behavior was seen in the reactions of the carbohydrate radical **26** (Scheme 2). In another example, the reactions described in equations 4 and 5 for simple organic molecules showed that polarity matching increased the rate of hydrogen-atom abstraction. Extending polarity matching to carbohydrate radicals offered a rationale for the electrophilic radical **22** abstracting an electron-rich hydrogen atom more rapidly than an electron-deficient one (Scheme 1). There is, of course, a limitation to extrapolation of results obtained from simple radicals to radicals that are more complicated. Identifying a limitation, as is done in the following section, can be useful and can lead to increased understanding of the reactivity of the more complicated radical.

B. A Limitation on Extrapolating Alkyl Radical Reactivity to Carbohydrate Radicals

Extrapolating results from reactions of structurally simple intermediates sometimes provides the only information available for judging reactivity of more complex ones. Successful extrapolation builds confidence in the models selected, but since model systems by their very nature have limitations, such extrapolation is always subject to some uncertainty. The reaction shown in eq 9 illustrates the need for caution in projecting reactivity from a simple to a more complex radical. The data in Table 2 show that rate constants for hydrogen-atom abstraction from compounds with H–Sn, H–S, and H–Si bonds are essentially independent of whether the abstracting radical is primary, secondary, or tertiary. (Steric factors have little effect on rate constants for hydrogen abstraction.[41]) Extending this reactivity pattern to compounds with H–Se bonds and knowing that the rate constant for hydrogen-atom abstraction from C_6H_5SeH by the primary radical **27** is 2.1 x 10^9 $M^{-1}s^{-1}$ at 25 °C[14] leads to the prediction that the rate constant for reaction of the pyranos-1-yl radical **9** with C_6H_5SeH should have a similar value. It does not; the value is far smaller (3.6 x 10^6 $M^{-1}s^{-1}$ at 78 °C).[15]



C. An Explanation for Unsuccessful Extrapolation: Loss of Transition-State Stabilization

In attempting to understand the smaller-than-expected rate constant for hydrogen-atom abstraction by the radical **9**, it is useful to recall from Chapter 6 (Section IV.A.2.c) that the conformation of pyranos-1-yl radicals depends on the quasi-anomeric effect, that is, on the stabilizing interaction of the σ* orbital of the C_2–O bond with the *p*-type orbitals on the ring oxygen atom and C-1. This effect is sufficiently powerful to cause **9** to adopt the otherwise unstable, boat conformation shown in Figure 12. Since quasi-anomeric stabilization can only exist in structurally complex systems, simple radicals are limited in their ability to model pyranos-1-yl radicals. The quasi-anomeric effect provides a basis for understanding the smaller-than-expected value for the rate constant for hydrogen-atom abstraction by the radical **9**.

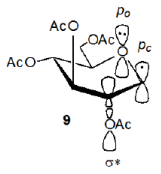


Figure 12. p_c, p_o, and σ* orbitals that undergo stabilizing interaction in a pyranos-1-yl radical

As the hydrogen-atom abstraction reaction shown in eq 9 (R· = **9**) moves toward the transition state, the orbital interactions (Figure 12) that cause the electron delocalization that stabilizes the radical **9** are disappearing. (They are totally gone when the product is reached.) This loss of stabilization means that the energy of activation for hydrogen-atom abstraction by **9** will be greater than that for the radical **27**, for which there is no comparable reduction in electron delocalization as the reaction progresses.[15] Hydrogen-atom abstraction, in effect, forces an electron localization that causes a loss of stabilization for the delocalized radical **9** but not for the localized one **27**. This decrease in stabilization at the transition state for reaction of a pyranos-1-yl radical reduces its rate constant for hydrogen-atom abstraction.

The proposal that transition-state loss of quasi-anomeric stabilization in pyranos-1-yl radicals is responsible for their reduced hydrogen-abstracting ability carries with it the prediction that carbohydrate radicals that are not so stabilized should have larger rate constants for hydrogen-atom abstraction. The quantitative information needed to evaluate this prediction does not exist, but there is qualitative information that supports the basic idea. As mentioned in Section V of Chapter 6, pyranos-1-yl radicals can be generated and observed in toluene or tetrahydrofuran but radicals centered on C-2, C-3, or C-4 (with no oxygen atom attached to the radical center and, hence, no quasi-anomeric stabilization possible) cannot be observed in these solvents because such radicals rapidly abstract hydrogen atoms from the solvent. (Only α-tetrahydrofuryl radicals are observed in reactions conducted in tetrahydrofuran and only benzyl radicals are detected in reactions in toluene.[42])

The possibility that a loss of transition-state stabilization due to diminishing delocalization is responsible for a smaller-than-expected rate constant for hydrogen-atom abstraction by a pyranos-1-yl radical leads to the proposal that a similar loss of stabilization should have a similar effect on hydrogen-atom abstraction by other radicals. Rate constants for abstraction from C_6H_5SH have a bearing on this proposal. Simple primary, secondary, and tertiary radicals all have rate constants for hydrogen-atom abstraction from C_6H_5SH near 1 x 10^8 $M^{-1}s^{-1}$ at 25 °C (Table 2), but the rate constant for abstraction from this thiol by the benzyl radical is far smaller (3.13 x 10^5 $M^{-1}s^{-1}$ 25 °C).[13] Because the benzyl radical loses resonance stabilization as hydrogen-atom abstraction takes place, it would be expected to parallel the pyranos-1-yl radical in having a smaller rate constant hydrogen-atom abstraction than the 1 x 10^8 $M^{-1}s^{-1}$ observed for unstabilized radicals. The fact that the rate constant for hydrogen-atom abstraction by the benzyl radical (3.13 x 10^5 $M^{-1}s^{-1}$) is a substantially smaller than 1 x 10^8 $M^{-1}s^{-1}$ strengthens the diminishing-delocalization explanation for reduced reactivity of the pyranos-1-yl radical **9.**

VII. Summary

Radicals often exhibit reactivity characteristic of either nucleophilic or electrophilic species. An electrophilic radical reacts more rapidly with an electron-rich center in a molecule, and a nucleophilic radical is more reactive toward an electron-deficient one.

A number of procedures exist for determining the philicity of a radical. These range from simple ones that involve assignment based on inspection of radical structure combined with a general knowledge of organic chemistry to complicated ones based on ab initio molecular orbital calculations. All procedures lead to the conclusion that nearly every carbohydrate radical is nucleophilic.

Most quantitative information about rates of reaction of carbohydrate radicals comes from extrapolation of data obtained from reaction of model radicals. Although this information is useful in understanding the philicity of carbohydrate radicals, it must be treated with caution when pyranos-1-yl radicals are under consideration. Simple radicals are unable to model the stereoelectronic effects that are critical to radical stability in pyranos-1-yl radicals and, consequently, do not always provide a good measure of their reactivity.

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CHAPTER OVERVIEW

8: Radical Reactivity: Reaction Rate Constants

As discussed in Chapter 4, any reaction that involves radical intermediates actually consists of two or more elementary reactions. The rate constants for these elementary reactions are critical in determining the success of an overall reaction. Knowing these rate constants then is essential to understanding existing radical reactions and being able to predict new ones.

This chapter is different from the others in this book in that it contains a large number of tables. These tables consist of collections of rate constants. Because relatively few rate constants for reactions of carbohydrates have been determined, most of the values in these tables come from reactions of simpler organic compounds; thus, they serve as models for carbohydrate reactivity. These rate constants do not represent an exhaustive list of those that have been determined; rather, they are ones of interest in understanding the reactions of carbohydrates.

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8: Radical Reactivity: Reaction Rate Constants

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Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation nor the US Department of Education.

II. Absolute and Relative Rate Constants

Two types of rate constants commonly are associated with radical reactions. One of these is the actual (sometimes call absolute) rate constant for a reaction, and the other is a relative rate constant, that is, a value determined by comparing the rate of one reaction to that of another.

The absolute rate constant k_a for the reaction shown in eq 1 is defined mathematically in eq 2.[1] Although the value of k_a is expressed in terms of the rate of disappearance of AB or appearance of RAB· and the concentrations of R· and AB, rarely can k_a be determined directly from this information. Because most radicals are highly reactive species that are present in a reaction mixture in concentrations typically too low to be measured accurately, direct determination of rate constants such as k_a seldom is possible. When a direct determination cannot be made, sometimes an indirect one can.

$$R\cdot + A{=}B \xrightarrow{k_a} RAB\cdot \quad (1)$$

$$-d[AB]/dt = d[RAB\cdot]/dt = k_a[R\cdot][AB] \quad (2)$$

On way for determining indirectly the rate constant for the reaction shown in eq 1 depends upon being able to measure the buildup of trace amounts of RAB· at different AB concentrations. Even though the actual concentration of RAB· is unknown, for some radicals it is possible to determine accurately their rate of appearance from the change in one of their properties (e.g., UV absorption). This information can provide a basis for indirectly determining the rate constant k_a.[2]

Relative rate constants are far easier to determine than actual rate constants because relative ones can be obtained without knowing radical concentrations or making any measurements on radicals. When CD and EF are present in the same reaction mixture, eq 5 describes a relation between the rate constants k_1 and k_2 for the competing reactions shown in equations 3 and 4. The ratio k_1/k_2 is determined by the concentrations of CD and EF and their rates of disappearance.[1] If, for example, the concentrations of CD and EF are equal and CD disappears ten times more rapidly than EF, the relative rate constants of 10 and 1 can be assigned to k_1 and k_2, respectively. Further, if the absolute rate constant is known for one of these two reactions, the relative rate constant for the other can be converted into an absolute one. More generally, if the absolute rate constant is known for one member of a group of reactions for which relative rate constants have been determined, the relative rate constants all can be converted into absolute ones.

$$R\cdot + C{=}D \xrightarrow{k_1} RCD\cdot \quad (3)$$

$$R\cdot + E{=}F \xrightarrow{k_2} REF\cdot \quad (4)$$

$$\frac{-d[CD]/dt}{-d[EF]/dt} = \frac{k_1[CD]}{k_2[EF]} \quad (5)$$

Although measuring product ratios provides relative rate constants for reactions of a radical with two or more compounds, determining the relative rate constants for reaction of two different radicals with a single compound is a much more difficult task. There is no reliable way to run a competition experiment. Comparing the reactivity of two (or more) radicals with a particular compound usually requires determining absolute rate constants.[3]

III. Generation of Carbon-Centered Radicals

A. Atom-Transfer Reactions

Carbon-centered radicals often are generated by atom-transfer reactions. The transfer usually is of a halogen atom, but hydrogen-atom transfer also can take place. Absolute rate constants for producing carbon-centered radicals by reaction of halogenated compounds with $Bu_3Sn\cdot$ are found in Table 1. Table 2 contains a similar set of rate constants that includes those for atom-transfer reactions involving $(Me_3Si)_3Si\cdot$ and $Et_3Si\cdot$. (Tables 1 and 2 also contain some group-transfer reactions.) To produce a radical selectively by atom transfer, one atom in the substrate must be more reactive than any other atom or group. A typical pair of propagation steps that selectively form a carbohydrate radical is shown in Scheme 1, where an iodine atom is transferred from a carbohydrate to a tin-centered radical.[8]

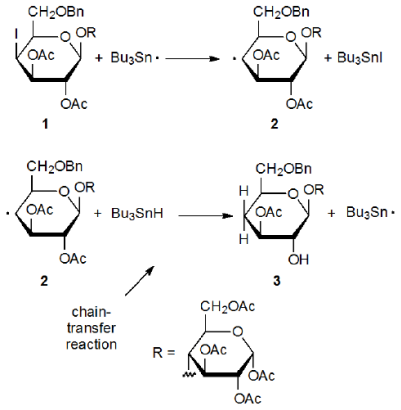
reactant	rate constant ($M^{-1}s^{-1}$)	temp	ref
$C_9H_{19}CH_2Cl$	7×10^3	25 °C	4
$(CH_3)_3CCl$	2.7×10^4	25 °C	5
$C_6H_5CH_2Cl$	1.1×10^6	25 °C	5
$CH_3(CH_2)_3OCH_2Cl$	1×10^5	25 °C	4
$C_7H_{15}CH_2Br$	3×10^7	25 °C	4
$(CH_3)_3CBr$	1.4×10^8	25 °C	5
CH_3I	4.3×10^9	25 °C	5
$CH_3(CH_2)_3OCH_2SC_6H_5$	1×10^3	25 °C	4
$CH_3(CH_2)_3OCH_2SeC_6H_5$	6×10^6	25 °C	4

Table 1. Rate constants for radical formation by reaction with the tri-*n*-butyltin radical

reactant	radical	rate constant ($M^{-1}s^{-1}$)	temp	ref
$(CH_3)_3CCl$	$(Me_3Si)_3Si\cdot$	4.0×10^5	25 °C	6
$CH_3(CH_2)_4Br$	$(Me_3Si)_3Si\cdot$	2.0×10^7	20 °C	6
$(CH_3)_3CBr$	$(Me_3Si)_3Si\cdot$	1.2×10^8	20 °C	6
c-$C_6H_{11}I$	$(Me_3Si)_3Si\cdot$	$>4 \times 10^9$	20 °C	7
$C_6H_5SC_{10}H_{21}$	$(Me_3Si)_3Si\cdot$	$<5 \times 10^6$	21 °C	2
$C_6H_5SeC_{10}H_{21}$	$(Me_3Si)_3Si\cdot$	9.6×10^7	21 °C	2
c-$C_6H_{11}OC(=S)SMe$	$(Me_3Si)_3Si\cdot$	1.1×10^9	21 °C	2
c-$C_6H_{11}NC$	$(Me_3Si)_3Si\cdot$	4.7×10^7	21 °C	2
$(CH_3)_3CNO_2$	$(Me_3Si)_3Si\cdot$	1.2×10^7	21 °C	2
$CH_3(CH_2)_4Cl$	$Et_3Si\cdot$	3.1×10^5	25 °C	6
$(CH_3)_3CCl$	$Et_3Si\cdot$	2.5×10^6	25 °C	6
$CH_3(CH_2)_4Br$	$Et_3Si\cdot$	5.4×10^8	27 °C	6
$(CH_3)_3CBr$	$Et_3Si\cdot$	1.1×10^9	27 °C	5,6
$CH_3(CH_2)_2I$	$Et_3Si\cdot$	4.3×10^9	27 °C	5
CH_3I	$Et_3Si\cdot$	8.1×10^9	29 °C	5

Table 2. Rate constants for radical formation by reaction with the tris(trimethylsilyl)silyl and triethylsilyl radicals

Scheme 1



Examining the rate constants in Tables 1 and 2 offers insight into why iodides and bromides are so frequently used in carbon-centered radical generation. Reactions of compounds containing these atoms are so rapid that rarely is there competition in radical formation from replacement of other groups or atoms commonly present in a reacting molecule. Chlorides are substantially less reactive than iodides and bromides; consequently, chlorine atom abstraction is a less effective way for selectively generating carbon-centered radicals. (Fluorides are effectively unreactive.) Another factor favoring the use of iodides and bromides is a synthetic one. Sulfonate esters, which are easily prepared from carbohydrates, are converted readily into the corresponding iodides and bromides by nucleophilic displacement reaction.

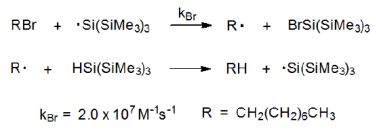
Because the rate constants listed in Tables 1 and 2 are for reactions of organic compounds that are structurally simpler than carbohydrates, in using these rate constants for carbohydrate reactions the assumption is that the same reactive substituent will have a similar rate constant for reaction in a more complex compound. Although such an assumption is reasonable, often necessary, and usually valid, extrapolation of rate constants from simple compounds to carbohydrates needs to be treated with caution because some of the structural features that affect the reactivity of carbohydrates and carbohydrate radicals cannot be adequately accounted for in simpler systems. (Such a situation involving pyranos-1-yl radicals was discussed in Sections VI.B. and VI.C. of Chapter 7.)

B. Group-Transfer Reactions

Group transfer can be a more complicated process than atom transfer because atom transfer consists of a single elementary reaction, but group transfer often requires two such reactions. Since the halogen-atom-transfer reactions shown in Tables 1 and 2 are irreversible, for each of these reactions the rate constant for halogen-atom transfer is the same as that for carbon-centered radical formation. The situation is different for group-transfer reactions because the first step in group transfer often is reversible. In such a situation the absolute rate constant for reaction of a substrate with Bu_3Sn·(Table 1) or $(Me_3Si)_3Si$· (Table 2) is larger than the rate constant for carbon-centered radical formation.

The effect on radical reactivity of a reversible reaction during group transfer can be seen by comparing three pairs of competing reactions.[2] The common reaction in each of these three is between 1-bromooctane and $(Me_3Si)_3Si$· (Scheme 2). Since this reaction gives the octyl radical R· in a single, irreversible step, the rate constant for reaction of the bromide with $(Me_3Si)_3Si$· is the same as the rate constant for formation of R·. Also, since R· then abstracts a hydrogen atom from $(Me_3Si)_3SiH$, the amount of octane formed is directly related to the number of octyl radicals produced.

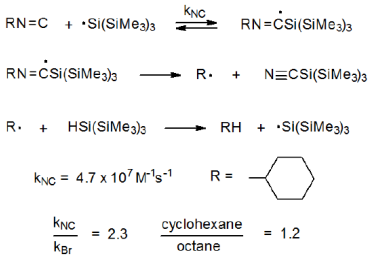
Scheme 2



The first comparison experiment involves reaction of molar-equivalent amounts of 1-bromooctane, cyclohexyl isonitrile, and tris(trimethylsilyl)silane.[2] A proposed mechanism for the reaction between the isonitrile and $(Me_3Si)_3Si$· is give in Scheme 3. If the addition of $(Me_3Si)_3Si$· to the isonitrile is irreversible, then the ratio of cyclohexane to octane in the product mixture would be the same as the ratio of the rate constants given the Table 2 for reactions of the isonitrile and the bromide, respectively. The information in Scheme 3 shows that these ratios are similar but not the same. One conclusion that can be drawn from this information is that the addition of $(Me_3Si)_3Si$· to cyclohexyl isonitrile is reversible. Whenever the reverse reaction takes place, it

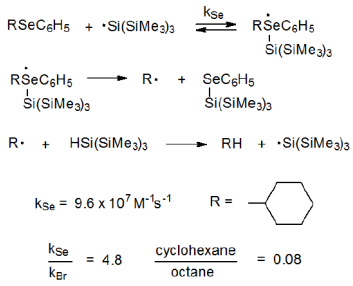
effectively reduces the rate of cyclohexane formation and causes the ratio of cyclohexane to octane to be smaller than that expected from the ratio of the rate constants k_{NC} and k_{Br} (Scheme 3).

Scheme 3

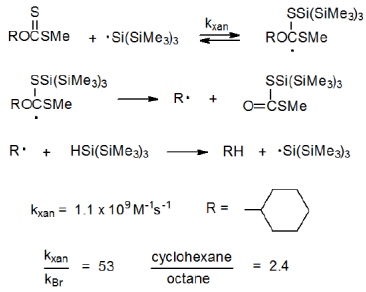


The addition of the $(Me_3Si)_3Si\cdot$ to cyclohexyl phenyl selenide (Scheme 4) and cyclohexyl xanthate (Scheme 5) presents a picture with more dramatic differences.[2] Competition experiments with 1-bromooctane show that the rate constants for group transfer from the selenide and the xanthate are substantially less than the rate constants shown in Table 2. This reduced reactivity can be explained by assuming that the addition of $(Me_3Si)_3Si\cdot$ to these compounds is a frequently reversed process.

Scheme 4



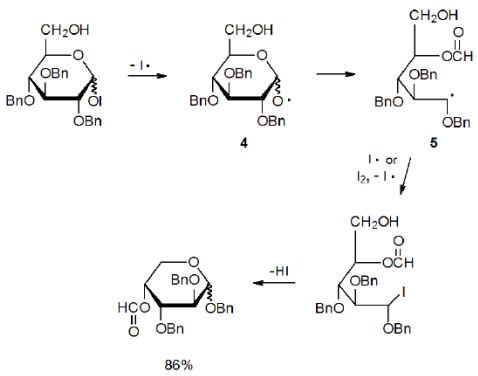
Scheme 5



C. Fragmentation Reactions

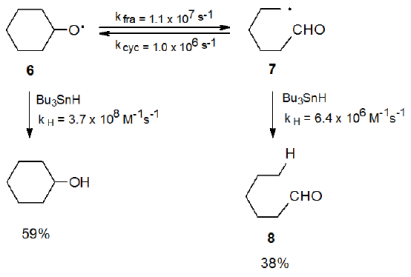
The basic structure of carbohydrates makes possible the formation of both carbon-centered and oxygen-centered (alkoxy) radicals. The reactions that characterize oxygen-centered radicals are hydrogen-atom abstraction and radical fragmentation. When an oxygen-centered radical fragments, the result is usually a radical centered on a carbon atom; thus, the alkoxy radical **4** fragments to give the ring-open, carbon-centered radical **5** (Scheme 6).[9] The lack of an effective hydrogen donor in the reaction mixture allows fragmentation to take place without competition from hydrogen-atom abstraction.

Scheme 6

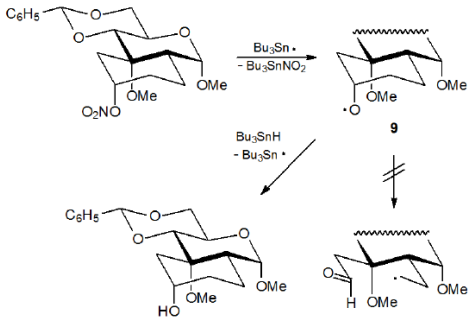


In the reaction shown in Scheme 7 the oxygen-centered radical **6** and the carbon-centered radical **7** exist in a pseudoequilibrium. Both radicals abstract hydrogen atoms from Bu_3SnH.[10] Due to the differences in the rate constants for ring opening (k_{fra} = 1.1 x 10^7 s^{-1} at 80 °C) and ring closure (k_{cyc} = 1.0 x 10^6 $s^{-1}M^{-1}$ at 80 °C), the ring-open radical **7** dominates the pseudoequilibrium, but because the rate constant for hydrogen-atom abstraction by **6** (k_H = 4.7 x 10^8 $s^{-1}M^{-1}$ at 80 °C) is so much larger than that for hydrogen-atom abstraction by **7** (k_H = 6.4 x 10^6 $s^{-1}M^{-1}$ at 80 °C), the major reaction product arises from hydrogen-atom abstraction by the oxygen-centered radical **6**. A related reaction that also is controlled by the large rate constant for hydrogen-atom abstraction by an oxygen-centered radical is pictured in Scheme 8, where abstraction by the alkoxy radical **9** is responsible for the only product formed.[11] There is no evidence for competing fragmentation of **9** leading to ring opening; in particular, no ring-open product is formed and no epimerization takes place at the hydroxyl-bearing carbon atom. (Epimerization would be expected if a ring opening took place that was followed by rapid ring closure.)

Scheme 7



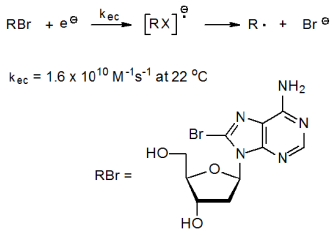
Scheme 8



D. Electron-Transfer Reactions

Dissociative electron transfer takes place when a compound containing a reactive atom or group accepts an electron and undergoes fragmentation (Scheme 9). Electron capture can be extremely rapid if an electron is free in solution; thus, the rate constant for capture of a solvated electron by the nucleoside **10** is 1.6 x 10^{10} $M^{-1}s^{-1}$ at 22 °C.[12,13]

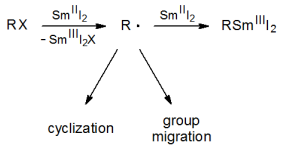
Scheme 9



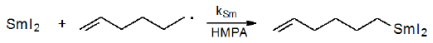
10

Radical formation by electron transfer also can take place by reaction between transition-metal complexes such as $(NH_4)_2Ce(NO_3)_6$, $Mn(OAc)_3$, SmI_2, and Cp_2TiCl and carbohydrate derivatives that include iodides, bromides, and sulfones; for example, complexes involving samarium(II) iodide frequently are electron donors in reactions of carbohydrates (Scheme 10). A common reaction for SmI_2 is a second electron transfer to the initially formed radical R· to produce an organosamarium compound (Scheme 10). This second electron transfer is fast enough that it can limit the ability of R· to undergo radical transforming reactions such as cyclization and group migration.

Scheme 10



Reactions involving SmI_2 typically are conducted in the presence of hexamethylphosphoramide (HMPA), a compound that complexes with SmI_2 and increases its ability to donate an electron. Greater electron-donating ability not only increases the rate constant for formation of the radical R· but it also increases the rate at which this radical reacts with a second molecule of SmI_2. The data in Table 3 show that when the 5-hexenyl radical reacts with SmI_2, the rate constants for reaction increase from 5 x 10^5 $M^{-1}s^{-1}$ to 6.8 x 10^6 M^{-1} s^{-1} at 25 °C as the amount of added HMPA increases.[14] The magnitude of these rate constants is such that if a radical is to do anything other than simple combination with a molecule of SmI_2, this "other reaction" must be rapid. An example of a reaction of a radical that does take place more rapidly than combination with SmI_2 is the cyclization shown in Scheme 11.[15,16] (Chapter 20 in Volume II contains further information about and discussion of the reactions of carbohydrate derivatives with SmI_2.)

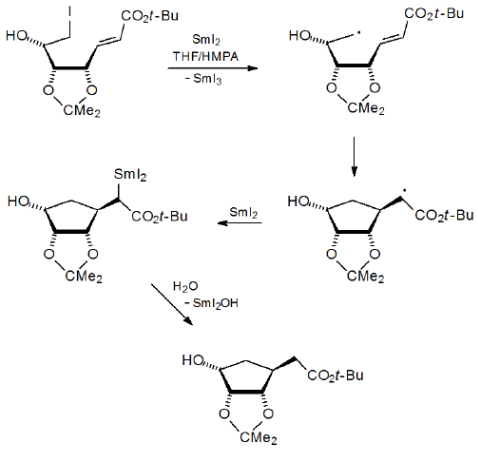


HMPA[a]	$k_{Sm}(M^{-1}s^{-1})$
2.3	5 x 10^5
2.8	6 x 10^5
3.2	2.8 x 10^6
3.7	5.3 x 10^6
4.4	6.4 x 10^6
5.1	6.8 x 10^6
6.0	6.5 x 10^6

[a]equivalents of HMPA $[Me_2N)_3PO]$ added relative to SmI_2 present

Table 3. Rate constants for reaction of 5-hexenyl radical with SmI_2 in the presence of HMPA at 25 °C[14]

Scheme 11



91%

IV. Transformation of Carbon-Centered Radicals

Although every propagation step in a radical chain reaction involves conversion of one radical into another, the potential for a synthetically useful reaction usually hinges on the transformation of a carbon-centered radical. Whether or not a transformation takes place depends on the relative rates for transforming and competing reactions. Because Bu_3SnH or $(Me_3Si)_3SiH$ often is present in a reaction mixture to provide a chain-carrying radical as well as to serve as a hydrogen donor after radical transformation has taken place, a common competing reaction for group migration, radical cyclization, and radical addition is hydrogen-atom abstraction before transformation occurs.

V. Chain Collapse

Chain collapse occurs when an intermediate radical undergoes a chain-stopping reaction more rapidly than the propagation reaction in which this radical is participating.[61] One cause of collapse is a chain-terminating step (e.g., radical dimerization) whose rate exceeds the rate of chain propagation. A second type of chain collapse occurs when an intermediate radical in a propagation sequence becomes part of a faster step in a propagation sequence leading to a different product. In such a situation chain collapse is caused by chain shift to the new reaction sequence.

VI. Summary

Generating a carbon-centered radical represents the beginning point for most radical reactions of carbohydrates. The identity of the radical formed is determined by the rate constant for atom or group transfer from the carbohydrate derivative to a radical that usually is centered on a tin or silicon atom. Compounds that contain iodine or bromine atoms are attractive starting materials for radical reactions because the rate constants for transfer of these atoms to tin- or silicon-centered radicals are quite large. Once a carbon-centered radical has formed, most reactions of importance include a radical transforming step (e.g., addition of a radical to a multiple bond or radical cyclization). Rate constants for radical transformation must be large enough that the desired reaction can take place before a competing process, often hydrogen-atom abstraction, intervenes. If a propagation step in a reaction is slower than a chain-terminating reaction, the reaction will undergo chain collapse.

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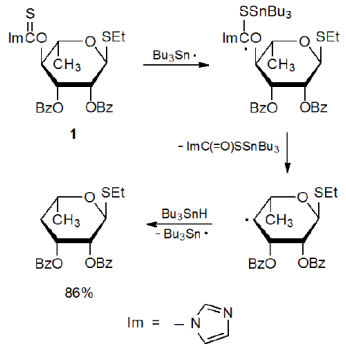
CHAPTER OVERVIEW

9: Chemoselectivity

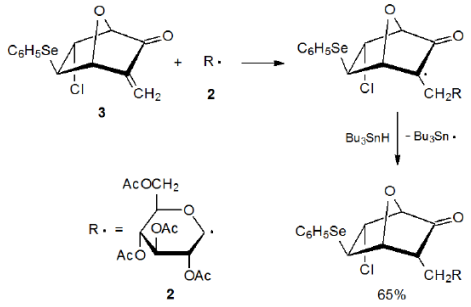
Chemoselectivity is a term that describes the ability of a reagent or intermediate to react with one group or atom in a molecule in preference to another group or atom present in the same molecule. Since most carbohydrate radicals trace their beginnings to reactions involving either a tin-centered [usually $Bu_3Sn\cdot$] or a silicon-centered [usually $(Me_3Si)_3Si\cdot$] radical, the chemoselectivity in reactions of these radicals plays a central role in carbohydrate radical formation. An example of a chemoselective reaction is found in Scheme 1, where the tri-*n*-butyltin radical abstracts the *O*-thiocarbonyl group from the thioglycoside **1** while the potentially reactive ethylthio group remains in place.[1]

Scheme 1



Chemoselective reaction also can occur when a carbohydrate radical reacts with another molecule present in the reaction mixture. Such a process is shown in Scheme 2, where the pyranos-1-yl radical **2** adds to the C–C double bond in **3** rather that reacting with the chlorine atom or phenylseleno group also present in this molecule (**3**).[2]

Scheme 2



Topic hierarchy

II. Formation of Carbon-Centered Radicals

III. Carbon-Centered Radicals

IV. Summary

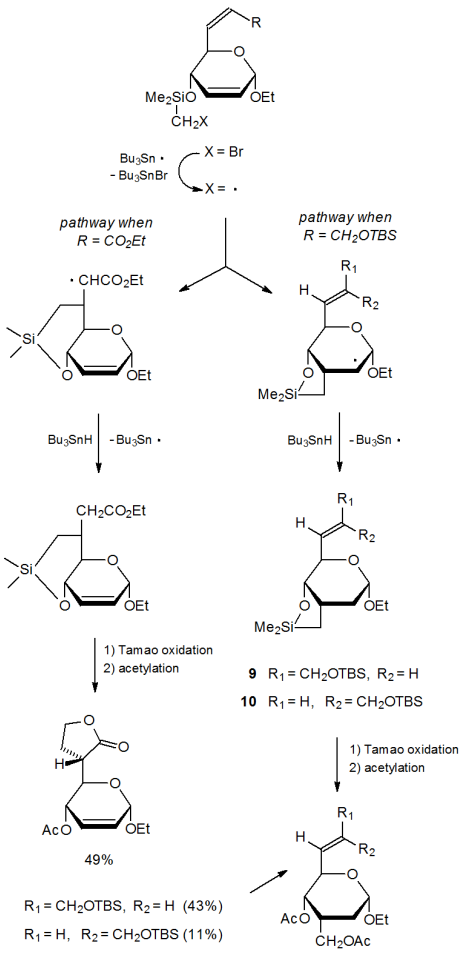
II. Formation of Carbon-Centered Radicals

The best method for determining the chemoselectivity of two groups in a particular reaction is to compare their reactivity in a substrate containing both. Since this type of testing rarely has taken place, another approach is needed if chemoselectivity in a particular reaction is to be established from existing data. One alternative is to construct an order of reactivity based on rates of reaction of compounds that each contains a single substituent. Such an order can be established from information that exists about rates of reaction of $Bu_3Sn\cdot$ and $(Me_3Si)_3Si\cdot$ with compounds that have a single reactive substituent.

III. Carbon-Centered Radicals

Although the primary reason for reacting carbohydrates with $(Me_3Si)_3Si\cdot$ or $Bu_3Sn\cdot$ is to generate carbon-centered radicals, the chemoselectivity of the reactions of carbohydrate radicals formed in this way also is a matter of importance. Nearly all carbon-centered radicals derived from carbohydrates are nucleophilic and, consequently, add more readily to carbon–carbon multiple bonds that are electron deficient than to ones that are electron rich. (The rationale behind this selectivity is discussed in Sections IV.A.1. and IV.B.1. of Chapter 7.) The cyclization reactions shown in Scheme 10 illustrate the influence of an electronegative substituent on the chemoselectivity of addition of a nucleophilic radical to a compound with two double bonds.[36,37] Reaction occurs at the double bond external to the ring when an electron-withdrawing substituent (R = CO_2Et) is present, but if the substituent is not electron-withdrawing (R=CH_2OTBS), addition is exclusively at the endocyclic double bond. (The *cis-trans* isomerization that takes place during formation of **9** and **10** results from reversible addition of $Bu_3Sn\cdot$ to the double bond external to the ring.)

Scheme 10



A variety of groups (e.g., acetal, acetoxy, carbonyl, cyano, hydroxy, and silyloxy groups) can be present in a reactant molecule but remain unchanged during carbon-centered radical addition to a carbon–carbon multiple bond. Carbon-centered radicals also participate less readily in substitution reactions with normally reactive substituents than do tin- and silicon-centered radicals; for example, Tables 1, 2, and 5 in Chapter 8 show the absolute rate constants for reaction of *tert*-butyl bromide with $Bu_3Sn\cdot$, $(Me_3Si)_3Si\cdot$, and $CH_3(CH_2)_6CH_2\cdot$ are 1.4 x 10^8 $M^{-1}s^{-1}$, 1.2 x 10^8 $M^{-1}s^{-1}$, 4.6 x 10^3 $M^{-1}s^{-1}$, respectively. This reluctance to become involved in substitution reactions is illustrated in Scheme 2 where the radical **2** does not react with the chlorine atom or phenylseleno group in **3** but rather adds to the C–C double bond in this molecule.[2]

IV. Summary

Chemoselectivity refers to ability of a reagent or intermediate (e.g., a free radical) to react with one group in a molecule in preference to a different, but potentially reactive, group present in the same molecule. Since most carbohydrate radicals trace their beginnings to reactions involving either the tri-*n*-butyltin [$Bu_3Sn\cdot$] or tris(trimethylsilyl)silyl [$(Me_3Si)_3Si\cdot$] radical, chemoselectivity in the reactions of these radicals plays a central role in carbohydrate radical formation. In many reactions a second opportunity for chemoselectivity arises when an initially formed, carbon-centered radical reacts selectively with another molecule present in solution.

The tri-*n*-butyltin radical adds to carbon–carbon, carbon–oxygen, and carbon–sulfur multiple bonds in a reversible fashion; consequently, for chemoselective reaction to occur, the reverse reaction must be blocked in some manner. Preventing reversal of radical addition usually is achieved by hydrogen-atom abstraction, addition to a multiple bond, or fragmentation of the adduct radical. Silicon–carbon bonds tend to be stronger than tin–carbon bonds so addition of some silyl radicals to unsaturated compounds is not reversible at normal reaction temperatures. The tris(trimethylsilyl)silyl radical, however, does add reversibly to unsaturated compounds.

Carbon-centered radicals tend to be quite chemoselective intermediates. They add readily to electron-deficient, carbon–carbon, multiple bonds but are less reactive in group and atom replacement reactions than $(Me_3Si)_3Si\cdot$ and $Bu_3Sn\cdot$

CHAPTER OVERVIEW

10: Regioselectivity

Topic hierarchy

I. Introduction

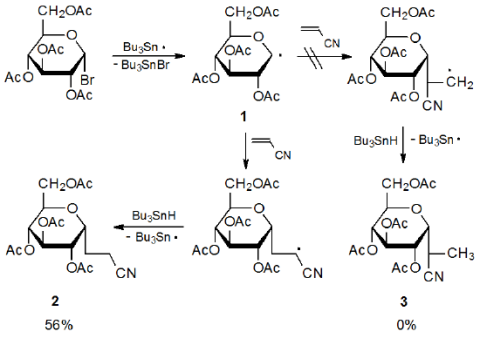
A. Definitions of Regiospecific and Regioselective Reactions

When the terms regioselective and regiospecific were first introduced into organic chemistry, they were defined in the following way: “If a reaction proceeds without skeletal rearrangement to give exclusively (within experimental error) one of two or more possible isomers, it is called *regiospecific*. If there is a significant preponderance of one isomer formed, it is said to be *regioselective*.[1]" Since a regiospecific reaction can be viewed as a special type of regioselective reaction (i.e., one that is totally selective), the term regioselective can be used to describe any reaction that produces one structural isomer in greater abundance than another.

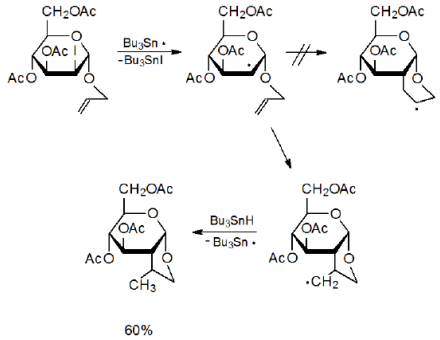
B. Regioselectivity in Radical Reactions of Carbohydrates

Among carbohydrates there are several types of radical reaction for which regioselectivity is an important consideration. The first of these (discussed in Section II) is the addition of a radical to the multiple bond in an unsaturated compound. An example of reaction of this type is found in Scheme 1, where addition of the pyranos-1-yl radical **1** takes place only at the unsubstituted carbon atom of the double bond in acrylonitrile.[2,3] A second type of regioselective reaction (described in Section III) is a variation on this addition process that occurs when the radical center and the multiple bond are part of the same molecule. In the reaction shown in Scheme 2, for example, regioselectivity arises because there is a choice between producing a five-membered or six-membered ring.[4] A third type of regioselective reaction, one involving β-fragmentation, is discussed in Section IV. An example is given in Scheme 3 where the oxygen-centered radical **4** undergoes ring opening to generate the carbon-centered radical **5** rather than the oxygen-centered radical **6**.[5] An example of the final type of regioselective radical reaction is found in Scheme 4, where abstraction of H-5 from the pentaacetate **7** takes place even though there are other hydrogen atoms present in **7** that could have been abstracted to form isomeric products.[6] This type of regioselectivity, sometimes referred to as site-selectivity, is described in Section V.

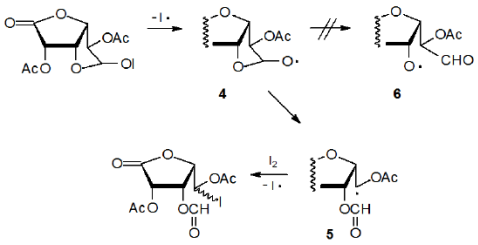
Scheme 1



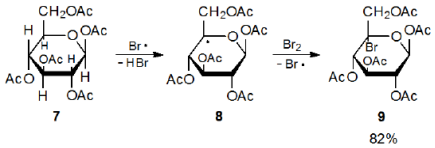
Scheme 2



Scheme 3



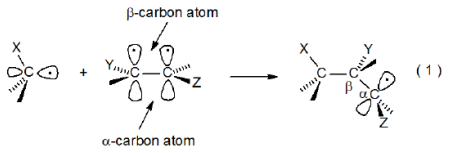
Scheme 4



II. Intermolecular Addition Reactions

A. General Reaction Equation

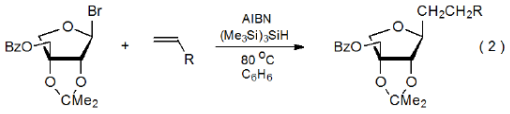
A useful terminology for describing radical addition reactions is given in eq 1. According to this description, when a carbon-centered radical reacts with a carbon–carbon double bond, it adds to the β-carbon atom and creates a new radical center on the α-carbon atom. The letters X, Y, and Z in eq 1 represent substituents attached to the three carbon atoms directly involved in the reaction.



(1)

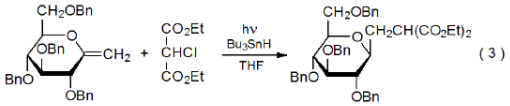
B. Reaction at the Less-Substituted Carbon Atom

A characteristic of radical addition reactions is that a carbon-centered radical adds regioselectively to the less-substituted atom in a C–C multiple bond.[7–10] The reaction shown in Scheme 1 provides a typical example. Other reactions involving double bonds with different substituents (eq 2)[11] and double bonds with more than one substituent (eq 3)[12.13] exhibit similar regioselectivity. Explaining regioselectivity in addition reactions begins by noting that they usually are not reversible;[14] therefore, information about transition-state structures is critical to understanding the selectivity in these kinetically controlled reactions.



(2)

R = CO_2Me, CN, COMe 57-83%



(3)

50%

C. Transition-State Structure

The structure for the transition state in a radical addition reaction, as determined from molecular-orbital calculations, is shown in-Figure 1.[8] Several aspects of this structure affect reaction regioselectivity. The first is that the structure is unsymmetrical.[7,8] An unsymmetrical transition state requires that radical addition to each carbon of the multiple bond represents a distinct reaction pathway; there is no common intermediate. Also, partial σ-bond formation between the α-carbon atom and the incoming, carbon-centered radical causes the groups attached to each of these atoms to assume a decidedly pyramidal arrangement; thus, reaction causes the groups attached to each center to move closer together.

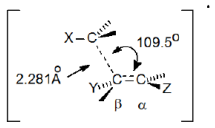


Figure 1. Transition-state structure for addition of a radical to an unsaturated compound. The numbers are calculated values for X = Y = Z = H.

D. Factors Controlling Regioselectivity

The unsymmetrical nature of the transition state structure shown in Figure 1 requires that addition to each carbon atom of an unsymmetrically substituted double bond has a different rate constant for reaction. Understanding regioselectivity in addition reactions then depends upon correctly analyzing the factors controlling these two rate constants. “The temperature dependence of the rate constants is well described by the Arrhenius equation $k = A\exp(-E_a/RT)$. Thus, at a given temperature, the rate variations with radical and substrate substitution can be caused by variations in the frequency factor (A) and/or the activation energy (E_a). For

polyatomic radicals, the frequency factors span a narrow range... Hence, the large variation in the rate constants is mainly because of variations in the activation energy".[8] The major factors determining activation energy [bond strengths, steric effects, stereoelectronic effects, and polar effects] are then the ones that need to be considered in determining reaction regioselectivity.[8]

1. Bond Strengths

A characteristic of many reactions that are similar in nature is that their energies of activation (E_a) can be determined from the Evans–Polanyi relation (eq 4).[8,10] (The Evans–Polanyi relation is discussed in Section I.A. of Chapter 7.) In such situations calculating these energies depends upon determining reaction enthalpies (H_r) and establishing values for the two constants in eq 4. For the addition of carbon-centered radicals to C–C double bonds the values for the experimentally determined constants are C=50 $kJmol^{-1}$ and α=0.25, when E_a and H_r are expressed in $kJmol^{-1}$.[8,15] The number 0.25 for the proportionality constant α means that the enthalpy change, which depends on the difference in the strengths of the bonds being broken and formed, needs to be large for it to have a significant impact on the energy of activation for the reaction. The 0.25 value for α is reasonable for a reaction with an early transition state.

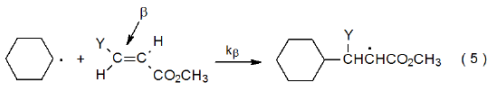
$$E_a = C + \alpha H_r \qquad (4)$$

E_a = energy of activation
H_r = reaction enthalpy
C and α are constants.

2. Steric Effects

Rehybridization of the β-carbon atom from sp^2 to sp^3 takes place during radical addition (eq 1). The necessary repositioning of groups that this rehybridization requires forces them closer together (i.e., causes group compression) as reaction proceeds. Any resistance to group compression caused by steric hindrance raises the energy required to reach the transition state for a reaction.[8–10] The transition state, therefore, becomes energetically more difficult to attain as the steric size of any of the groups attached to the β-carbon atom increases. A similar steric compression of the groups attached to the carbon atom bearing the radical center in the adding radical also takes place, but the effect should be smaller because a typical radical center has a structure that already is at an intermediate stage between sp^2 and sp^3 hybridization.[8–10]

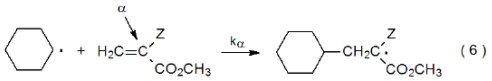
In addition to group compression, steric interactions at the transition state also arise between groups attached to the β-carbon atom and those bonded to the adding radical (Figure 1). Experimental support for significant interaction comes from the finding that the rate constants for radical addition to the β-carbon atom of an alkene change dramatically when sterically demanding groups are introduced on this atom.[7,16] In the reactions represented in eq 5 increasing the steric size of the Y group significantly decreases the rate constant for β addition.[7] While it may be difficult to decide how much rate constant reduction is attributable to group compression and how much to interaction between groups on the β-carbon atom and the incoming radical, the relative rate constants shown in eq 5 leave little doubt that steric effects play a major role in determining the rates of radical addition reactions.[7]



(5)

Y	k_β
H	20,000
CH_3	220
CH_3CH_2	132
$(CH_3)_2CH$	30
$(CH_3)_3C$	1

Since the separation at the transition state between the adding radical and the α-carbon atom in an addition reaction is considerable (Figure 1), it is reasonable to expect that any steric hindrance involving α-substituents should be small.[7,16] The relative rate constants shown in eq 6 support this expectation because a dramatic change in the steric size of groups attached to the α-carbon atom has only a small effect on the value of these constants; the largest and the smallest differ only by a factor of 4.2.[7]

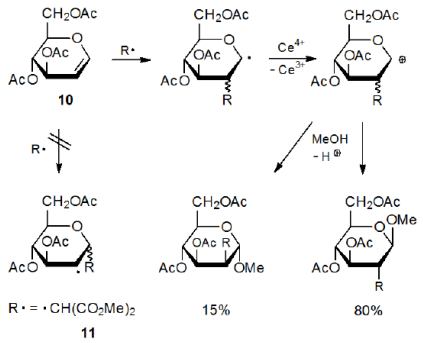


Z	k_α
H	4.2
CH_3	3.0
CH_3CH_2	2.3
$(CH_3)_2CH$	1.8
$(CH_3)_3C$	1.0

Steric effects have a more important role in determining addition-reaction regioselectivity than do the strengths of the bonds being broken or formed. The reason for this situation can be traced to the nature of the addition process. In the competing reactions that determine regioselectivity [i.e., addition to either the α or β carbon atom in a multiple bond of an unsaturated compound] the same number and types of bonds are being broken and formed; consequently, there should be little difference in activation energies for these two reactions based on bond strengths alone.

Although the primary role of steric effects in determining regioselectivity in radical addition reactions is clear, these effects are not always the sole determining factor. It would be difficult, for example, to explain preferential addition to C-2 in the glycal **10** (Scheme 5) on the basis of steric effects alone because C-2 is, if anything, more hindered than C-1.[17–19] Clearly, another factor also affects regioselectivity in reactions of this type.

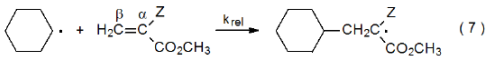
Scheme 5



3. Polar Effects

Polar effects are influences on reactivity caused by unequal electron distribution within a molecule or reactive intermediate. In radical addition reactions these effects can originate with substituent groups and can be transmitted to the reacting atoms either through bonds or through space. Polar effects also can arise from electron delocalization that produces unequal electron distribution.

The data shown in eq 7 illustrate the importance that polar effects have on radical addition reactions.[7] These data describe the relative rate constants for addition of the nucleophilic cyclohexyl radical ($C_6H_{11}\cdot$) to substituted α,β-unsaturated esters. The rate constant is large when a strongly electron-withdrawing substituent (e.g., CN, CO_2Me) is attached to the α-carbon atom in one of these unsaturated esters. Electron withdrawal from the double bond by either CN or CO_2Me is due primarily to delocalization that shifts electron density to one of these the α-substituents. In the case where the α-substituent is a methoxycarbonyl group (Z = CO_2Me), the electron-density shift can be seen in the contributing resonance structures shown in Figure 2. Although the polar effects being described are those that exist in the reactants, the rate constants in eq 7 support the idea that these effects remain significant at the transition state.



(7)

Z	k_{rel}	Z	k_{rel}
CN	1940	H	6
CO_2CH_3	940	CH_3	5
Cl	75	CH_3O	1

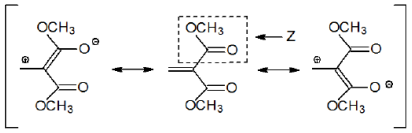
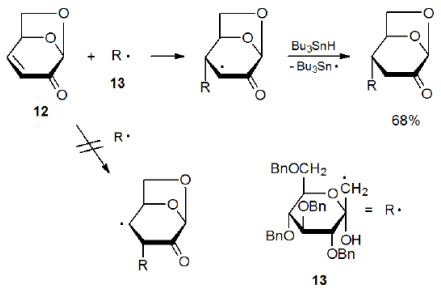


Figure 2. Resonance structures showing a shift of electron density to the carbonyl groups

Polar effects not only explain the difference in rate constants for the reactions shown in eq 7 but they also rationalize the regioselectivity of these reactions. The resonance hybrid pictured in Figure 2 indicates a reduced electron density at the β-carbon atom in the carbon–carbon double bond of the ester; consequently, this atom represents a point of attraction for a nucleophilic radical. In such a situation regioselective, β-carbon-atom addition can be expected. An example of this type of addition is shown in Scheme 6 where the nucleophilic carbohydrate radical **13** adds regioselectively to the β-carbon atom of the α,β-unsaturated ketone **12**.[20]

Scheme 6



Addition of a nucleophilic radical to an electron-rich double bond is too slow to compete with other radical reactions, but if the radical is electrophilic, addition takes place. The dimethylmalonyl radical **11**, for example, adds to the electron-rich double bond in the D-glucal **10** (Scheme 5).[17–19] As the resonance hybrid pictured in Figure 3 indicates, C-2 in **10** has greater electron density than C-1; thus, the electrophilic radical **11** not only adds to the double bond in **10** but it does so regioselectivity at C-2 (Scheme 5).

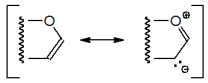
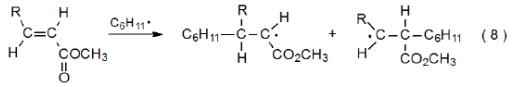


Figure 3. Resonance structures showing a shift of electron density to C-2

Since steric and polar effects often favor formation of the same product in a radical addition reaction (i.e., that from addition to the least substituted carbon atom in the double bond of the unsaturated reactant), it is sometimes difficult to determine the relative contribution of each effect to the regioselectivity of a reaction. A series of experiments designed to test these contributions is shown in eq 8.[7] The first experiment involves addition of the cyclohexyl radical to methyl acrylate (eq 8, R = H). In this reaction both steric and polar effects favor addition of the nucleophilic cyclohexyl radical to the less substituted carbon atom in the carbon–carbon double bond, but as the R group becomes sterically larger, the regioselectivity of the reaction decreases. For the sterically largest R group the favored direction of addition actually changes. The message here is that steric effects can overwhelm polar effects in establishing reaction regioselectivity, but a sterically quite demanding group (e. g., a *t*-butyl group) is necessary to overcome a strong polar effect.



(8)

14 **15**

relative yield of **14**	R	relative yield of **15**
99.8	H	0.2
92	CH_3	8
88	CH_3CH_2	12
75	$(CH_3)_2CH$	25
20	$(CH_3)_3C$	80

Another indication of the significance of polar effects in radical addition reactions can be seen by returning to the Evans-Polanyi relation (eq 4). This relation applies to radical addition reactions in which polar factors are not important. For reactions where polar factors are important, energies of activation are lower than those calculated from eq 4. In such situations a modified equation (eq 9), one including the multiplicative terms F_n and F_e, reflecting nucleophilic and electrophilic polar effects, respectively, is more accurate.[8,15]

$$E_a = (C + \alpha H_r)F_nF_e \quad (9)$$

$$0 < F_n, F_e < 1$$

E_a = energy of activation

H_r = reaction enthalpy

F_n = a nucleophilic polar factor

F_e = an electrophilic polar factor

C and α are constants.

4. Frontier-Orbital Interactions

Because radical addition reactions have early transition states,[7] frontier-orbital interactions are able to provide an alternative approach for explaining reaction regioselectivity. The first step in this approach is identifying the frontier orbitals in the reaction of interest; for example, in the addition of the dimethylmalonyl radical **11** to the electron-rich double bond in the D-glucal **10** (Scheme 5), the primary interaction is between the SOMO of **11** and the HOMO of **10** (Figure 10 in Chapter 7). Identifying the frontier-orbital interactions in a reaction does not, by itself, explain reaction regioselectivity, but orbital identification is a critical first step for such understanding because from frontier orbitals come the atomic-orbital coefficients that form the basis for explaining regioselectivity.

Atomic orbital coefficients are valuable in determining the regioselectivity of a reaction with an early transition state because the rate constant for the bond-forming reaction between two atoms in such a reaction depends to a large extent on the magnitude of the coefficients in their interacting frontier orbitals.[17,18] In the reaction pictured in Scheme 5 the most effective bonding is between the radical **11** and C-2 in the D-glucal **10** because the atomic orbital coefficient at C-2 for the HOMO in **10** is larger than that at C-1 (Figure 4);[21] consequently, regioselective addition to C-2 is favored.[17,18]

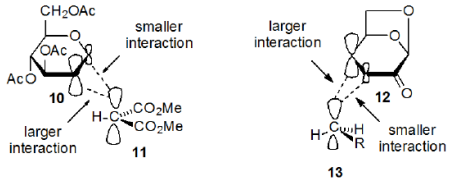
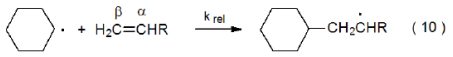


Figure 4. Frontier orbital interactions that affect reaction regioselectivity

Frontier-orbital interactions also explain regioselectivity in the addition reaction shown in Scheme 6, where a nucleophilic radical (**13**) is adding to an electron-deficient double bond.[20] Addition of the radical **13** to C-4, rather than C-3, in the α,β-unsaturated ketone **12** cannot be explained by steric effects, but frontier-orbital interactions do provide a basis for understanding the observed regioselectivity. The most important interaction in this case is between the SOMO of **13** and the LUMO of **12**. (A justification for this being the primary, frontier-orbital interaction is given in Section IV.B.1 of Chapter 7) For a LUMO such as that in **12** the largest atomic orbital coefficient is associated with the *p* orbital at C-4 (Figure 4);[21] consequently, regioselective addition to C-4 is favored.[22]

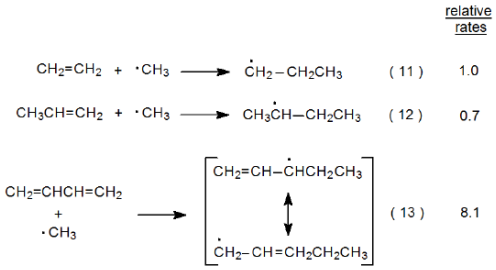
5. Adduct-Radical Stabilization

Adduct-radical stabilization as a possibility for explaining regioselective addition of a carbon-centered radical to a multiple bond is not highly regarded because the exothermic nature of and probable early transition state for radical addition reactions argue against significant, transition-state stabilization due to the developing radical. Evidence from study of model compounds that is cited in support of this point of view is that the cyclohexyl radical adds more rapidly to acrolein and acrylonitrile than to styrene (eq 10),[7,23] even though a phenyl group is more effective at stabilizing a radical center than is a carbonyl or cyano group.[7,24] This information indicates that adduct-radical stabilization is less important than polar effects at the transition state for an addition reaction; thus, polar effects are primarily responsible for the differences in reactivity of the unsaturated compounds, differences such as those shown in eq 10.[7] (As discussed in Section II.D.2 and seen in eq 6, steric hindrance from the α substituents used in the reactions shown in eq 10 should be inconsequential.) Since reactions between electron-deficient alkenes and nucleophilic radicals are stabilized at the transition state by polar effects, these effects could mask less important, adduct-radical stabilization. A better test of the importance of adduct-radical stabilization on regioselective addition would be one in which polar effects could not be the determining factor.



R	k_{rel}
CHO	34
CN	24
C_6H_5	1

The addition reactions shown in equations 11 and 12 are ones for which polar effects should be minimal.[10] The similarity in relative rates for the two reactions indicates that adduct-radical stabilization is inconsequential at the transition state. These reactions also underscore the difficulty in eliminating completely the influence of polar effects when comparing radical reactions. The slightly reduced rate for the reaction shown in eq 12, when compared to that in eq 11, could be due to the effect of the weakly electron-donating methyl group in propene reducing to a small extent the rate of addition of a nucleophilic radical to a slightly more electron-rich double bond. (As mentioned in Chapter 7, Sections III.C. and III.E., there is not complete agreement about the nucleophilicity of the methyl radical.)



The reaction shown in eq 13 supports the idea that the stability of the developing radical can be a factor in reducing transition-state energy.[10] The greater rate for this reaction, when compared to those shown in equations 11 and 12, can be explained by resonance stabilization in the developing radical contributing significantly to transition-state stabilization. The limited data in equations 11-13 are consistent with the idea that adduct-radical stability is only a factor in radical addition reactions when such stabilization is considerable. Once again, however, polar effects cloud this interpretation. 1,3-Butadiene can be viewed as a molecule in which each double bond has an ethenyl substituent attached. Such a substituent should be electron-withdrawing or, at least, less electron-donating than a methyl group; consequently, the double bonds in 1,3-butadiene should be more reactive toward the methyl radical than is the double bond in propene. This difference could explain, at least in part, the difference in relative rates for the reactions shown in eq 12 and eq 13.

III. Intramolecular Addition (Cyclization) Reactions

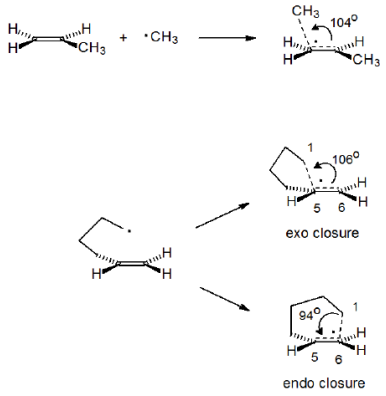
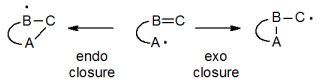


Figure 5. Transition state structures for addition of the methyl radical to propene and cyclization of the 5-hexenyl radical

In addition to describing cyclization reactions by the size of the ring produced, the terms exo and endo indicate the way in which the ring is formed. The meaning of these terms is illustrated in the reactions shown is Scheme 8. When the exo/endo terminology is used to describe ring formation from reaction of the 5-hexenyl radical, the five-membered ring is seen as arising from exo closure and the six-membered one from endo closure (Scheme 7).

Scheme 8



2. Transition-State Structure

Transition-state structures for radical addition and radical cyclization are given in Figure 6 in a general form. For cyclization reactions not only ring size but also ring conformation affect transition-state energy; thus, both chair-like[25,27] and boat-like[27,30] structures are possible during five-membered ring formation. For the unsubstituted 5-hexenyl radical the chair-like transition state leading to a five-membered ring is calculated to be lower in energy, but only slightly so, than the boat-like transition state (Scheme 9).[27] (The “flagpole” interactions that contribute to making the boat conformation of cyclohexane much less stable than the chair conformation are less severe in the boat-like transition state for radical cyclization.) Both transition states (boat-like and chair-like) leading to a five-membered ring (Scheme 9) are calculated to be lower in energy than any transition states leading to a six-membered ring. These calculations match well the experimental observation that cyclization of the 5-hexenyl radical gives a five-membered ring in a highly regioselective fashion (eq 14, R = H).[25,31]

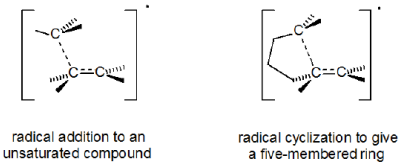
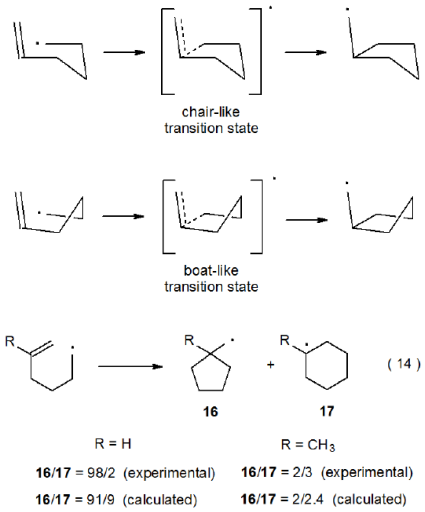


Figure 6. Favored transition states for radical addition and cyclization

Scheme 9

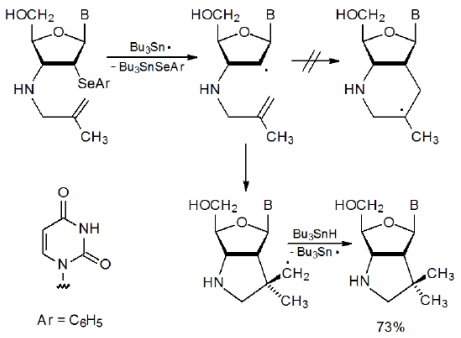


3. Altering Normal Regioselectivity

a. Steric Interactions and Adduct-Radical Stability

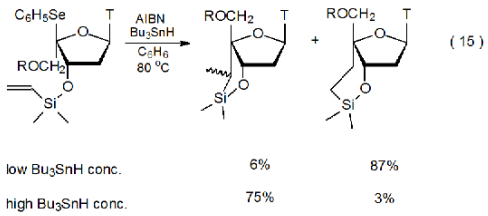
Although ring size is the primary factor affecting regioselectivity in cyclization reactions, other factors sometimes have a modifying effect; for example, in the reaction of the 5-methyl-5-hexenyl radical the presence of the methyl group increases the amount of six-membered-ring formation (eq 14, R = CH_3).[25,27] In this reaction steric effects and adduct-radical stability both favor a six-membered ring. The transition state in this reaction presumably is reached late enough that either steric effects or adduct-radical stability or both have a substantial impact on regioselectivity. Predicting when the transition state in this type of reaction will be early enough to cause highly regioselective, five-membered-ring formation is not easy. In the reaction shown in Scheme 10, where steric interactions and adduct-radical stability favor six-membered-ring formation at least as much as they do in the reaction shown in eq 14 (R=CH_3), only a product with a five-membered ring forms.[32]

Scheme 10

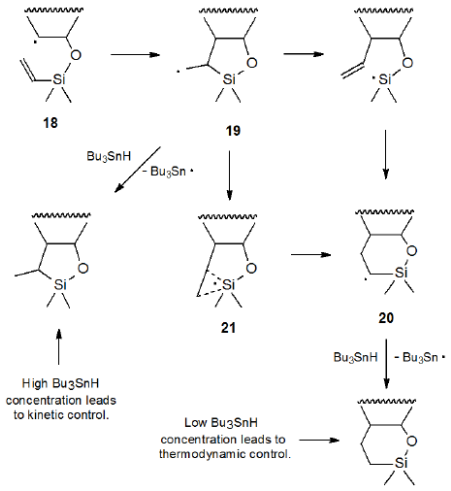


b. Thermodynamic Control

Although kinetically controlled reaction is the norm in radical cyclization, thermodynamic control is observed in the reaction shown in eq 15 where the substrate is an unsaturated silyl ether and the hydrogen donor (Bu_3SnH) is maintained at a low level.[33] When this reaction is conducted with a high Bu_3SnH concentration, kinetically controlled, five-membered ring formation is the major reaction pathway. An explanation for this dependence on hydrogen-donor concentration begins with the radical **18** cyclizing to form **19**, a radical with a new five-membered ring (Scheme 11). If the concentration of Bu_3SnH is high, hydrogen-atom abstraction rapidly completes the reaction, but if the donor concentration is low, rearrangement to the more stable radical **20**, via the transition state **21**, takes place before hydrogen-atom abstraction can occur.[34] Hydrogen-atom abstraction by **20** then gives the thermodynamically favored product. An alternative mechanism for this reaction, also shown in Scheme 11, is that ring opening of **19** produces a silicon-centered radical that undergoes ring closure to give the intermediate radical **20**.[35]



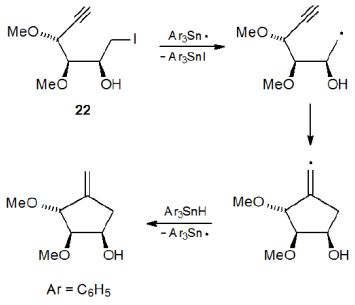
Scheme 11



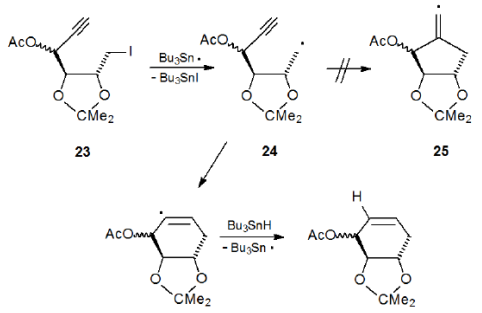
c. Reversal Due to Stereochemistry

One situation where six-membered ring formation is favored consistently over reaction producing a five-membered ring is when cyclization would produce a pair of trans-fused, five-membered rings. Reactions of iodides **22** and **23** illustrate the effect that stereochemistry can have on radical cyclization. The acyclic iodide **22** undergoes an expected cyclization to give a five-membered ring (Scheme 12),[36] but reaction of the iodide **23** forms a six-membered ring (Scheme 13).[37] Since a *trans* fusion between two five-membered rings would produce the highly strained radical **25**, the stereochemistry of the radical **24** dictates the regioselectivity of the cyclization reaction. Six-membered-ring formation also occurs in the reaction shown in Scheme 14[38], again, because the other option would force the formation of trans-fused, five-membered rings.

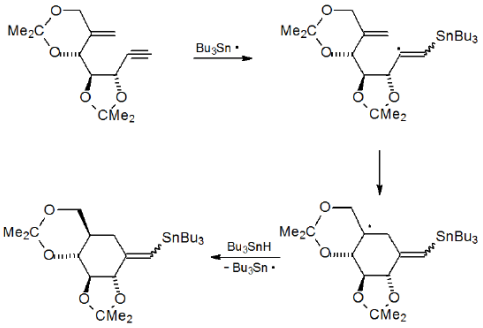
Scheme 12



Scheme 13



Scheme 14



IV. β-Fragmentation Reactions

β-Fragmentation is an elementary reaction that exhibits regioselectivity in ring opening and in radical expulsion. Regioselective ring opening occurs when a radical centered on an atom attached to a ring preferentially fragments one of the ring bonds. Regioselective radical expulsion takes place when one of the bonds to an atom β-related to a radical center preferentially cleaves to generate two fragments, one a new radical and the other an unsaturated compound.

V. Site-Selective Reactions

The regioselectivity discussed thus far has involved reactions in which a compound with a single functional group generates products that include two or more structural isomers. The term regioselectivity also can be used to describe the preference for reaction of a particular atom or group in a molecule that contains at least one other atom or group of the same type. Regioselectivity of this sort is sometimes referred to as site selectivity. An example of a site-selective reaction is shown in Scheme 4, where H-5 is abstracted even though there are other hydrogen atoms present in the molecule that potentially could have been abstracted.[6]

Although there are a large number of radical reactions in carbohydrate chemistry that involve group and atom replacement, only for hydrogen-atom abstraction is regioselectivity a common consideration. Nearly all carbohydrates have the hydrogen atoms necessary to make site-selective abstraction conceivable, but few carbohydrates have the two or more other groups or atoms required to make selective reaction of one of these groups (or atoms) a possibility. Hydrogen-atom abstraction, therefore, provides the pool from which most site-selective reactions are drawn.

VI. Summary

Intramolecular hydrogen-atom abstraction often involves reaction of an oxygen-centered radical. Since the most stable transition state for internal hydrogen-atom transfer nearly always has a six-membered ring, the 1,5-hydrogen migration (1,5-radical translocation) that occurs is a highly regioselective reaction. Only the most reactive carbon-centered radicals (vinylic and primary) consistently are able to abstract hydrogen atoms from carbon–hydrogen bonds. Such abstraction usually is an intramolecular reaction.

Site selectivity occurs in reactions of compounds with groups and atoms other than hydrogen, but such reactions are rare because few carbohydrates contain two or more of the same reactive groups (or atoms). Compounds with two of the same *O*-thiocarbonyl groups or two isocyano groups are known to react selectively with the tri-*n*-butyltin radical. In such reactions significant selectivity exists if there is a choice between forming a primary or a secondary radical.

CHAPTER OVERVIEW

11: Stereoselectivity

Topic hierarchy

I. Introduction

A. Definitions

Stereoselectivity is “the preferential formation of one stereoisomer over another in a chemical reaction”.[1] This selectivity can be divided into diastereoselectivity and enantioselectivity. “Enantioselectivity in a reaction is either the preferential formation of one enantiomer of the product over the other or the preferential reaction of one enantiomer of the (usually racemic) starting material over the other...Diastereoselectivity is the preferential formation in a reaction of one diastereoisomer of the product over others.”[2] Although diastereoselectivity almost always refers to product formation, it also can apply to preferential consumption of one diastereomer.[3]

B. Factors Affecting Stereoselectivity

Stereoselectivity in radical reactions is determined by a combination of factors that includes steric, stereoelectronic, conformational, torsional, and configurational effects as well as reaction temperature.[4] Each of these effects can be linked to a particular aspect of structure. Steric effects are the repulsive interactions that develop between closely approaching species (e.g., a neutral molecule and a free radical) or between two groups within the same structure. Stereoelectronic effects are geometry-dependent, orbital interactions that favor formation or consumption of one stereoisomer over another. Conformational effects are differences in stereoselectivity due to differences in the population of various conformers. Torsional effects are the destabilizing interactions that develop as electrons in bonds on adjacent atoms move closer to each other. Finally, configurational effects in radical reactions are differences in stereoselectivity due to pyramidal radicals that undergo reaction faster than inversion of configuration.

Although stereoselectivity in a reaction often results from a combination of the effects just described, it is possible to identify three important situations where a particular effect appears to be dominant. First, in addition and abstraction reactions, where the radical center is not adjacent to a ring oxygen atom, the greater role of steric effects causes reaction to occur along the least-hindered pathway. When a radical is centered on an atom adjacent to a ring oxygen atom (as occurs in pyranos-1-yl and furanos-1-yl radicals) orbital interactions become the factor most frequently determining stereoselectivity. Finally, in reactions that form new five- and six-membered rings, stereoselectivity usually is determined by maximizing stability of a chair-like or boat-like transition state.

II. Minimizing Steric Interactions: The Least-Hindered Pathway

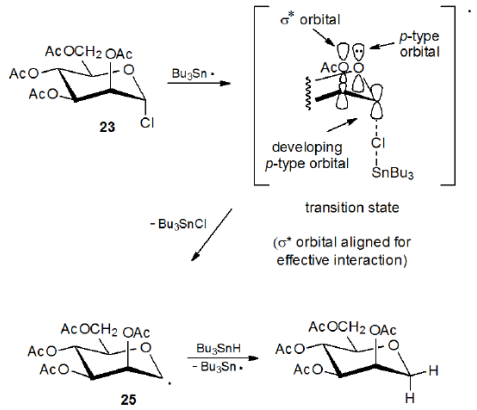
As mentioned in the previous section, stereoselectivity in reactions of carbohydrate radicals depends on the location of the radical center. When a radical is centered on a carbon atom adjacent to a ring oxygen atom a combination of stereoelectronic, conformational, and steric effects determines stereoselectivity, but reactions of radicals centered on other carbon atoms are controlled primarily by steric effects. For the latter group the major stereoisomer in a bimolecular reaction is the one produced by a molecule and a radical approaching each other along the least-hindered pathway.

III. Maximizing Transition-State Stabilization by Orbital Interactions: The Kinetic Anomeric Effect

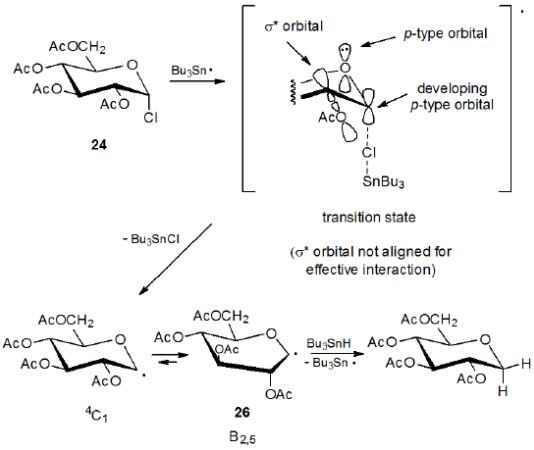
A. Radical Formation

The reactions of the glycosyl chlorides **23** and **24** provide examples of stereoselectivity in pyranos-1-yl radical formation that depend on orbital interactions (Schemes 9 and 10).[25,26] The difference in their reaction rates is linked to the orientation of the C_2–O bond in each of these stereoisomers. The D-mannopyranosyl chloride **23** reacts with tri-*n*-butyltin hydride 7.8 times more rapidly than does the epimeric D-glucopyranosyl chloride **24**. For **23** the C-2 acetoxy group has an orientation that allows transition-state stabilization by the orbital interactions shown in Scheme 9. These are the same interactions associated with the quasi-anomeric effect. (The quasi-anomeric effect, discussed in Section V of Chapter 6, provides an explanation for the conformations adopted by pyranos-1-yl radicals.[27,28]) Since these orbital interactions are developing at the transition state, they should be responsible, at least in part, for the greater reactivity of **23** when compared to **24**. Such stabilization is minimal for reaction of **24** because the σ* orbital associated with the C_2–O bond does not have the proper, transition-state orientation to assist significantly in stabilization (Scheme 10).

Scheme 9



Scheme 10



A critical assumption about the reactions shown in Schemes 9 and 10 is that the first step (chlorine-atom abstraction by the tri-*n*-butyltin radical), rather than the second step (hydrogen-atom abstraction from tri-*n*-butyltin hydride by the carbohydrate radical) is rate-determining. Such an assumption is reasonable because chlorine-atom abstraction in free-radical dehalogenation of alkyl chlorides is known to be rate-determining,[29] but it is not a certainty because for reaction of iodides, bromides, and some very reactive chlorides, hydrogen-atom abstraction from tri-*n*-butyltin hydride is the rate-determining step.

B. Radical Reaction

1. The Role of Radical Conformation

a. The Curtin-Hammett Principle

Consider conformations X and Y of a radical that is undergoing an addition reaction to give the products P_x and P_y (Scheme 11). One possibility is that interconversion of X and Y is rapid compared to their reactions. In this situation the Curtin–Hammett principle applies; that is, the ratio of the products depends only on the relative energies of the transition states leading to their formation. (A more detailed statement of the Curtin-Hammet principle is "the relative amounts of products formed from two pertinent conformers are completely independent of the relative populations of the conformers and depend only on the difference in free energy of the transition states, provided the rates of reaction are slower than the rates of conformational interconversion".[30]) An energy diagram showing a situation in which the Curtin-Hammet principle applies is found in Figure 2. If in this reaction P_x and P_y are stereoisomers, the overall process will form P_y stereoselectively, even though conformer X is present in greater amount.

Scheme 11

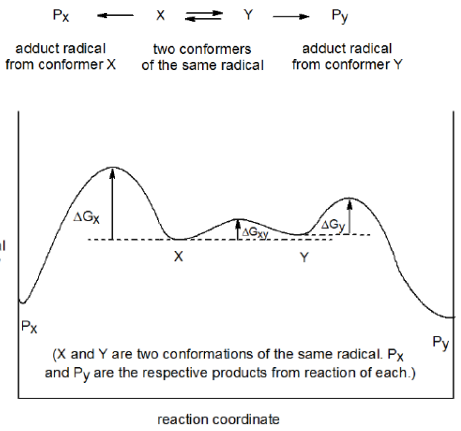


Figure 2. Potential energy diagram for reaction of readily interconvertable radical conformers X and Y.

A different situation exists for the reaction shown in Figure 3. In this case the interconversion of radicals X and Y is slow compared to their reactions. Under these conditions (the Curtin–Hammett principle not in effect) the conformation present in greatest amount determines the stereoselectivity of the reaction; thus, if X is the major conformer, P_x will be formed preferentially.

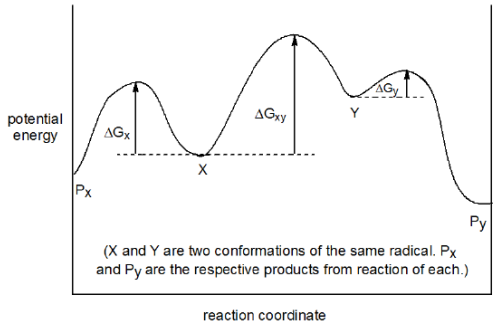


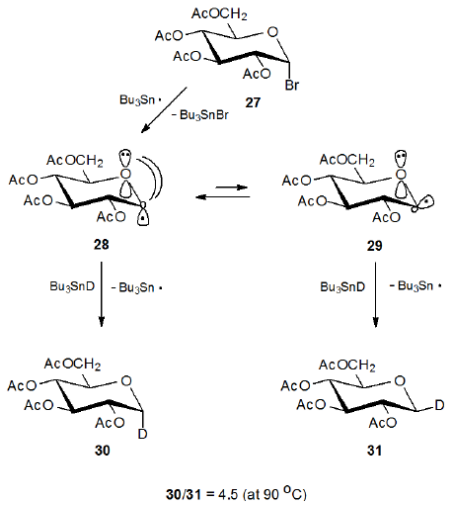
Figure 3. Potential energy diagram for reaction of radical conformations (X and Y) that react more rapidly than they interconvert.

b. An Initial Proposal

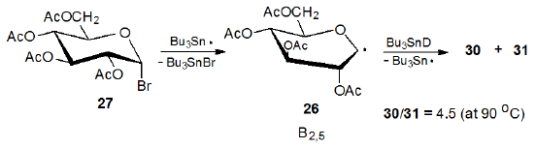
The explanation for the stereoselectivity of the reactions of pyranos-1-yl radicals has changed over time as new information about radical structure has become available. The first proposal for the stereoselective formation of the reduction products **30** and **31** from reaction of the D-glucopyranosyl bromide **27** with tri-*n*-butyltin deuteride was that product yields reflected the relative amounts of **28** and **29** present in the reaction mixture (Scheme 12).[31] (Inherent in this proposal was the assumption that **28** and **29** were the most stable structures for this pyranos-1-yl radical and that they reacted more rapidly than they equilibrated.) The major component in this proposed pseudoequilibrium was thought to be **28** because this radical would be stabilized more effectively than **29** by inter-

action of the orbital centered on C-1 with the *p*-type orbital on the ring oxygen atom (Scheme 12). This interpretation subsequently had to be revised because ESR spectral analysis showed that neither **28** nor **29** was as stable as the distorted $B_{2,5}$ boat conformation **26** (Scheme 13).[27,28]

Scheme 12



Scheme 13

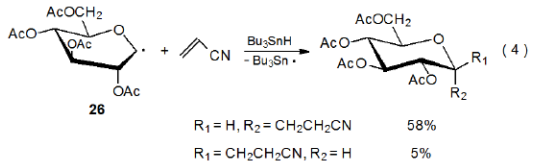


c. A Revised Explanation

(1). Steric Effects

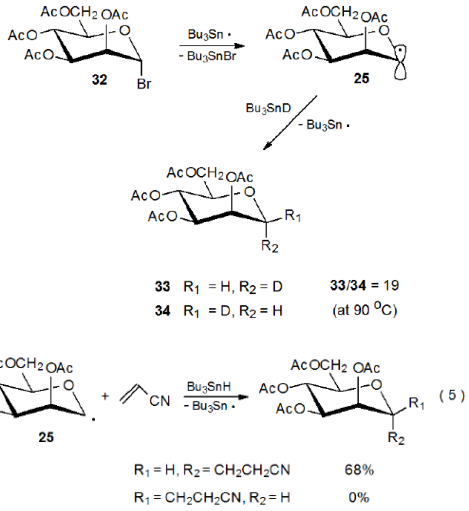
One possible explanation for stereoselectivity in reactions involving the D-glucopyranos-1-yl radical **26** is that steric effects are determining this selectivity just as they do in the reactions of many other carbohydrate radicals. For this explanation to be correct, approach to C-1 by Bu_3SnD from the α face of **26** would have to be less hindered than a similar approach to its β face. With the neighboring 2-*0*-acetyl group shielding α-face reaction at C-1 (Scheme 13), it is difficult to see how the least hindered pathway to C-1 would involve approach to the α face of the radical.

Another view of the difficulty with steric interactions being the controlling factor in stereoselectivity of the reactions of **26** comes from comparing these reactions with those of the pyranos-4-yl radical **7** and the pyranos-3-yl radical **8** (Table 3). For neither **7** nor **8** is the stereoselectivity of reaction with Bu_3SnD large, but for each the major stereoisomer comes from reaction on the face of the radical opposite to that containing the shielding groups on the adjacent carbon atoms. This result stands in contrast to the reaction of the pyranos-1-yl radical **26**, where the stereoselectivity is not only much larger, but Bu_3SnD approaches this radical from the face containing the only shielding group on a neighboring carbon atom. The α-face stereoselectivity of **26** is not limited to reaction with Bu_3SnD. Addition of this radical to acrylonitrile also is stereoselectively from the more hindered α face (eq 4).



The D-mannopyranos-1-yl radical **25** exhibits even greater α-face selectivity in deuterium abstraction (Scheme 14) and addition to acrylonitrile (eq 5) than does its D-gluco epimer **26** (Scheme 13, eq 4). While steric effects could explain the stereoselectivity in the reactions of **25**, they are unable to rationalize the selectivity in the reactions of both **25** and **26**; however, for each of these radicals stereoselectivity does have a link to radical conformation.

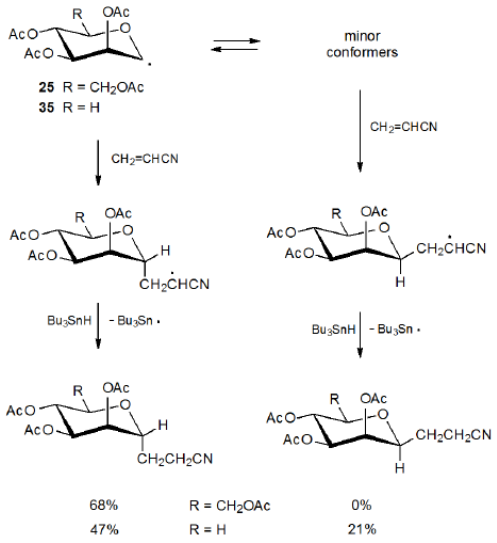
Scheme 14



(2). Interconversion of Conformations

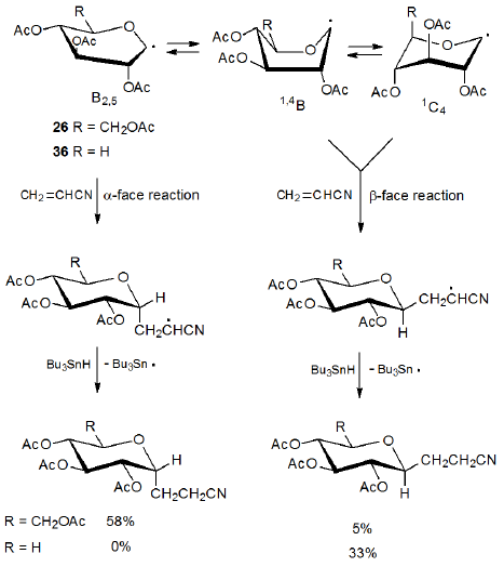
For the D-mannopyranos-1-yl (**25**) and D-lyxopyranos-1-yl (**35**) radicals only the $^4C_1$ chair conformation can be detected in the ESR spectrum of each (Scheme 15).[27,28,32] Structurally these radicals differ only at C-5 where the equatorial CH_2OAc substituent in **25** is replaced by a hydrogen atom in **35**. Even though the structures **25** and **35** are quite similar in the vicinity of the radical center, the stereoselectivity of their reactions is quite different. The radical **25** adds stereoselectively to acrylonitrile to give only the product arising from reaction at its α face, but the radical **35** reacts from both its α and β faces (Scheme 15).[32]

Scheme 15



Since an equatorial substituent at C-5 is remote from the reacting center at C-1, steric effects alone cannot explain the difference in reactivity between these two (**25** and **35**). Findings concerning the reactivity of **25** and **35** (Scheme 15) are echoed in the reactions of the D-glucopyranos-1-yl radical **26** and the D-xylopyranos-1-yl radical **36** (Scheme 16), further; observable conformations and reactivity **26** and **36** point to a possible explanation for the difference in stereoselectivity in the reactions of this pair (**26** and **36**) as well as the difference in stereoselectivity in the reactions of **25** and **35**.

Scheme 16



The ESR spectrum of **26** shows it to exist in a distorted $B_{2,5}$ boat conformation, but for **36** $B_{2,5}$ boat, $^{1,4}B$ boat, and $^{1}C_4$ chair conformations also can be detected.[6] Conformational population, therefore, changes considerable when the CH_2OAc substituent at C-5 in **26** is replaced by a hydrogen atom. This finding raises the possibility that the difference in stereoselectivity in the reactions of these radicals many be related to population and reactivity of conformational isomers (Scheme 16).

(3). Conformational Mobility

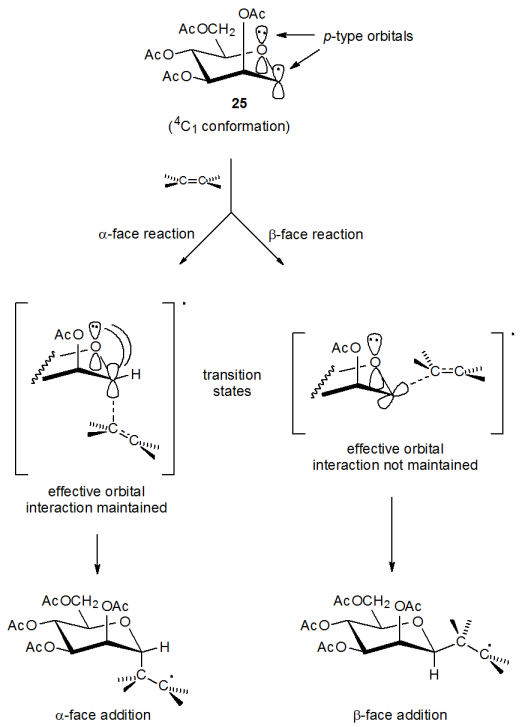
If $B_{2,5}$ conformations react from their α face, and $^{1,4}B$ or $^{4}C_1$ conformers (or both) from their β face (Scheme 16), conformational population and mobility could explain the observed stereoselectivity in the reactions of radicals **26** and **36**.[6] According to this explanation, interconversion among conformers of the radical **36** would need to be more rapid than reactions of these radicals (Curtin-Hammett principle in effect). Since the assumption is that $^{1,4}B$ boat or $^{1}C_4$ conformers give β-face reaction products,[6] the conclusion is that one or both of these conformers is much more reactive than the $B_{2,5}$ conformation and that this very reactive conformation does so in a highly stereoselective fashion. A further part of this argument is that the CH_2OAc substituent attached to C-5 in the radical **26** stabilizes the $B_{2,5}$ conformation and, in so doing, increases its population to the point that little reaction occurs from other conformers (Scheme 16).

A similar explanation exists for the difference in stereoselectivity between radicals **25** and **35** (Scheme 15). If interconversion among the conformers of the radical **35** is faster than reaction with acrylonitrile, it is possible to form a β-*C*-glycoside by reaction with a minor conformer. For the radical **25** the equatorial CH_2OAc substituent at C-5 must stabilize the $^{4}C_1$ conformation sufficiently that the concentration of minor conformers is too small for them to account for significant product formation.

(4). Transition-State Stabilization: The Kinetic Anomeric Effect

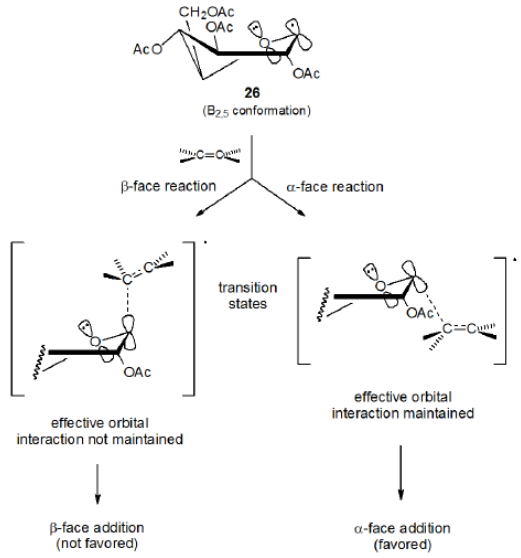
To understand how radical conformation can have such a pronounced effect on stereoselectivity in the reactions of pyranos-1-yl radicals, it is instructive to examine transition-state stabilization. The major stereoisomer formed in these reactions results from a radical adopting a conformation that allows the stabilizing interaction between the *p*-type orbitals on C-1 and the ring oxygen atom to be maintained to the greatest extent in the transition-state. This conformation-dependent, stereoelectronic, transition-state stabilization is referred to as the kinetic[33,34] or radical[35,36] anomeric effect. (We will use “kinetic anomeric effect” in describing this phenomenon.)

Scheme 17



The kinetic anomeric effect offers a rationale for the D-mannopyranos-1-yl radical **25** adding to acrylonitrile exclusively from the α face of the pyranoid ring (Scheme 15). Only for α-face reaction will stabilizing interaction between the *p*-type orbitals on the ring oxygen atom and the singly occupied orbital on C-1 be maintained in the transition state (Scheme 17). Predicting stereoselectivity in the reaction of a conformationally mobile radical can be a challenging task because more than one conformation is accessible and determining which conformation is the most reactive may be difficult. This means that minor conformers, even ones that cannot be detected by ESR spectroscopy, can play a major role in determining reaction stereoselectivity. For the D-glucopyranos-1-yl radical **26** the only conformation detectable by ESR spectroscopy is a distorted $B_{2,5}$ boat,[27,28] but $^{1,4}B$ and $^{1}C_4$ conformations may be only modestly higher in energy and, therefore, easily accessible. For the $B_{2,5}$ conformation, reaction from the α-face of the pyranoid ring maintains stabilizing orbital interaction more effectively than reaction from its β face (Scheme 18).

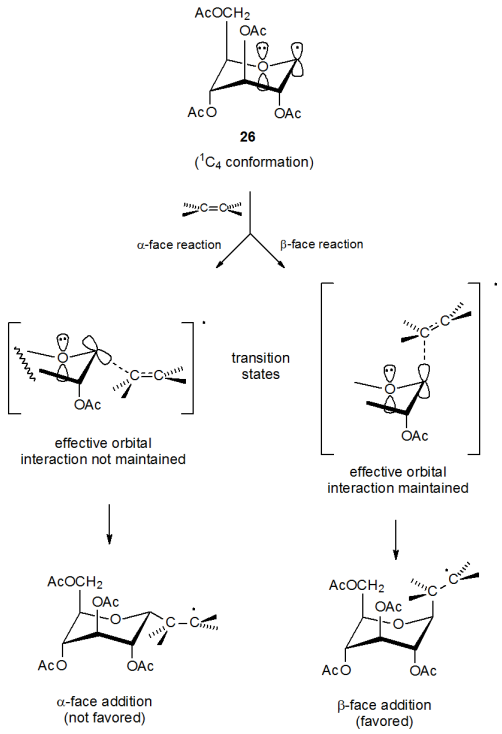
Scheme 18



Reaction does occur, however, to a small extent (5%) from the β face of the pyranoid ring in the radical **26**. The β anomer formed as a minor product could come from an accessible but undetected conformation, such as the $^{1}C_4$. Maintaining orbital interactions in

a $^1C_4$ chair conformation would favor the β-face addition that leads to the minor product (Scheme 19). If this is the way in which β-face addition takes place, then stereoselectivity depends not only on which conformations are accessible and highly reactive but also on which face of a given conformer maintains the reaction-promoting orbital interaction that stabilizes the transition state.

Scheme 19



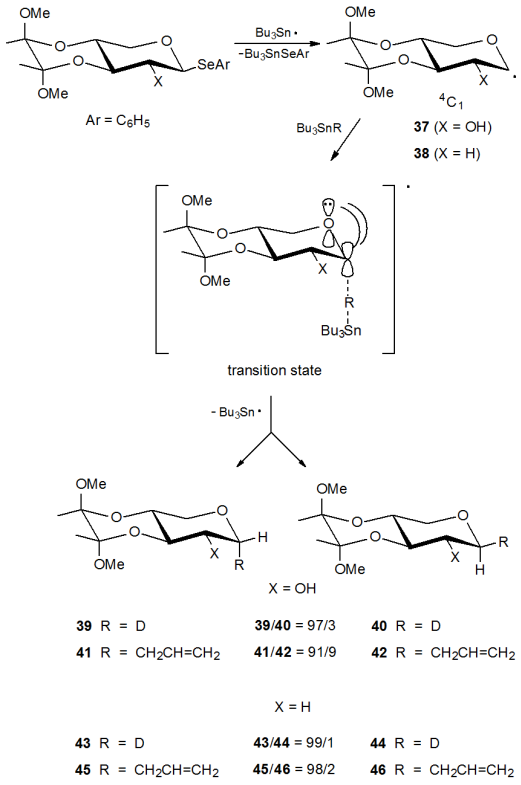
Another explanation for the formation of the minor product in the reaction of the radical **26** is that this product results from a small amount of β-face addition to the radical in its $B_{2,5}$ conformation. Such an explanation, however, fails to explain greater β-face addition for the radical **36**, when compared to **26** (Scheme 16), and is incompatible with the information, discussed in the next section, on reactions of radicals with restricted conformations.

Although the case is strong for radical conformation playing a critical role in stereoselectivity of reactions of pyranos-1-yl radicals, uncertainty remains about how to identify the reactive conformation when several may be present and undergoing reaction. This uncertainty is effecttively eliminated where radicals with restricted conformations are concerned. Study of such radicals has provided considerable insight into the power of the kinetic anomeric effect in determining reaction stereoselectivity.

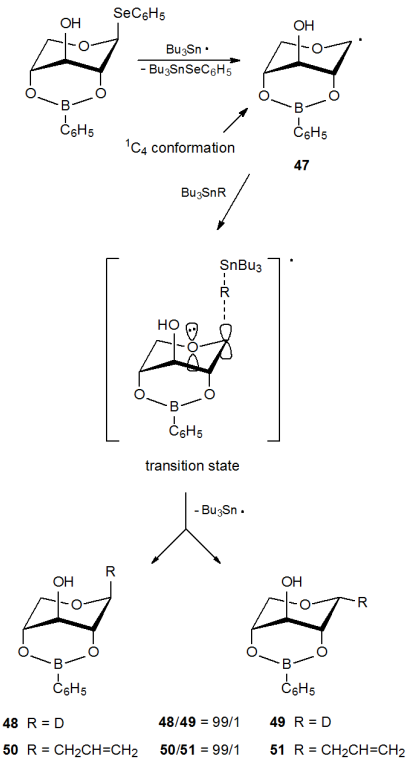
(5). Restricted Conformations

A restricted conformation for a radical is one that is highly favored over others due to some structural feature, such as an additional ring system. The radicals **37** (Scheme 20) and **47** (Scheme 21) have pyranoid rings restricted to $^4C_1$ and $^1C_4$ chair conformations, respectively. This restriction is caused by the presence of appropriately placed, additional rings.[33] A second ring restricts conformational change in the radical **37** by creating a *trans*-decalin-type structure. For the radical **47** a bridge produces a bicyclic structure that creates a rigid, conformationally restricted system.

Scheme 20



Scheme 21



(a). Explanation for Reaction Stereoselectivity

For the radical **47** maintaining stabilizing orbital interaction in the transition state requires approach of a reacting molecule, such as tri-*n*-butyltin deuteride, to the β-face of the pyranoid ring (Scheme 21). This means that reaction proceeding according to the kinetic anomeric effect will give a product (**48**) with an axial deuterium atom at C-1. The high stereoselectivity of this reaction (**48**/**49** = 99/1) supports the idea that conformational and stereoelectronic effects together have a powerful influence on the reactions of pyranos-1-yl radicals. Such an idea is reinforced in a dramatic fashion by the reaction of the radical **37** (Scheme 20). In this case in order to benefit from kinetic anomeric stabilization, the deuterium donor must approach the radical from the α face of the pyranoid ring. α-Face selectivity (**39**/**40** = 97/3) in this reaction (the pyranoid ring restricted to a $^4C_1$ conformation) is nearly as great as the β-face selectivity (**48**/**49**= 99/1) in the reaction of **47** (pyranoid ring restricted to a $^1C_4$ conformation). Changing the radical conformation then completely changes reaction stereoselectivity;[33] furthermore, the selectivity observed in each case is that predicted by the kinetic anomeric effect.

When $Bu_3SnCH_2CH{=}CH_2$ replaces Bu_3SnD as the molecule reacting with the radical **37**, the stereoselectivity decreases somewhat, although it remains high.[33] [The ratio of α-face to β-face reaction decreases from 97/3 (**39**/**40**) to 91/9 (**41**/**42**) (Scheme 20).] This modest decrease in stereoselectivity disappears when the hydroxy group at C-2 is replaced by a hydrogen atom: that is, the stereoselectivity for the reaction of the 2-deoxy radical **38** with Bu_3SnD is essentially the same as that for reaction with $Bu_3SnCH_2CH{=}CH_2$ (Scheme 20). Steric hindrance associated with the C-2 hydroxy group, therefore, may be responsible for the small difference in stereoselectivity observed for reactions of the radical **37** with Bu_3SnD and $Bu_3SnCH_2CH{=}CH_2$. The overall picture, however, remains one in which steric effects have, at most, a minor role in determining stereoselectivity in the reactions of these two radicals (**37** and **38**).

(b). σ*-Orbital Interaction

The σ* orbital of the C_2–O bond in a pyranos-1-yl radical contributes to the stability of these radicals by interacting with the *p*-type orbitals on C-1 and the ring oxygen atom. Radical stabilization of this type plays a critical role in determining preferred radical conformation (see Section IV.A.2.d. of Chapter 6). A question raised by these orbital interactions concerns whether this type of stabilization also affects stereoselectivity in reactions of pyranos-1-yl radicals. The more rapid reaction of the D-mannopyranosyl chloride **23** (Scheme 9) when compared to the epimeric D-glucopyranosyl chloride **24** (Scheme 10) indicates that it may. Even for **24**, however, σ*-orbital interaction is not essential because reaction still takes place (although less rapidly) even with minimal participation from this orbital (Scheme 10). Study of radicals with restricted conformations helps to clarify the role of the C_2–O σ* orbital in stereoselectivity of reactions of pyranos-1-yl radicals.

Because the pyranoid rings in radicals **37** and **38** (Scheme 20) are restricted to $^4C_1$ conformations by their *trans*-decalin-like ring systems, the reactions of these radicals provide insight into the effect of a C_2–O bond (in particular, its σ*-orbital) on the stereoselectivity of the reactions of pyranos-1-yl radicals. The radical **37**, for example, reacts in a highly stereoselective fashion with tri-*n*-butyltin deuteride even though the σ* orbital of the C_2–O bond is not aligned to assist in transition-state stabilization (Figure 4). The radical **38** completely lacks a C-2 substituent; yet, it also undergoes highly stereoselective reaction (Scheme 20). σ*-Orbital interaction involving the C_2–O bond, therefore, is not essential to the stereoselectivity of the reactions of the radicals **37** and **38**. The reactions of these radicals, however, point to the critical factor in determining reaction stereoselectivity, namely, maintaining effective interaction in the transition state between the singly occupied, *p*-type orbital on C-1 and the *p*-type orbital on the ring oxygen atom.

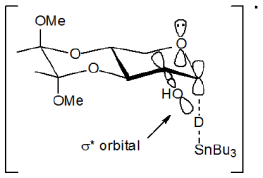


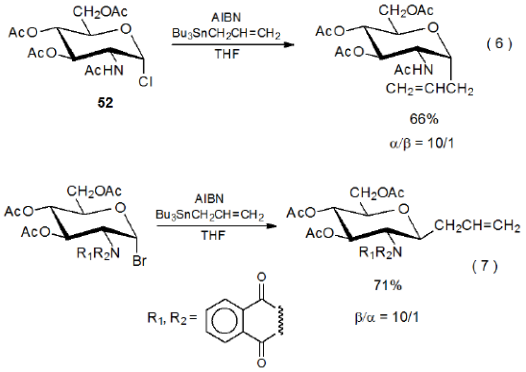
Figure 4. Allignment of the σ* orbital at C-2 during reaction of the radical **37** with Bu_3SnD

Study of the reactions of radicals with restricted conformations generates a powerful argument in favor of the control that conformational and stereoelectronic effects have on the reactivity of pyranos-1-yl radicals. Among the radicals of this type discussed thus far, there is little indication that steric effects have other than a minor role in determining stereoselectivity. Study of compounds that have particularly well shielded radical centers, however, shows that steric effects can be significant in the stereoselectivity of some pyranos-1-yl radical reactions.

(6). Steric Effects Revisited

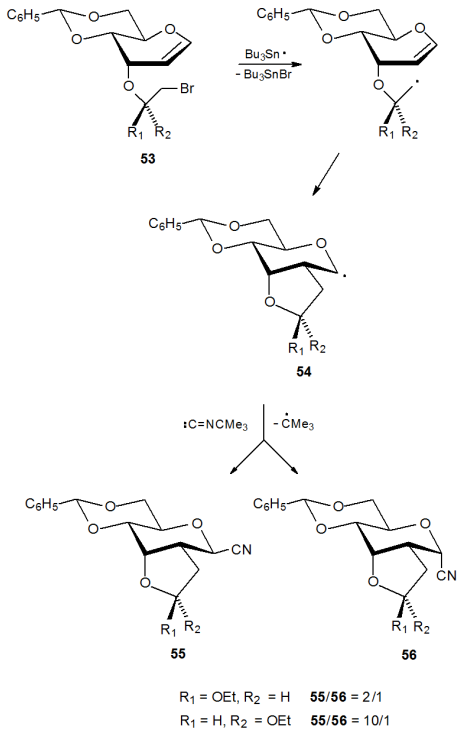
(a). Pyranos-1-yl Radicals

Even though conformational and stereoelectronic effects usually have the dominant role in determining stereoselectivity in the reactions of pyranos-1-yl radicals, comparing the reactions shown in equations 6 and 7 shows that steric effects can assert themselves when a sufficiently effective shielding group is present in a reacting molecule. Reaction of the glycosyl chloride **52** with allyltri-*n*-butyltin follows the now familiar pattern of α-face reaction that maintains transition-state interaction between orbitals on C-1 and the ring oxygen atom (eq 6).[37] This reaction stands in contrast to that shown in eq 7 where the sterically demanding phthalimido group at C-2 causes a reversal of stereoselectivity in *C*-glycoside formation. This second reaction (eq 7) is a striking example of steric effects overwhelming the conformational and stereoelectronic effects that normally control stereoselectivity in reactions of pyranos-1-yl radicals.[37,38]



Reaction of the bromide **53** with *tert*-butyl isocyanide gives additional insight into the competition between steric and stereoelectronic effects in determining the stereoselectivity of reaction of pyranos-1-yl radicals (Scheme 22).[35] The C-1 configuration in products **55** and **56** is determined by the stereoselectivity of the reaction between the radical **54** and *tert*-butyl isocyanide. In this reaction steric effects, which favor β-face reaction of **54**, are more powerful than the stereoelectronic effects, which favor forming the product with an α configuration. In addition to shielding due to the methylene carbon atom attached to C-2, the shape of the radical in the vicinity of the ethoxy group has major impact on the steric effects directing the approach of *tert*-butyl isocyanide (Scheme 22).

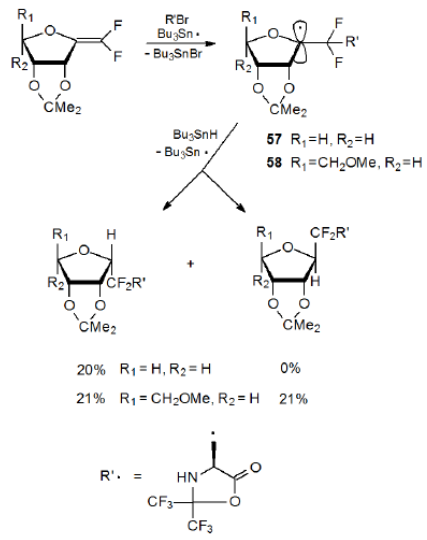
Scheme 22



(b). Furanos-1-yl Radicals

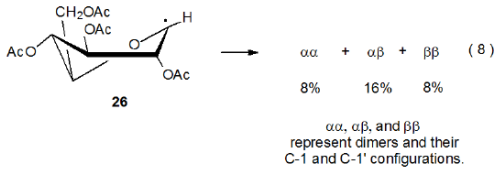
Study of pyranos-1-yl radicals has identified conformational mobility as a “key” factor in the stereoselectivity of their reactions. This selectivity depends not only on which conformation is the major one but also on the accessibility and reactivity of other conformations. For furanos-1-yl radicals the same factors are involved, but their relative importance may differ. Conformational mobility is greater for furanos-1-yl radicals than for their pyranos-1-yl counterparts. Also, due to the shape of the furanoid ring, maintaining effective, transition-state interaction between *p*-type orbitals on C-1 and the ring oxygen atom (i.e., the interaction necessary for kinetic-anomeric stabilization) in many conformations is possible during reaction from both α and β faces of the ring. These observations lead to the proposal that conformational and stereoelectronic effects may be less important in determining stereoselectivity in furanos-1-yl radical reaction than in reactions of pyranos-1-yl radicals. The available information on stereoselectivity of the reactions of furanos-1-yl radicals is not sufficient to draw a firm conclusion about the relative importance of the kinetic anomeric effect when compared to steric effects. Exclusive hydrogen-atom transfer to the less-hindered β face of the radical **57** is consistent with steric effects controlling stereoselectivity; in addition, the fact that the radical **58**, for which the β face is more hindered, is less stereoselective in its reaction also is consistent with steric effects primarily determining reaction stereo-selectivity (Scheme 23).[39]

Scheme 23



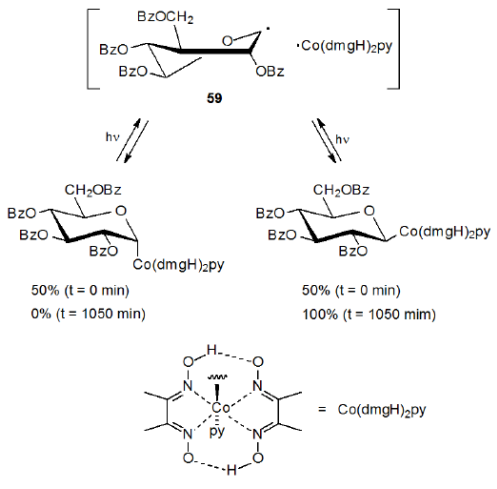
(c). Supersteric Radicals

Although bonding between two radicals normally is a rare event, such a reaction can become significant when other processes (e.g., hydrogen-atom abstraction or addition to an unsaturated compound) take place too slowly. Bonding between two radicals begins at a sufficiently long distance that differences in transition-state energies leading to different products sometimes are too small to be of consequence; as a result, little or no stereoselectivity is observed (eq 8).[40]



If one of the radicals involved in a coupling process has steric requirements that are great enough, even radical coupling becomes stereoselective. The "supersteric" $Co(dmgH)_2py$ radical, for example, has such a large steric requirement that its reaction with the pyranos-1-yl radical **59** occurs much more rapidly from the β face of the pyranoid ring in **59** than from its α face (Scheme 24).[41] Having the $Co(dmgH)_2py$ substituent in an equatorial position (β anomer) is so much more stable than having it in the more crowded axial orientation (α anomer) that this difference significantly affects the transition-state energies leading to these two anomers. The steric size of the $Co(dmgH)_2py$ substituent is so great that it overcomes the usually more important kinetic anomeric effect in determining reaction stereoselectivity.

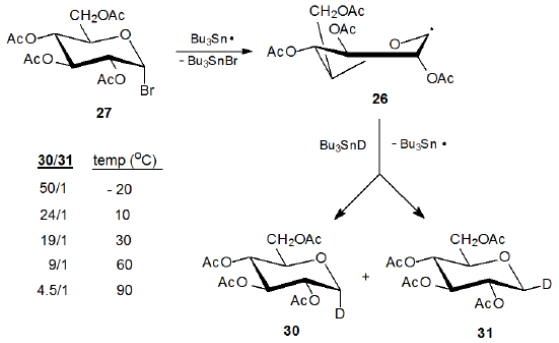
Scheme 24



2. Effect of Temperature on Stereoselectivity

A final point with respect to stereoselectivity in bimolecular radical reactions concerns reaction temperature. In the process shown in Scheme 25 stereoselectivity is determined by the approach of Bu_3SnD to the intermediate pyranos-1-yl radical **26**.[31] According to the kinetic anomeric effect [Section III.B.1.c.(4).] stereoselective deuterium transfer to the α face of **26** (to give **30**) should have a lower transition-state energy than transfer to its β face (to give **31**). At low temperature the stereoselectivity is high, but as the temperature rises, stereoselectivity decreases because a progressively larger percentage of radicals are able to react with Bu_3SnD and transcend the barriers leading to both products (**30** and **31**). The results shown in Scheme 25 can be viewed as a general response of reaction stereoselectivity to changes in temperature.

Scheme 25



30/31	temp (°C)
50/1	- 20
24/1	10
19/1	30
9/1	60
4.5/1	90

IV. Maximizing Transition-State Stability During Ring Formation

Whenever a radical center and the group with which it is reacting are part of the same molecule, new factors become important in determining both regio- and stereoselectivity.[42–44] Since the reaction taking place is an internal radical addition to a π system, the size of the ring being formed and the constraints placed on reactivity by existing structural features (e.g., other ring systems) both contribute to determining selectivity. Regioselectivity in ring formation is discussed in Chapter 10 (Section III). The discussion here is concerned with the stereoselectivity of reactions that create new ring systems.

V. Stereoselectivity in Synthesis

The primary thrust of the discussion in this chapter is to understand the factors controlling stereoselectivity in radical reactions. Many of the reactions examined provide both basic understanding of radical-reaction stereoselectivity and examples of how stereoselectivity can achieve a particular synthetic goal. The emphasis in discussion in this part of the chapter shifts to reactions where the primary goal is to solve a particular synthetic problem by taking advantage of knowledge about stereoselectivity in radical reactions. Even though the purpose in conducting these reactions is synthetic, their investigation has increased basic understanding of radical-reaction stereoselectivity.

VI. Summary

Stereoselectivity is the preferential formation or consumption of one stereoisomer rather than another in a chemical reaction. In radical reactions stereoselectivity is controlled by a combination of conformational, steric, stereoelectronic, and torsional effects. The stereoselectivity caused by these effects is generally increased by conducting reactions at lower temperature. For radicals not centered on C-1, steric effects direct reaction to occur along the least-hindered pathway. A primary factor in determining this pathway is the way in which various groups shield a radical center.

As the steric size of a molecule reacting with a carbohydrate radical increases, the extent to which the least-hindered pathway is followed also increases. As this size of reacting molecules becomes smaller, stereoselectivity decreases but does not completely disappear; rather, a low level of selectivity remains due to torsional interactions.

Stereoelectronic effects operate in conjunction with conformational effects to determine stereoselectivity in reactions of pyranos-1-yl radicals. The critical factor in forming a particular stereoisomer in a reaction is the ability of the reactants to maintain in the transition state a stabilizing interaction between orbitals on C-1 and the ring oxygen atom. Maintaining this interaction causes different conformations of a radical to yield stereoisomerically different products. This stereoelectronic, conformation-dependent, transition-state stabilization gives rise to a phenomenon known as the kinetic anomeric effect. This effect provides a basis for predicting and rationalizing stereoselectivity of pyranos-1-yl radical reactions.

Radical cyclization places additional requirements on reaction stereoselectivity. Prominent among these is that in most situations a reaction proceeds through a chair-like transition state that has substituents located in pseudoequatorial positions. In some instances a boat-like transition state is lower in energy than a chair-like one. This is often the case when structural features such as allylic strain or pseudo-1,3-diaxial interactions destabilize a chair-like transition state. The stereoselectivity of radical reactions provides the basis for several synthetic processes. These include the synthesis of β-glycosides, the use carbohydrates as chiral auxiliaries, and the incorporation of carbohydrates into enantioselective syntheses.

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D

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References

Chapter 1: Free-Radical Reactions in Carbohydrate Chemistry

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