

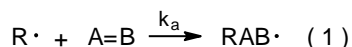
Chapter 8

Radical Reactivity: Reaction Rate Constants

I.	Introduction.....	148
II.	Absolute and Relative Rate Constants.....	149
III.	Generation of Carbon-Centered Radicals.....	150
	A. Atom-Transfer Reactions.....	150
	B. Group-Transfer Reactions.....	152
	C. Fragmentation Reactions.....	155
	D. Electron-Transfer Reactions.....	156
IV.	Transformation of Carbon-Centered Radicals.....	158
	A. Hydrogen-Atom Abstraction.....	158
	B. Iodine-Atom Abstraction.....	159
	C. Radical Cyclization.....	162
	D. Radical Addition.....	165
	E. Group Migration.....	167
	F. Hydrogen-Atom Abstraction by Pyranos-1-yl Radicals.....	171
V.	Chain Collapse.....	173
	A. Collapse Due to Chain Termination.....	173
	B. Collapse Due to Chain Shift.....	174
VI.	Summary.....	175
VII.	References.....	175

I. Introduction

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.



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

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.

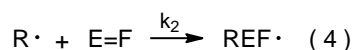
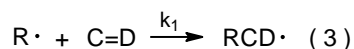
These rate constants do not represent an exhaustive list of those that have been determined; rather, they are ones of interest in understanding the reactions of carbohydrates.

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.

One 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



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

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.

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

<u>reactant</u>	<u>rate constant</u> (M ⁻¹ s ⁻¹)	<u>temp</u>	<u>ref</u>
C ₉ H ₁₉ CH ₂ Cl	7 x 10 ³	25 °C	4
(CH ₃) ₃ CCl	2.7 x 10 ⁴	25 °C	5
C ₆ H ₅ CH ₂ Cl	1.1 x 10 ⁶	25 °C	5
CH ₃ (CH ₂) ₃ OCH ₂ Cl	1 x 10 ⁵	25 °C	4
C ₇ H ₁₅ CH ₂ Br	3 x 10 ⁷	25 °C	4
(CH ₃) ₃ CBr	1.4 x 10 ⁸	25 °C	5
CH ₃ I	4.3 x 10 ⁹	25 °C	5
CH ₃ (CH ₂) ₃ OCH ₂ SC ₆ H ₅	1 x 10 ³	25 °C	4
CH ₃ (CH ₂) ₃ OCH ₂ SeC ₆ H ₅	6 x 10 ⁶	25 °C	4

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

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 Bu₃Sn· are found in Table 1. Table 2 contains a similar set of rate constants that includes those for atom-transfer reactions involving (Me₃Si)₃Si· and Et₃Si·. (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

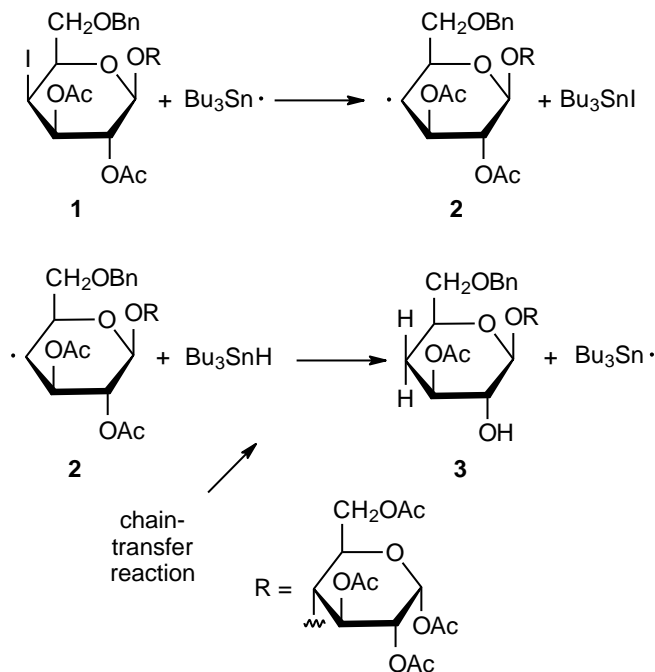
<u>reactant</u>	<u>radical</u>	<u>rate constant</u> (M ⁻¹ s ⁻¹)	<u>temp</u>	<u>ref</u>
(CH ₃) ₃ CCl	(Me ₃ Si) ₃ Si·	4.0 x 10 ⁵	25 °C	6
CH ₃ (CH ₂) ₄ Br	(Me ₃ Si) ₃ Si·	2.0 x 10 ⁷	20 °C	6
(CH ₃) ₃ CBr	(Me ₃ Si) ₃ Si·	1.2 x 10 ⁸	20 °C	6
c-C ₆ H ₁₁ I	(Me ₃ Si) ₃ Si·	>4 x 10 ⁹	20 °C	7
C ₆ H ₅ SC ₁₀ H ₂₁	(Me ₃ Si) ₃ Si·	<5 x 10 ⁶	21 °C	2
C ₆ H ₅ SeC ₁₀ H ₂₁	(Me ₃ Si) ₃ Si·	9.6 x 10 ⁷	21 °C	2
c-C ₆ H ₁₁ OC(=S)SMe	(Me ₃ Si) ₃ Si·	1.1 x 10 ⁹	21 °C	2
c-C ₆ H ₁₁ NC	(Me ₃ Si) ₃ Si·	4.7 x 10 ⁷	21 °C	2
(CH ₃) ₃ CNO ₂	(Me ₃ Si) ₃ Si·	1.2 x 10 ⁷	21 °C	2
CH ₃ (CH ₂) ₄ Cl	Et ₃ Si·	3.1 x 10 ⁵	25 °C	6
(CH ₃) ₃ CCl	Et ₃ Si·	2.5 x 10 ⁶	25 °C	6
CH ₃ (CH ₂) ₄ Br	Et ₃ Si·	5.4 x 10 ⁸	27 °C	6
(CH ₃) ₃ CBr	Et ₃ Si·	1.1 x 10 ⁹	27 °C	5,6
CH ₃ (CH ₂) ₂ I	Et ₃ Si·	4.3 x 10 ⁹	27 °C	5
CH ₃ I	Et ₃ Si·	8.1 x 10 ⁹	29 °C	5

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

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.

Scheme 1



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.)

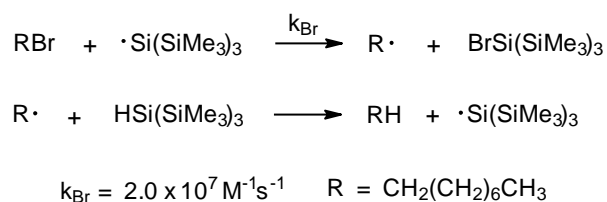
B. Group-Transfer Reactions

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

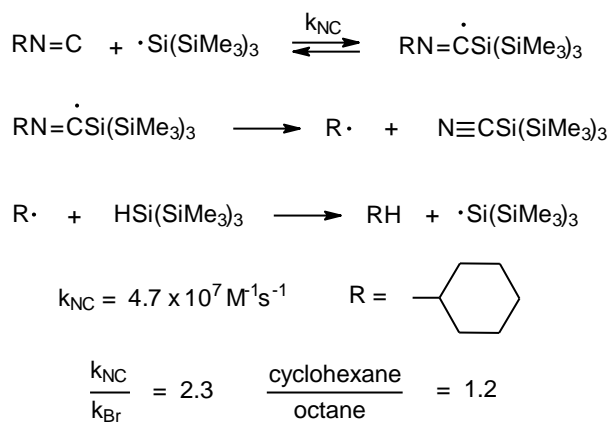
with $\text{Bu}_3\text{Sn}\cdot$ (Table 1) or $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ (Table 2) is larger than the rate constant for carbon-centered radical formation.

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 $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ (Scheme 2). Since this reaction gives the octyl radical $\text{R}\cdot$ in a single, irreversible step, the rate constant for reaction of the bromide with $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ is the same as the rate constant for formation of $\text{R}\cdot$. Also, since $\text{R}\cdot$ then abstracts a hydrogen atom from $(\text{Me}_3\text{Si})_3\text{SiH}$, the amount of octane formed is directly related to the number of octyl radicals produced.

Scheme 2



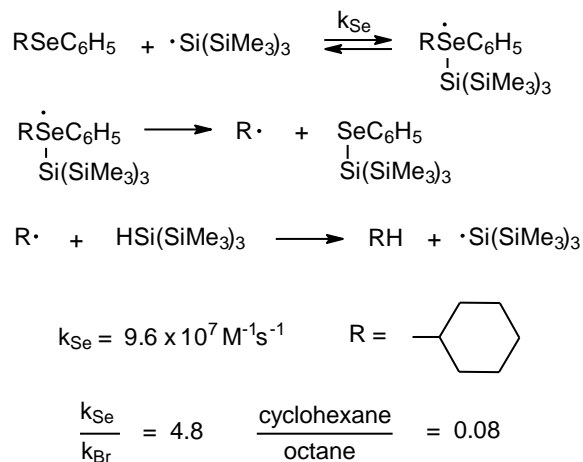
Scheme 3



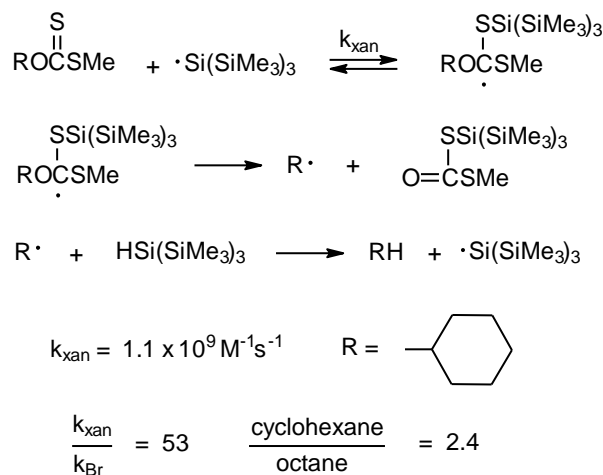
The first comparison experiment involves reaction of molar-equivalent amounts of 1-bromooctane, cyclohexyl isonitrile, and tris(trimethylsilyl)silane.² A proposed mechanism for the reaction between the isonitrile and $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ is given in Scheme 3. If the addition of $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ 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 in 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 $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ 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 4



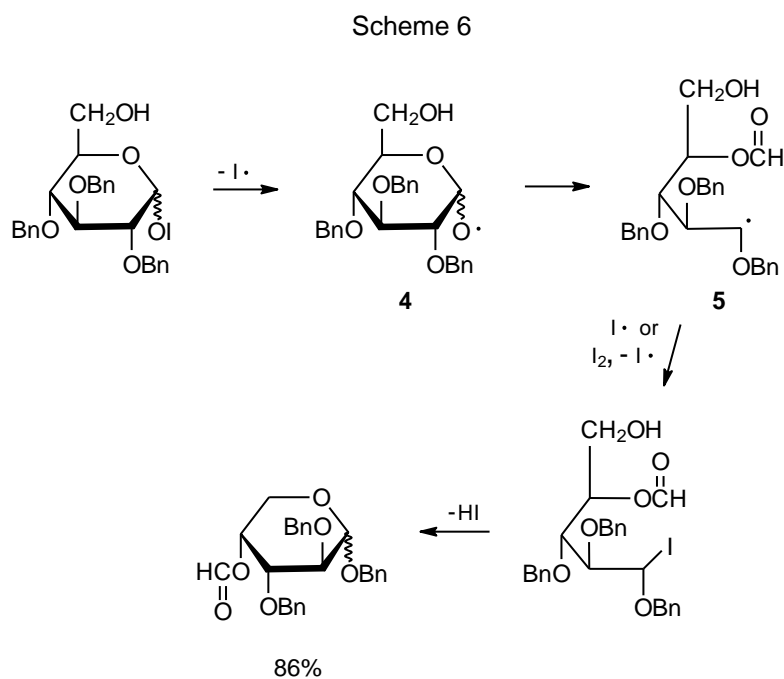
Scheme 5



The addition of the $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ 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 $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ to these compounds is a frequently reversed process.

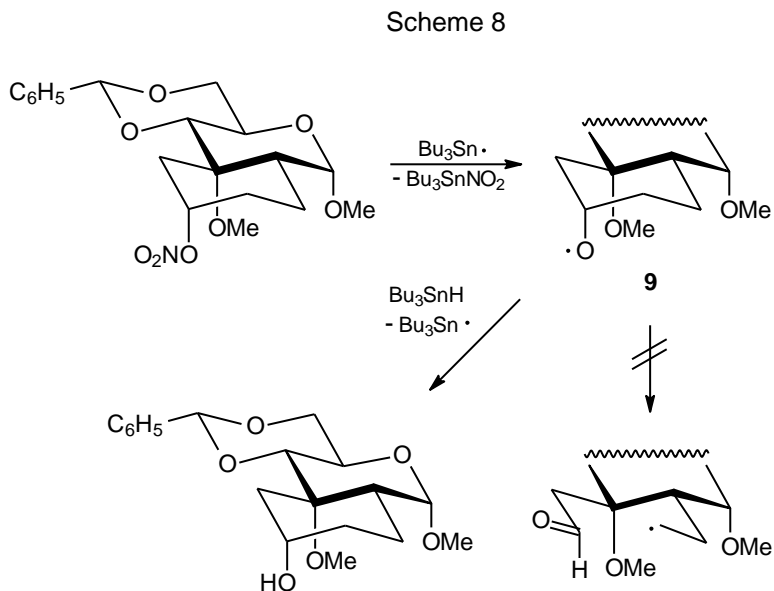
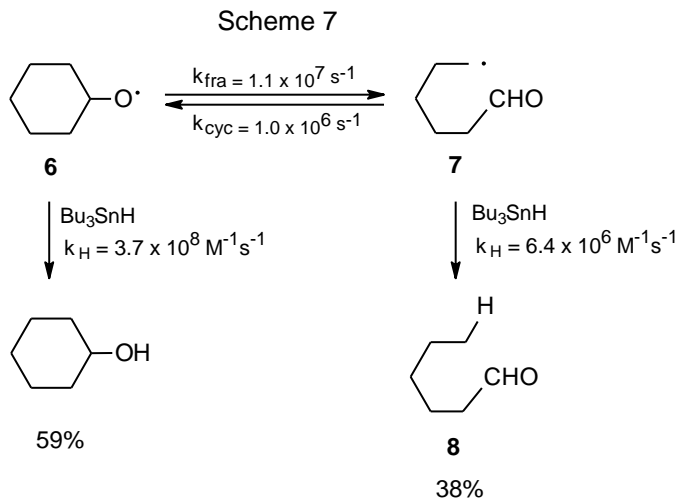
C. Fragmentation Reactions

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-atom donor in the reaction mixture allows fragmentation to take place without competition from hydrogen-atom abstraction.



In the reaction shown in Scheme 7 the oxygen-centered radical **6** and the carbon-centered radical **7** exist in a pseudo equilibrium. Both radicals abstract hydrogen atoms from Bu_3SnH .¹⁰ Due to the differences in the rate constants for ring opening ($k_{\text{fra}} = 1.1 \times 10^7 \text{ s}^{-1}\text{M}^{-1}$ at 80°C) and ring closure ($k_{\text{cyc}} = 1.0 \times 10^6 \text{ s}^{-1}\text{M}^{-1}$ at 80°C), the ring-open radical **7** dominates the pseudo equilibrium, but because the rate constant for hydrogen-atom abstraction by **6** ($k_{\text{H}} = 4.7 \times 10^8 \text{ s}^{-1}\text{M}^{-1}$ at 80°C) is so much larger than that for hydrogen-atom abstraction by **7** ($k_{\text{H}} = 6.4 \times 10^6 \text{ s}^{-1}\text{M}^{-1}$ 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.)



D. Electron-Transfer Reactions

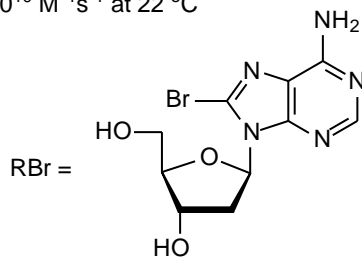
Dissociative electron transfer takes place when a compound containing a reactive atom or group accepts an electron and undergoes fragmentation (Scheme 9). Electron capture can be extremely rapid if an electron is free in solution; thus, the rate constant for capture of a solvated electron by the nucleoside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

Radical formation by electron transfer also can take place by reaction between transition-metal complexes such as $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$, $\text{Mn}(\text{OAc})_3$, 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 $\text{R}\cdot$ to produce an organosamarium compound (Scheme 10). This second electron transfer is fast enough that it can limit the ability of $\text{R}\cdot$ to undergo radical transforming reactions such as cyclization and group migration.

Scheme 9

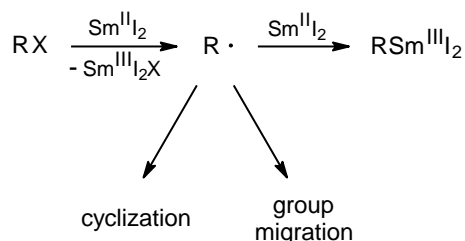


$$k_{ec} = 1.6 \times 10^{10} \text{ M}^{-1}\text{s}^{-1} \text{ at } 22^\circ\text{C}$$



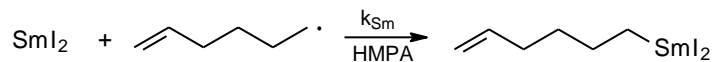
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Scheme 10



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 $\text{R}\cdot$ 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 $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $6.8 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ 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	$k_{\text{Sm}}(\text{M}^{-1}\text{s}^{-1})$
2.3	5×10^5
2.8	6×10^5
3.2	2.8×10^6
3.7	5.3×10^6
4.4	6.4×10^6
5.1	6.8×10^6
6.0	6.5×10^6

^aequivalents of HMPA $[\text{Me}_2\text{N})_3\text{PO}]$
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 °C¹⁴

IV. Transformation of Carbon-Centered Radicals

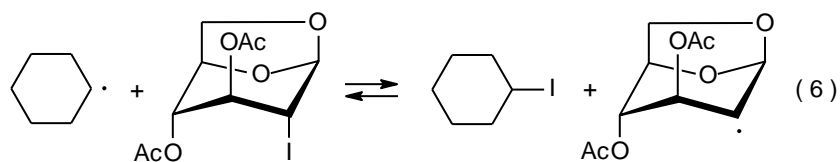
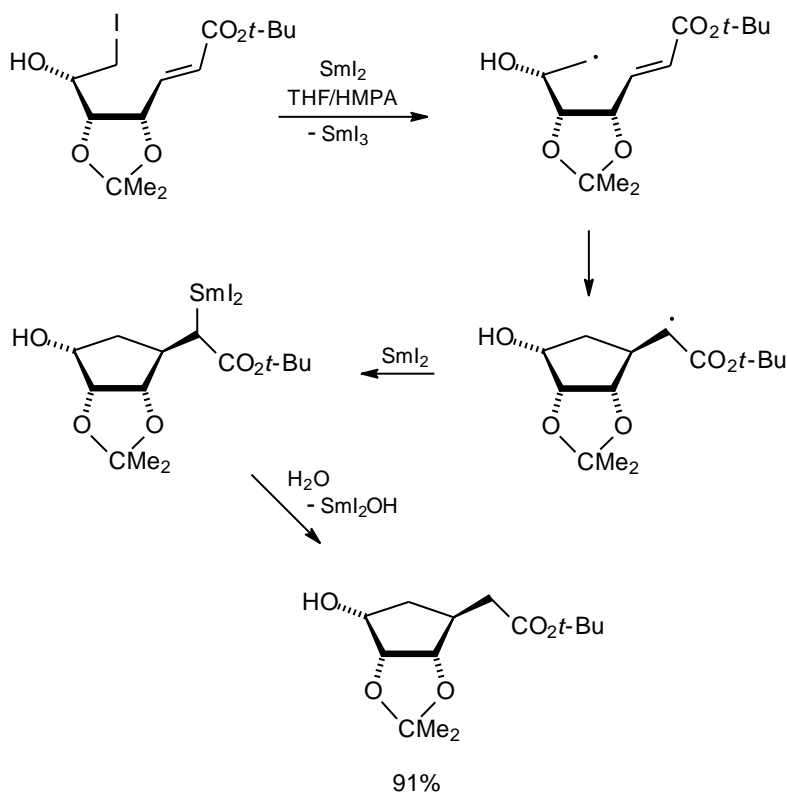
Although every propagation step in a radical chain reaction involves conversion of one radical into another, the potential for a synthetically useful reaction usually hinges on the transformation of a carbon-centered radical. Whether or not a transformation takes place depends on the relative rates for transforming and competing reactions. Because Bu_3SnH or $(\text{Me}_3\text{Si})_3\text{SiH}$ often is present in a reaction mixture to provide a chain-carrying radical as well as to serve as a hydrogen-atom 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.

A. Hydrogen-Atom Abstraction

Once a carbohydrate radical has been generated, sometimes the desired next step is simply to have this radical abstract a hydrogen atom from a donor present in solution. Such a situation exists when the deoxyiodo sugar **1** is converted into the deoxy sugar **3** (Scheme 1).⁸ In order for this reaction to give a high yield of **3** not only must the radical-generating step selectively abstract only the iodine atom, but the most rapid reaction for the resulting radical **2** must be hydrogen-atom

abstraction. The high yield of the deoxy sugar **3** testifies to the fact that the hydrogen-atom-abstracting, chain-transfer reaction shown in Scheme 1 is faster than other processes open to the carbon-centered radical **2**. Rate constants for hydrogen-atom abstraction by carbon-centered radicals from tri-*n*-butyltin hydride and other hydrogen-atom donors are given in Table 4. [Discussion of rate constants for hydrogen-atom abstraction by pyranos-1-yl radicals is delayed until later in this Chapter (Section IV.F.) because group-migration reactions need to be considered first.]

Scheme 11



B. Iodine-Atom Abstraction

It is possible to transform one carbon-centered radical into another by reaction involving an organic iodide (eq 6).²⁸ Rate constants for iodine-atom transfer (Table 5) are large enough for this reaction to be competitive with other reactions of carbon-centered radicals. Halogenated com-



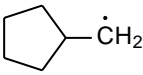
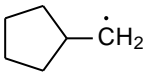
radical	hydrogen donor	rate constant (M ⁻¹ s ⁻¹)	temp	ref
CH ₃ (CH ₂) ₂ CH ₂ ·	Bu ₃ SnH	2.5 × 10 ⁶	27 °C	17,18
CH ₃ (CH ₂) ₂ CH ₂ ·	Bu ₃ SnD	1.2 × 10 ⁶	27 °C	17,18
CH ₃ CH ₂ ·	Bu ₃ SnH	2.3 × 10 ⁶	27 °C	17,18
(CH ₃) ₂ CH·	Bu ₃ SnH	1.5 × 10 ⁶	27 °C	17,18
	Bu ₃ SnH	2.2 × 10 ⁶	27 °C	17
	Bu ₃ SnD	4.4 × 10 ⁵	25 °C	18
(CH ₃) ₃ C·	Bu ₃ SnH	1.9 × 10 ⁶	27 °C	17
(CH ₃) ₃ C·	Bu ₃ SnD	2.7 × 10 ⁵	25 °C	18
(CH ₃) ₃ C·	(C ₆ H ₅) ₃ SnH	3.1 × 10 ⁶	25 °C	19
(CH ₃) ₂ C=ĊH	Bu ₃ SnH	3.5 × 10 ⁸	30 °C	20
CH ₂ =CH(CH ₂) ₃ CH ₂ ·	(Me ₃ Si) ₃ SiH	3.8 × 10 ⁵	25 °C	21
CH ₂ =CH(CH ₂) ₃ ĊHCH ₃	(Me ₃ Si) ₃ SiH	1.4 × 10 ⁵	25 °C	21
CH ₂ =CH(CH ₂) ₃ Ċ(CH ₃) ₂	(Me ₃ Si) ₃ SiH	2.6 × 10 ⁵	25 °C	21
	(C ₆ H ₅) ₃ SiH	3.4 × 10 ⁴	50 °C	22
CH ₂ =CHCH ₂ Ċ(CH ₃) ₂	(C ₆ H ₅) ₃ SiH	9 × 10 ³	50 °C	22
	Et ₃ SiH	7 × 10 ³	50 °C	22

Table 4. Rate constants for hydrogen and deuterium abstraction by carbon-centered radicals


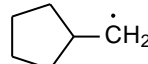



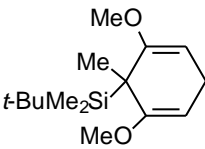
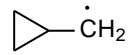
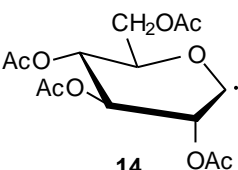
radical	hydrogen donor	rate constant (M ⁻¹ s ⁻¹)	temp	ref
CH ₂ =CHCH ₂ \dot{C} (CH ₃) ₂	Et ₃ SiH	3 x 10 ³	50 °C	22
C ₆ H ₅ C(CH ₃) ₂ CH ₂ ·	Et ₃ SiH	6.4 x 10 ²	25 °C	23
(CH ₃) ₃ C·	C ₆ H ₅ SH	1.5 x 10 ⁸	25 °C	24
(CH ₃) ₂ CH·	C ₆ H ₅ SH	1.1 x 10 ⁸	25 °C	24
CH ₃ (CH ₂) ₂ CH·	C ₆ H ₅ SH	1.4 x 10 ⁸	25 °C	24
CH ₂ =CHC(CH ₃) ₂ \dot{C} H ₂	(CH ₃) ₃ CSH	1.0 x 10 ⁷	50 °C	22
CH ₂ =CHCH ₂ \dot{C} (CH ₃) ₂	(<i>o</i> -C ₆ H ₁₁) ₂ PH	1.1 x 10 ⁶	50 °C	22
CH ₂ =CH(CH ₂) ₃ \dot{C} H ₂	(<i>o</i> -C ₆ H ₁₁) ₂ PH	7.0 x 10 ⁵	50 °C	22
CH ₂ =CHCH ₂ \dot{C} (CH ₃) ₂		2 x 10 ³	50 °C	22
 \dot{C} H ₂		6 x 10 ³	50 °C	22
CH ₂ =CHCH ₂ \dot{C} (CH ₃) ₂		4.8 x 10 ⁵	50 °C	22
CH ₂ =CH(CH ₂) ₃ CH ₂ ·		2.3 x 10 ⁵	50 °C	22
RCH ₂ ·		1.0 x 10 ⁵	70 °C	25
 \dot{C} H ₂	C ₆ H ₅ SeH	2.1 x 10 ⁹	25 °C	26
18				
	C ₆ H ₅ SeH	3.6 x 10 ⁶	78 °C	27
14				

Table 4. Rate constants for hydrogen and deuterium abstraction by carbon-centered radicals (cont.)

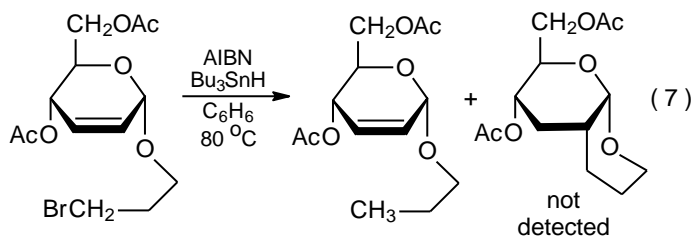
pounds other than iodides generally react too slowly to participate in such reactions (Table 5). Conversion of one iodide into another by atom transfer can be a reversible process (eq 6).

radical	halide	rate constant ($M^{-1}s^{-1}$)	temp	ref
$CH_3(CH_2)_6CH_2\cdot$	$(CH_3)_2CHI$	5.6×10^5	50 °C	29
$CH_3(CH_2)_6CH_2\cdot$	CH_3CH_2I	1.7×10^5	50 °C	29
$CH_3(CH_2)_6CH_2\cdot$	$CH_3(CH_2)_3I$	1.1×10^5	22 °C	30
$CH_3(CH_2)_6CH_2\cdot$	c-C ₆ H ₁₁ I	2.6×10^5	22 °C	30
$CH_3(CH_2)_6CH_2\cdot$	$(CH_3)_3C-I$	3×10^6	50 °C	29
$CH_3(CH_2)_6CH_2\cdot$	$CH_3(CH_2)_3Br$	6×10^2	50 °C	29
$CH_3(CH_2)_6CH_2\cdot$	$(CH_3)_3CBr$	4.6×10^3	50 °C	29
$CH_3(CH_2)_6CH_2\cdot$	$(CH_3)_3CCl$	6×10^2	50 °C	29
c-C ₆ H ₁₁ ·	I ₂	1.2×10^{10}	23 °C	31

Table 5. Rate constants for halogen abstraction

C. Radical Cyclization

A typical example of radical cyclization involving a carbohydrate is given in Scheme 12.³² In this reaction the carbon-centered radical that undergoes ring formation is produced by atom transfer from a halogenated carbohydrate to Bu₃Sn·. Since the source of the tin-centered radical is Bu₃SnH, the ever-present possibility exists that hydrogen-atom abstraction by the radical **11** will take place before cyclization can occur. This does not happen in the reaction shown in Scheme 12 because five-membered ring formation is too rapid, but since six-membered-ring formation is slower, hydrogen-atom abstraction does occur before cyclization in the reaction shown in eq 7. The difference in ring-forming ability in these two reactions (Scheme 12 and eq 7) provides an example of the general phenomenon that for radicals with similar structures five-membered rings form more rapidly than six-membered ones. Rate constants for ring formation for a variety of radicals are given in Table 6.



form more rapidly than six-membered ones. Rate constants for ring formation for a variety of radicals are given in Table 6.

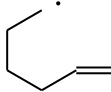
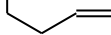
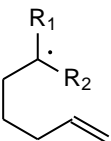
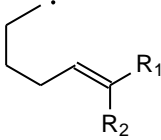
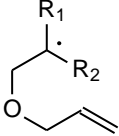
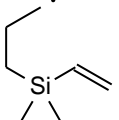
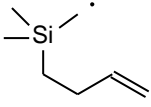
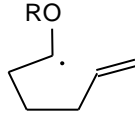
radical before cyclization	substituent identity	rate constant (s ⁻¹)	ring size	temp	ref
		2.3 x 10 ⁵	5	25 °C	33
		4.6 x 10 ³	6	25 °C	33
	R ₁ = CH ₃ , R ₂ = H	1.0 x 10 ⁵	5 ^a	25 °C	34
		2.9 x 10 ⁴	5 ^b	25 °C	34
	R ₁ = CH ₃ , R ₂ = CH ₃	3.3 x 10 ⁵	5	25 °C	34
	R ₁ , R ₂ = H	6 x 10 ⁵	5	50 °C	35
	R ₁ , R ₂ = H, CN	1.6 x 10 ⁸	5	50 °C	35
	R ₁ , R ₂ = H, OCH ₃	1.5 x 10 ⁶	5	50 °C	35
	R ₁ , R ₂ = CN, OCH ₃	2.5 x 10 ⁸	5	50 °C	35
	R ₁ = R ₂ = H	2.6 x 10 ⁷	5	80 °C	36
	R ₁ = Me, R ₂ = H	9.3 x 10 ⁶	5	65 °C	37
	R ₁ = R ₂ = CH ₃	3.4 x 10 ⁷	5	80 °C	38
		6.5 x 10 ⁴	5	25 °C	39
		4.3 x 10 ³	6	25 °C	39
		6.6 x 10 ³	5	25 °C	39
		1.4 x 10 ⁴	6	25 °C	39
	R = (CH ₂) ₂ SSnBu ₃	2.5 x 10 ⁵	5	80 °C	40
	R = C(=O)CH ₂ SSnBu ₃	1.4 x 10 ⁶	5	80 °C	40

Table 6. Rate constants for radical cyclization reactions.

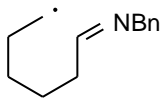
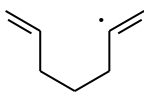
radical before cyclization	substituent identity	rate constant (s ⁻¹)	ring size	temp	ref
	R = CH ₂ CH ₂ CH=CH ₂	1.1 x 10 ⁸	5 ^a	80 °C	41
	R = CH ₂ CH ₂ CH=CH ₂	4.6 x 10 ⁷	5 ^b	80 °C	41
	R = CH ₂ CH ₂ CH=CH ₂	9.4 x 10 ⁵	5 ^a	80 °C	41
	R = CH ₂ CH ₂ CH=CH ₂	9.4 x 10 ⁵	5 ^b	80 °C	41
Ar = C ₆ H ₅					
		4.2 x 10 ⁷	5	80 °C	42
		2.4 x 10 ⁶	6	80 °C	42
		4.0 x 10 ³	5	25 °C	43
		9.4 x 10 ³	3	40 °C	44
		6.0 x 10 ⁶	5	80 °C	45
		6.7 x 10 ⁵	6	80 °C	45
		1.2 x 10 ⁸	5	60 °C	46
		1.6 x 10 ⁵	6	25 °C	47

^aRing substituents in the product are cis related in the product.

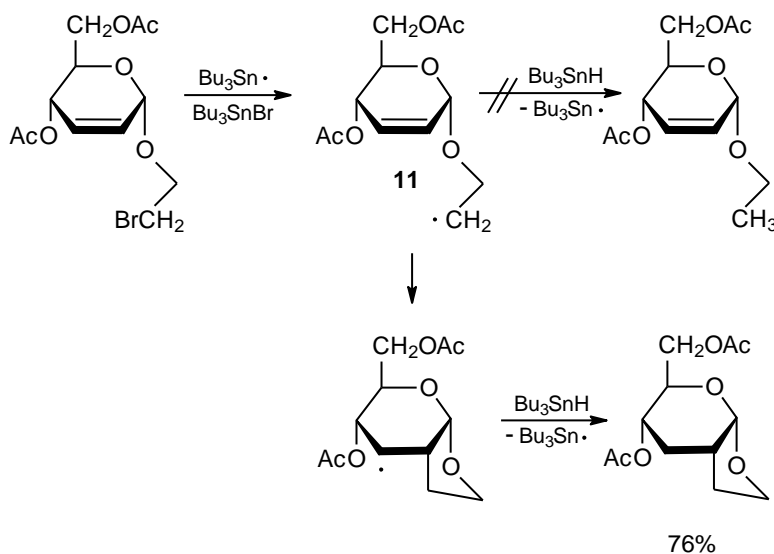
^bRing substituents in the product are trans related in the product.

Table 6. (cont.) Rate constants for radical cyclization reactions

Table 6. (cont.) Rate constants for radical cyclization reactions

<u>radical before cyclization</u>	<u>substituent identity</u>	<u>rate constant (s⁻¹)</u>	<u>temp</u>	<u>ref</u>
		6.7×10^5	80 °C	45
		1.2×10^8	60 °C	46

Scheme 12



D. Radical Addition

As with most radical reactions of carbohydrates, addition typically begins by group or atom transfer from a carbohydrate derivative to a tin- or silicon-centered radical to produce a carbon-centered radical (Scheme 13). Since tin- and silicon-centered radicals usually are formed from the corresponding hydrides, successful reaction depends on the rate of addition of the carbon-centered radical to an unsaturated compound being faster than hydrogen-atom abstraction by this radical from a hydride that has been added to the reaction mixture. The rate constants for hydrogen-atom abstraction from Bu_3SnH ($k_{\text{H}} = 2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 27 °C) and $(\text{Me}_3\text{Si})_3\text{SiH}$ ($k_{\text{H}} = 3 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ at 25 °C) are large enough that potential, radical-addition reactions can be thwarted by hydrogen-atom abstraction before addition can occur. (Rate constants for hydrogen-atom abstraction from tin and silicon hydrides are given in Table 2 in Chapter 7, and rate constants for

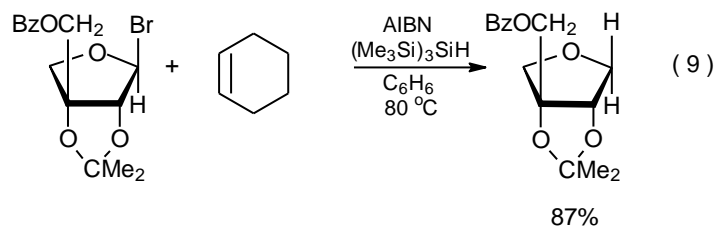
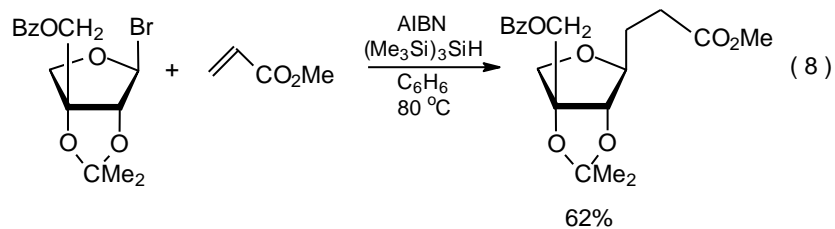
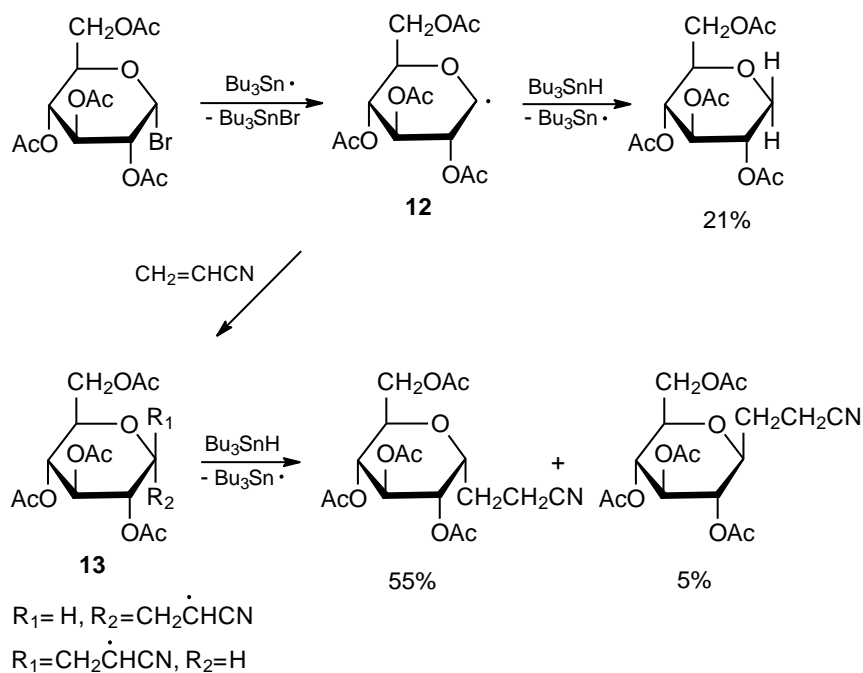
radical addition reactions are given in Table 7 in this Chapter). In order to have radical addition occur before hydrogen-atom abstraction takes place, it is necessary to select the most reactive, unsaturated compounds as reactants. Even these more reactive compounds may need to be present in higher concentration than the added hydride. The reactions shown in equations 8 and 9 draw attention to the fact that in a successful addition reaction an electron-withdrawing substituent needs to be attached to the multiple bond in the unsaturated reactant.⁵⁰

<u>radical</u>	<u>unsaturated compound</u>	<u>rate constant</u> (M ⁻¹ s ⁻¹)	<u>ref</u>
• CH ₂ OH	H ₂ C=CH ₂	4.1 x 10 ²	48
• CH ₂ OH	H ₂ C=CHCH ₃	2.7 x 10 ²	48
• CH ₂ OH	H ₂ C=CHOEt	1.8 x 10 ²	48
• CH ₂ OH	H ₂ C=CHOAc	5.9 x 10 ²	48
• CH ₂ OH	H ₂ C=CHCO ₂ Me	7.1 x 10 ⁵	48
• CH ₂ OH	H ₂ C=CHCN	1.1 x 10 ⁶	48
• CH ₂ OH	H ₂ C=CHCHO	2.1 x 10 ⁶	48
• CH ₂ CN	H ₂ C=CH ₂	3.3 x 10 ³	48
• CH ₂ CN	H ₂ C=CHCH ₃	1.2 x 10 ⁴	48
• CH ₂ CN	H ₂ C=CHOEt	4.3 x 10 ⁴	48
• CH ₂ CN	H ₂ C=CHOAc	1.3 x 10 ⁴	48
• CH ₂ CN	H ₂ C=CHCO ₂ Me	1.1 x 10 ⁵	48
• CH ₂ CN	H ₂ C=CHCN	1.1 x 10 ⁵	48
• CH ₂ CN	H ₂ C=CHCHO	2.5 x 10 ⁴	48
• C ₁₄ H ₂₈	H ₂ C=CHCH ₂ SnBu ₃	3.0 x 10 ⁴	49

^aReactions involving the hydroxymethyl radical were conducted at room temperature, and those for the cyanomethyl radical were conducted at 5 °C.

Table 7. Rate Constants for carbon-centered radical addition to compounds with carbon-carbon multiple bonds^a

Scheme 13



E. Group Migration

Scheme 14 describes one of the acyloxy-group migration reactions for which the rate constants are listed in Table 8. Rate constants for phosphatoxy-group migration are shown in Table 9. In the reaction pictured in Scheme 14, hydrogen-atom abstraction from Bu_3SnH competes with acyloxy-group migration to determine the fate of the radical **14**.⁵¹ The rate constant for migration

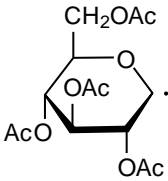
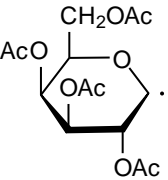
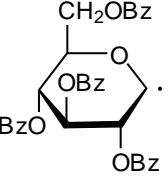
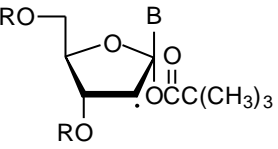
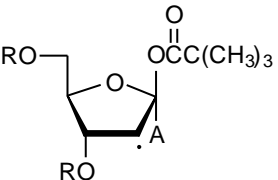
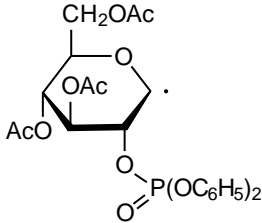
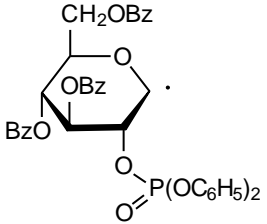
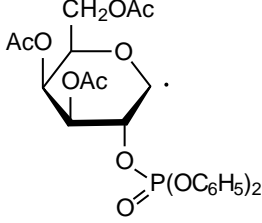
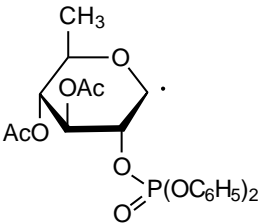
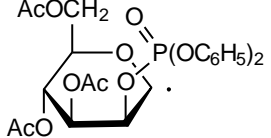
<u>radical prior to migration</u>	<u>rate constant</u> (s ⁻¹)	<u>temp</u>	<u>ref</u>
	4.0 x 10 ²	75 °C	51,52
	5.4 x 10 ³	75 °C	51,52
	3 x 10 ⁵	130 °C	53
			
R = SiMe ₂ t-Bu			
B = U	6.6 x 10 ⁴	80 °C	54-56
B = A	5.5 x 10 ⁴	80 °C	54, 55
	1.3 x 10 ⁵	80 °C	54
R = SiMe ₂ t-Bu			

Table 8. Rate constants for acyloxy group migration

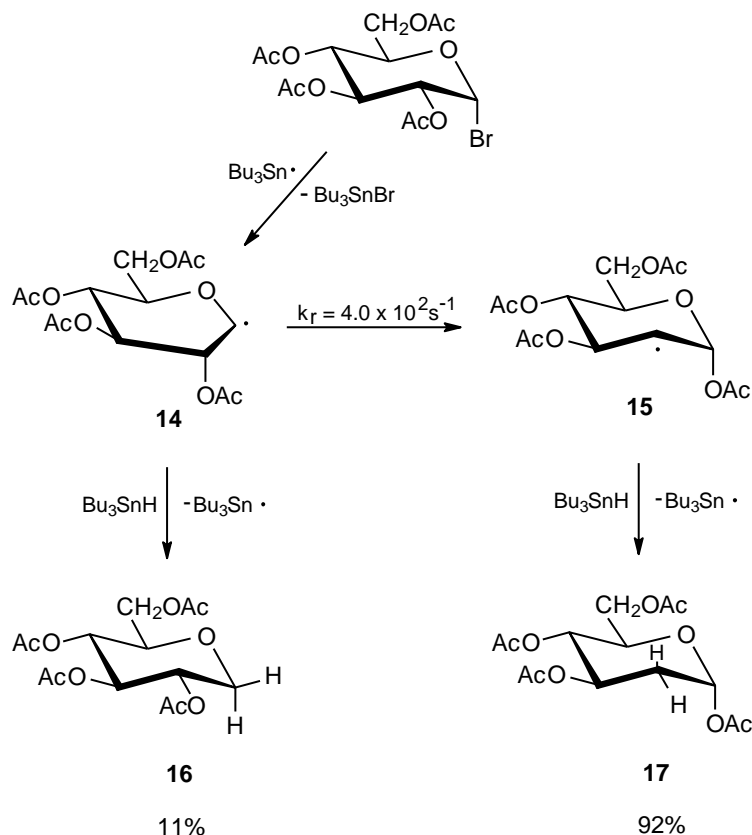
<u>radical prior to migration</u>	<u>rate constant</u> (s ⁻¹)	<u>ref</u>
	80 x 10 ⁵ s ⁻¹	57,58
	45 x 10 ⁵ s ⁻¹	57
	46 x 10 ⁵ s ⁻¹	57
	2000 x 10 ⁵ s ⁻¹	57
	1 x 10 ⁵ s ⁻¹	57

^a All reactions were conducted at 27 °C.

Table 9. Rate constants for phosphatoxy group migration^a

($k_r = 4 \times 10^2 \text{ s}^{-1}$ at $75 \text{ }^\circ\text{C}$)⁵² is far smaller than that for hydrogen-atom abstraction ($k_H = 2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at $27 \text{ }^\circ\text{C}$);¹⁷ consequently, migration (**14** \rightarrow **15**) will not be competitive unless the Bu_3SnH concentration is maintained at a low level. In practice this reduced concentration is achieved by slow addition of Bu_3SnH to the reaction mixture.

Scheme 14



A change in the hydrogen-atom donor can have a significant impact on product distribution during acetoxy group migration (Table 10). If the hydrogen-atom donor selected has a smaller rate constant for abstraction than does Bu_3SnH , greater opportunity will exist for rearrangement before abstraction. This situation exists when Bu_3SnH ($k_H = 2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at $27 \text{ }^\circ\text{C}$) is replaced by $(\text{Me}_3\text{Si})_3\text{SiH}$ ($k_H = 3 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ at $25 \text{ }^\circ\text{C}$).⁵⁹ In contrast, having $\text{C}_6\text{H}_5\text{SeH}$ ($k_H = 2.1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ at $25 \text{ }^\circ\text{C}$) present in a reaction mixture has the opposite effect because group migration effectively is prevented by the very rapid hydrogen-atom abstraction from this donor.⁶⁰

hydrogen donor	product distribution		ref
	16	17	
C ₆ H ₅ SeH	>95%	<5%	27, 60
Bu ₃ SnH	11%	89%	60
(Me ₃ Si) ₃ SiH	---	100%	59

Table 10. Product distribution from acetoxy group migration in the D-glucopyranos-1-yl radical **14** in the presence of three hydrogen donors

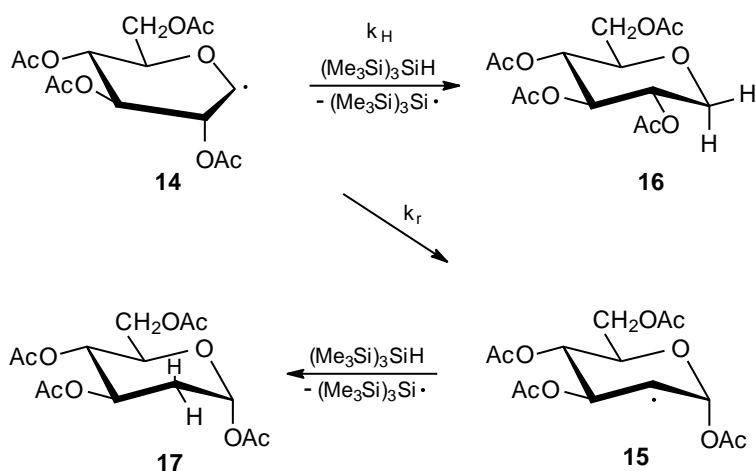
F. Hydrogen-Atom Abstraction by Pyranos-1-yl Radicals

The rate constants listed at the end of Table 4 show that hydrogen-atom abstraction from C₆H₅SeH by the pyranos-1-yl radical **14** ($k_H = 3.6 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 78 °C) has a much smaller rate constant for reaction than does the comparable abstraction by the structurally simpler, primary radical **18** ($k_H = 2.1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ at 25 °C). (A rationale for this difference in reactivity is discussed in Section VI.B. of Chapter 7.) If the reduced hydrogen-atom-abstracting ability of **14** is a characteristic of pyranos-1-yl radicals, then it should extend to reaction with other hydrogen-atom donors; unfortunately, at present, rate constants for hydrogen-atom abstraction by **14** from other donors are not known. Group migration, however, provides an indirect means for estimating the rate constant for hydrogen-atom abstraction from (Me₃Si)₃SiH.

Acetoxy group migration in **14** takes place in the presence of 0.05 M (Me₃Si)₃SiH without hydrogen-atom abstraction occurring prior to migration (Scheme 15).⁵⁹ Since neither group migration nor hydrogen-atom abstraction is reversible, the ratio of the hydrogen-atom-abstraction product **16** to the radical **15** and that of **16** to the migration product **17** (assuming **15** is converted exclusively into **17**) can be expressed in terms of the rate constants and concentrations shown in Scheme 15. The migration product **17** is formed in 71% yield, but because the hydrogen-atom-abstraction product **16** was not reported, its yield must have been very low. Even a 2% yield of **16** would mean that the rate constant for hydrogen-atom abstraction from (Me₃Si)₃SiH by **14** would be $2.3 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ at 75 °C, a value far smaller than $3 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ at 25 °C for

hydrogen-atom abstraction by simple organic radicals (Table 2 in Chapter 7). (The difference in these rate constants should be even larger if both were determined at the same temperature.) Even if all of the unidentified product from reaction of **14** were **16** (a highly unlikely possibility considered only for illustration purposes), the value for k_H ($3.3 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$ at 75°C) still would be far less than the reported $3 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ at 25°C ; therefore, the rate constant for hydrogen-atom abstraction by **14** from $(\text{Me}_3\text{Si})_3\text{SiH}$ estimated from group-migration reaction supports the proposal that reduced hydrogen-atom-abstracting ability is a characteristic of this (and perhaps all)

Scheme 15



$$\frac{\text{yield of } \mathbf{16}}{\text{yield of } \mathbf{15}} = \frac{\text{yield of } \mathbf{16}}{\text{yield of } \mathbf{17}} = \frac{k_H[(\text{Me}_3\text{Si})_3\text{SiH}][\mathbf{14}]}{k_r[\mathbf{14}]}$$

$$k_H = \frac{k_r(\text{yield of } \mathbf{16})}{[(\text{Me}_3\text{Si})_3\text{SiH}](\text{yield of } \mathbf{17})} \quad \begin{array}{l} k_r = 4.0 \times 10^2 \text{ s}^{-1} \text{ at } 75^\circ\text{C} \\ [(\text{Me}_3\text{Si})_3\text{SiH}] = 5.0 \times 10^{-2} \text{ M} \end{array}$$

$$k_H = \frac{(4.0 \times 10^2 \text{ s}^{-1})(\text{yield of } \mathbf{16})}{(5.0 \times 10^{-2} \text{ M})(\text{yield of } \mathbf{17})}$$

$$k_H = (8 \times 10^3 \text{ M}^{-1}\text{s}^{-1}) \frac{(\text{yield of } \mathbf{16})}{(\text{yield of } \mathbf{17})}$$

$$\text{If } \frac{\text{yield of } \mathbf{16}}{\text{yield of } \mathbf{17}} = \frac{2}{71}, \quad k_H = 2.3 \times 10^2 \text{ M}^{-1}\text{s}^{-1} \text{ at } 75^\circ\text{C}$$

$$\text{If } \frac{\text{yield of } \mathbf{16}}{\text{yield of } \mathbf{17}} = \frac{29}{71}, \quad k_H = 3.3 \times 10^3 \text{ M}^{-1}\text{s}^{-1} \text{ at } 75^\circ\text{C}$$

pyranos-1-yl radicals.

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.

A. Collapse Due to Chain Termination

In mathematical terms, chain collapse by chain termination is considered to take place in a reaction when r_p/r_t is less than unity.⁶² If in such a reaction r_p is the rate for a propagation step involving hydrogen-atom abstraction by the radical $R\cdot$ (eq 10), and r_t is the rate for the chain-terminating dimerization of R (eq 11), it is possible to calculate the minimum rate needed for the propagation step shown in eq 10 in order to avoid chain collapse.⁶² This calculation, given in eq 12, assumes k_t is determined by the rate of diffusion in the solution and, therefore, is in the range of $10^9 - 10^{10} \text{ M}^{-1}\text{s}^{-1}$. (The rate constants for some termination reactions are given in Table 11). Additional assumptions are that the radical concentration is $1 \times 10^{-7} \text{ M}$ and that the hydrogen-atom donor concentration is 1 M .⁶² The result from this calculation is that chain collapse ($r_p/r_t < 1$) will occur when the rate constant for reaction of an intermediate radical is less than $10^2\text{-}10^3 \text{ M}^{-1}\text{s}^{-1}$.

$$r_p = k_p [R\cdot][MH] \quad (10)$$

$$r_t = k_t [R\cdot][R\cdot] \quad (11)$$

$$\frac{r_p}{r_t} = \frac{k_p [MH]}{k_t [R\cdot]} = \frac{k_p [1 \text{ M}]}{[10^9\text{-}10^{10} \text{ M}^{-1}\text{s}^{-1}][1 \times 10^{-7} \text{ M}]} = \frac{k_p}{[10^2\text{-}10^3 \text{ M}^{-1}\text{s}^{-1}]} \quad (12)$$

$$\text{If } r_p/r_t < 1, \text{ then } k_p < 10^2\text{-}10^3 \text{ M}^{-1}\text{s}^{-1}$$

The reaction shown in Scheme 13 provides an example of a situation in which changing one of the reactants could cause chain collapse. If in this reaction Et_3SiH ($k_H = 6.4 \times 10^2 \text{ M}^{-1}\text{s}^{-1}$ at 25°C)²³ replaces Bu_3SnH ($k_H = 2 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ at 27°C)¹⁷ as the hydrogen-atom donor, the radical **12** will have more time to add to acrylonitrile rather than abstracting a hydrogen atom, but the entire reaction will be put “at risk” because the rate constant for the final step, hydrogen-atom abstraction from Et_3SiH by the radical **13**, will be in the region where chain collapse becomes a distinct possibility. In practice this small rate constant for hydrogen-atom abstraction is cited as the reason for triethylsilane being too unreactive to support chain reactions under normal conditions.^{7,23}

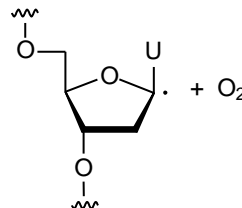
<u>reactant radical</u>	<u>rate constant</u> (M ⁻¹ s ⁻¹)	<u>temp</u>	<u>ref</u>
2 CH ₃ (CH ₂) ₅ CH ₂ ·	2.2 x 10 ⁹	25 °C	19
2 c-C ₆ H ₁₁ ·	2.7 x 10 ⁹	25 °C	19
2 Bu ₃ Sn·	1.4 x 10 ⁹	25 °C	19
Bu ₃ Sn· + O ₂	7.5 x 10 ⁹	27 °C	64
(CH ₃) ₂ ĊOH + O ₂	3.9 x 10 ⁹	27 °C	64
	1 x 10 ⁹	23 °C	63

Table 11. Rate constants for termination reactions

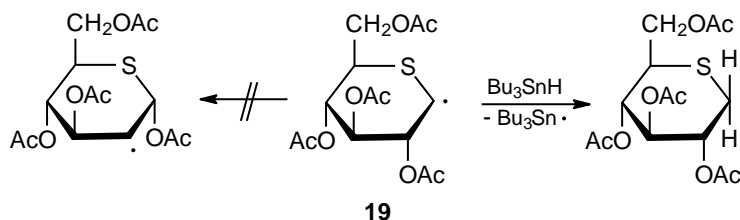
Using the term “chain collapse” might seem to indicate that an abrupt transition occurs when r_p/r_t becomes less than unity. Actually, this is not the case because the change is a gradual one. As the rates of propagation and termination reactions become increasingly similar, chain length becomes progressively shorter, and the yield of the termination product increases at the expense of the desired product. Shorter chain lengths mean that more initiator must be added to the reaction mixture to obtain complete reaction. As the reaction approaches the “collapse” state, complete reaction will require not a catalytic but a nearly equal-molar amount of initiator.

B. Collapse Due to Chain Shift

Realizing that chain collapse occurs when the rate constant for a propagation step is in the range of 10^2 - 10^3 M⁻¹s⁻¹ leads one to the conclusion that the acetoxy group migration shown in Scheme 14 ($k_r = 4.0 \times 10^2$ s⁻¹ at 75 °C) is slow enough that chain collapse is possible. Because the radical **14** is part of two propagation sequences operating simultaneously, the primary process competing with acetoxy group migration is not a termination step that stops the chain but rather a hydrogen-atom abstraction that causes chain shift to a simple-reduction sequence. The information in Scheme 14 shows that chain shift already is occurring to a minor extent (11%) in the reaction of the radical **14** when Bu₃SnH is the hydrogen-atom donor. If the rate constant for a migration reaction is smaller than 4×10^2 s⁻¹ at 75 °C, chain shift could effectively eliminate the migration process. This appears to happen for the radical **19** because although it is capable of undergoing acyloxy group migration, **19** is reported to give only the simple reduction product (Scheme 16).⁵²

Other carbohydrate radicals that undergo acyloxy group migration have rate constants for reaction greater than $4 \times 10^2 \text{ s}^{-1}$ at $75 \text{ }^\circ\text{C}$ (Table 8).

Scheme 16



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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