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$_3$Sn$^-$ are found in Table 1. Table 2 contains a similar set of rate constants that includes those for atom-transfer reactions involving (Me$_3$Si)$_3$Si$^-$ and Et$_3$Si$. (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.\textsuperscript{8}

\begin{table}
\begin{tabular}{lll}
\textbf{reactant} & \textbf{rate constant} (M$^{-1}$s$^{-1}$) & \textbf{temp} & \textbf{ref} \\
C$_6$H$_5$CH$_2$Cl & $7 \times 10^3$ & 25 $^\circ$C & 4 \\
(CH$_3$)$_3$CCl & $2.7 \times 10^4$ & 25 $^\circ$C & 5 \\
C$_6$H$_5$CH$_2$Cl & $1.1 \times 10^5$ & 25 $^\circ$C & 5 \\
CH$_3$(CH$_2$)$_2$OCH$_2$Cl & $1 \times 10^5$ & 25 $^\circ$C & 4 \\
C$_7$H$_5$CH$_2$Br & $3 \times 10^7$ & 25 $^\circ$C & 4 \\
(CH$_3$)$_2$CBr & $1.4 \times 10^9$ & 25 $^\circ$C & 5 \\
CH$_3$I & $4.3 \times 10^9$ & 25 $^\circ$C & 5 \\
CH$_3$(CH$_2$)$_2$OCH$_2$SC$_6$H$_5$ & $1 \times 10^3$ & 25 $^\circ$C & 4 \\
CH$_3$(CH$_2$)$_2$OCH$_2$SeC$_6$H$_5$ & $6 \times 10^6$ & 25 $^\circ$C & 4 \\
\end{tabular}
\caption{Rate constants for radical formation by reaction with the tri-$n$-butyltin radical}
\end{table}
<table>
<thead>
<tr>
<th>reactant</th>
<th>radical</th>
<th>rate constant (M⁻¹s⁻¹)</th>
<th>temp</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₃)₂CCl</td>
<td>(Me₃Si)₃Si</td>
<td>4.0 x 10⁶</td>
<td>25 °C</td>
<td>6</td>
</tr>
<tr>
<td>CH₃(CH₂)₂Br</td>
<td>(Me₃Si)₃Si</td>
<td>2.0 x 10⁷</td>
<td>20 °C</td>
<td>6</td>
</tr>
<tr>
<td>(CH₃)₂CBr</td>
<td>(Me₃Si)₃Si</td>
<td>1.2 x 10⁶</td>
<td>20 °C</td>
<td>6</td>
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<tr>
<td>c-C₆H₃H₅l</td>
<td>(Me₃Si)₃Si</td>
<td>&gt;4 x 10⁹</td>
<td>20 °C</td>
<td>7</td>
</tr>
<tr>
<td>C₆H₄SC₆H₄H₂</td>
<td>(Me₃Si)₃Si</td>
<td>&lt;5 x 10⁶</td>
<td>21 °C</td>
<td>2</td>
</tr>
<tr>
<td>C₆H₄SeC₆H₄H₂</td>
<td>(Me₃Si)₃Si</td>
<td>9.6 x 10⁷</td>
<td>21 °C</td>
<td>2</td>
</tr>
<tr>
<td>c-C₆H₁₁OC(=S)Me</td>
<td>(Me₃Si)₃Si</td>
<td>1.1 x 10⁹</td>
<td>21 °C</td>
<td>2</td>
</tr>
<tr>
<td>c-C₆H₁₁NC</td>
<td>(Me₃Si)₃Si</td>
<td>4.7 x 10⁷</td>
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<tr>
<td>(CH₃)₃CNO₂</td>
<td>(Me₃Si)₃Si</td>
<td>1.2 x 10⁷</td>
<td>21 °C</td>
<td>2</td>
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<tr>
<td>CH₃(CH₂)₄Cl</td>
<td>Et₃Si</td>
<td>3.1 x 10⁷</td>
<td>25 °C</td>
<td>6</td>
</tr>
<tr>
<td>(CH₃)₂CBr</td>
<td>Et₃Si</td>
<td>2.5 x 10⁶</td>
<td>25 °C</td>
<td>6</td>
</tr>
<tr>
<td>CH₃(CH₂)₂Br</td>
<td>Et₃Si</td>
<td>5.4 x 10⁶</td>
<td>27 °C</td>
<td>6</td>
</tr>
<tr>
<td>(CH₃)₂CBr</td>
<td>Et₃Si</td>
<td>1.1 x 10⁹</td>
<td>27 °C</td>
<td>5,6</td>
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<tr>
<td>CH₃(CH₂)₂I</td>
<td>Et₃Si</td>
<td>4.3 x 10⁹</td>
<td>27 °C</td>
<td>5</td>
</tr>
<tr>
<td>CH₃I</td>
<td>Et₃Si</td>
<td>8.1 x 10⁹</td>
<td>29 °C</td>
<td>5</td>
</tr>
</tbody>
</table>

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.

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 Bu₃Sn⁻ (Table 1) or (Me₃Si)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-bromo octane and (Me₃Si)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 (Me₃Si)₃Si⁻ is the same as the rate constant for formation of R·. Also, since R· then abstracts a hydrogen atom from (Me₃Si)₃SiH, the amount of octane formed is directly related to the number of octyl radicals produced.

\[
\text{Scheme 2}
\]

\[
R\text{Br} + \cdot\text{Si(SiMe}_{3}\text{)}_{3} \quad \xrightarrow{k_{\text{Br}}} \quad R\cdot + \text{BrSi(SiMe}_{3}\text{)}_{3}
\]

\[
R\cdot + \text{HSi(SiMe}_{3}\text{)}_{3} \quad \longrightarrow \quad \text{RH} + \cdot\text{Si(SiMe}_{3}\text{)}_{3}
\]

\[
k_{\text{Br}} = 2.0 \times 10^{7} \text{M}^{-1}\text{s}^{-1} \quad R = \text{CH}_{2}(\text{CH}_{2})_{8}\text{CH}_{3}
\]

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 (Me₃Si)₃Si⁻ is given in Scheme 3. If the addition of (Me₃Si)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 (Me₃Si)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 \(k_{\text{NC}}\) and \(k_{\text{Br}}\) (Scheme 3).

\[
\text{Scheme 3}
\]

\[
\text{RN=C} + \cdot\text{Si(SiMe}_{3}\text{)}_{3} \quad \xrightarrow{k_{\text{NC}}} \quad \text{RN=CSi(SiMe}_{3}\text{)}_{3}
\]

\[
\text{RN=CSi(SiMe}_{3}\text{)}_{3} \quad \longrightarrow \quad R\cdot + \text{NΞC} \cdot\text{Si(SiMe}_{3}\text{)}_{3}
\]

\[
R\cdot + \text{HSi(SiMe}_{3}\text{)}_{3} \quad \longrightarrow \quad \text{RH} + \cdot\text{Si(SiMe}_{3}\text{)}_{3}
\]

\[
k_{\text{NC}} = 4.7 \times 10^{7} \text{M}^{-1}\text{s}^{-1} \quad R = \text{C}_8\text{H}_{16}
\]

\[
\frac{k_{\text{NC}}}{k_{\text{Br}}} = 2.3 \quad \frac{\text{cyclohexane}}{\text{octane}} = 1.2
\]

The addition of the (Me₃Si)₃Si⁻ 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 $(\text{Me}_3\text{Si})_3\text{Si}$· to these compounds is a frequently reversed process.

\[ \text{RSeC}_6\text{H}_5 + \cdot\text{Si(}\text{Me}_3\text{)}_3 \rightarrow \text{RSeC}_6\text{H}_5 + \cdot\text{Si(}\text{Me}_3\text{)}_3 \]

\[ \frac{k_{\text{Se}}}{k_{\text{Br}}} = 4.8 \quad \frac{\text{cyclohexane}}{\text{octane}} = 0.08 \]

\[ \text{R}^\cdot + \text{HSi(}\text{Me}_3\text{)}_3 \rightarrow \text{RH} + \cdot\text{Si(}\text{Me}_3\text{)}_3 \]

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). The lack of an effective hydrogen 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 pseudoequilibrium. Both radicals abstract hydrogen atoms from Bu$_3$SnH.$^{10}$ Due to the differences in the rate constants for ring opening ($k_{fra} = 1.1 \times 10^7 \text{ s}^{-1}\text{M}^{-1}$ at 80 °C) and ring closure ($k_{cyc} = 1.0 \times 10^6 \text{ s}^{-1}\text{M}^{-1}$ at 80 °C), the ring-open radical 7 dominates the pseudoequilibrium, but because the rate constant for hydrogen-atom abstraction by 6 ($k_H = 4.7 \times 10^8 \text{ s}^{-1}\text{M}^{-1}$ at 80 °C) is so much larger than that for hydrogen-atom abstraction by 7 ($k_H = 6.4 \times 10^6 \text{ s}^{-1}\text{M}^{-1}$ 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.\textsuperscript{12,13}

Radical formation by electron transfer also can take place by reaction between transition-metal complexes such as (NH\textsubscript{4})\textsubscript{2}Ce(NO\textsubscript{3})\textsubscript{6}, Mn(OAc)\textsubscript{3}, Sml\textsubscript{2}, and Cp\textsubscript{2}TiCl 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 Sml\textsubscript{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.
Reactions involving Sm\(_2\) typically are conducted in the presence of hexamethylphosphoramide (HMPA), a compound that complexes with Sm\(_2\) and increases its ability to donate an electron. Greater electron-donating ability not only increases the rate constant for formation of the radical R\(\cdot\) but it also increases the rate at which this radical reacts with a second molecule of Sm\(_2\). The data in Table 3 show that when the 5-hexenyl radical reacts with Sm\(_2\), the rate constants for reaction increase from 5 \(\times\) 10\(^5\) M\(^{-1}\)s\(^{-1}\) to 6.8 \(\times\) 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 Sm\(_2\), this “other reaction” must be rapid. An example of a reaction of a radical that does take place more rapidly than combination with Sm\(_2\) 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 Sm\(_2\).)

\[ \text{Scheme 10} \]

\[
\text{RX} + \text{Sm}^{II}_2 \xrightarrow{\text{HMPA}} \text{R\(\cdot\)} + \text{Sm}^{II}_2 \xrightarrow{\text{k}_{SD}} \text{RSm}^{III}_2
\]

\(\text{cyclization} \quad \text{group migration}\)

---

**Table 3.** Rate constants for reaction of 5-hexenyl radical with Sm\(_2\) in the presence of HMPA at 25 °C.\(^{14}\)

<table>
<thead>
<tr>
<th>HMPA (^{eq})</th>
<th>(k_{SD}(\text{M}^{-1}\text{s}^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3</td>
<td>5 (\times) 10(^5)</td>
</tr>
<tr>
<td>2.8</td>
<td>6 (\times) 10(^5)</td>
</tr>
<tr>
<td>3.2</td>
<td>2.8 (\times) 10(^6)</td>
</tr>
<tr>
<td>3.7</td>
<td>5.3 (\times) 10(^6)</td>
</tr>
<tr>
<td>4.4</td>
<td>6.4 (\times) 10(^6)</td>
</tr>
<tr>
<td>5.1</td>
<td>6.8 (\times) 10(^6)</td>
</tr>
<tr>
<td>6.0</td>
<td>6.5 (\times) 10(^6)</td>
</tr>
</tbody>
</table>

\(^{eq}\text{equivalents of HMPA [Me}_2\text{N)}\text{PO] added relative to Sm}_2\text{ present}\)
Contributors

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