Chapter 1
Advantages and Disadvantages of Radical Reactions

I. Introduction

Whenever a structural change is needed in a molecule, an early (if not the first) question is “What is the best way to accomplish this change?” For many years the answer to this question rarely involved a radical reaction (unless polymerization was taking place) because the synthetic potential of radical reactions was viewed in a negative light. As understanding of radical reactions
blossomed during the latter part of the 20th Century, this situation changed, and radical-based processes were seen increasingly not only as synthetically viable possibilities but often as the best choice. Nowhere was the option of conducting a radical reaction more attractive than in carbohydrate chemistry because the combined chemoselectivity, regioselectivity, and stereoselectivity of these reactions was particularly well suited for structural change in polyfunctional molecules.

When deciding whether or not to conduct a radical reaction, certain information is crucial. It is important to know as completely as possible how intermediate radicals will form and, once formed, how these radicals will react with various reagents and solvents present in the reaction mixture. This information not only points to the expected product but also answers questions such as: What side reactions could take place? How might these reactions be avoided or minimized? What is the outcome of reactions that have been reported for similar compounds? A fitting way to begin framing the answers to these questions is by looking at the advantages and disadvantages of radical reactions.

II. Advantages of Radical Reactions

Some advantages of radical reactions can be traced to the mild conditions under which they are conducted; others to the stability of common protecting groups during reaction. Ease in performing group and atom replacement is still another benefit, but the greatest value radical reactions bring to carbohydrate synthesis is in forming new, carbon–carbon bonds; in other words, even though radical reactions are capable of causing a variety of structural changes, their most valuable role is their most basic one, namely, building more complicated structures from less complicated ones.
A. Radical Addition Reactions Are Capable of Forming Thermodynamically Less Stable Products.

Addition of a carbon-centered radical to a carbon–carbon multiple bond normally is a kinetically controlled process with an early transition state;\(^2\,^3\) consequently, the steric effects and radical stability that greatly affect reactions with later transition states (and especially reactions under thermodynamic control) are less significant for radical addition and cyclization. The consequences of the early-transition-state, kinetic-control combination can be seen in the cyclization reactions shown in Schemes 1\(^\text{4,5}\) and 2\(^\text{6}\). In each of these reactions the transition state is reached before radical stability and unfavorable steric interactions become controlling; as a result, a primary radical with a new, five-membered ring forms in each reaction rather than a more stable secondary or tertiary radical with a six-membered ring. Thermodynamically less stable products are not inherently more valuable than more stable ones, but since they are usually more difficult to prepare, a reaction that creates them has special synthetic potential.

![Scheme 2](image)

B. Radical Reactions Can Produce Compounds With Sterically Crowded Carbon Atoms

Unlike ions, radicals are intermediates that are not heavily solvated or associated with counter ions.\(^3\) When this fact is combined with the early transition states that generally occur in radical addition reactions, together they create the possibility for forming compounds that are strained by sterically demanding groups being attached to the same carbon atom.\(^2\,^7\,^8\) Since, as
noted in the previous section, radical addition normally takes place under kinetic control, sterically crowded radicals, once formed, do not revert to starting materials; therefore, reactions such as that shown in Scheme 3, can generate strained products.\(^9\)

\[ Z = I, \text{Br}, \text{Cl}, \text{SR}, \text{SeC}_6\text{H}_5, \text{NO}_2, \text{N} = \text{C}, \text{OC}(=\text{S})\text{Me}, \text{OC}(=\text{S})\text{OC}_6\text{H}_5 \]

C. Radical Addition and Cyclization Reactions Usually Are Not Plagued by Competition from \(\beta\) Fragmentation.

A critical element to the success of carbon–carbon bond formation by addition of a carbohydrate radical to a compound with a multiple bond is avoiding \(\beta\) fragmentation of the radical (eq 1) before addition can occur. Factors favoring fragmentation include: (a) a weak bond from the \(\beta\)-carbon atom to an attached substituent \((Z)\),\(^{10}\) (b) the ability of this substituent to depart as a relatively stable radical,\(^3\) (c) relief of ring strain,\(^{11}\) and (d) formation of a carbonyl group during reaction.\(^{12}\) The atoms and groups with the necessary reactivity to participate in \(\beta\) fragmentation are shown in eq 1; however, as described in the following paragraphs, the structure of most carbohydrates presents a natural barrier to \(\beta\) fragmentation.

When a single substituent from among the group \(\text{I, Br, Cl, SR, SeC}_6\text{H}_5, \text{NO}_2, \text{N} = \text{C}, \text{OC}(=\text{S})\text{Me}, \) and \(\text{OC}(=\text{S})\text{OC}_6\text{H}_5\) is present in a carbohydrate, radical formation easily occurs. If \(\beta\) fragmentation
is to follow formation of a carbon-centered radical, a second substituent from among this same group typically departs as the double bond forms (Scheme 4). Since having two such substituents adjacent to each other in a molecule nearly always is a planned event, $\beta$ fragmentation of the type shown in eq 1 rarely competes unexpectedly with addition and cyclization reactions.

Absent from the list of reactive substituents shown in eq 1 are the hydroxyl group and various hydroxyl protecting groups. These groups are missing because the carbon–oxygen bonds connecting each of them to the carbohydrate framework are quite strong and any oxygen-centered radical that would be produced by fragmentation of such a bond would be highly energetic; thus, elimination of a $\beta$ substituent by homolytic cleavage of a carbon–oxygen bond cannot compete
with other radical reactions. In particular, this means that radicals centered on the carbohydrate framework undergo cyclization (eq 2)\textsuperscript{15} and addition (eq 3)\textsuperscript{16} reactions without competition from β fragmentation.

Anionic and organometallic intermediates readily cleave β-related, carbon–oxygen bonds to form unsaturated compounds and oxygen-centered anions. This facile bond cleavage, combined with the presence of many carbon–oxygen bonds in carbohydrates, effectively renders addition and cyclization reactions involving these intermediates unable to compete with β elimination. The radical reactions pictured in equations 2 and 3 would have little chance of occurring if anionic or organometallic intermediates were involved. The reaction shown in Scheme 5, which takes place at room temperature, illustrates how easily elimination can occur from an organometallic compound in which carbon–metal and carbon–oxygen bonds are β-related.\textsuperscript{17,18} Formation of the d-glucal 2 directly from the radical 1 (Scheme 5) is not a viable possibility because when 1 is generated in the absence of an effective electron donor (e.g., SmI\textsubscript{2}), 2 is not formed.

Radical reactions that eliminate adjacent O-thiocarbonyl groups deserve special comment because a C–O bond adjacent to the radical center must be broken in order to form a C–C double bond. Although normally difficult, homolytically cleaving the C–O bond in a O-thiocarbonyl group is possible because reaction is not a simple bond fragmentation but rather a cyclization-fragmentation sequence. The fragmentation step that breaks the C–O bond can do so because this reaction also produces a carbonyl group and generates a stabilized, sulfur-centered radical (Scheme 6).
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Scheme 6

\[ \text{Reactant} \quad \text{Radical} \quad \text{Rate Constant} \quad \text{Temp} \quad \text{Ref} \\
(\text{CH}_3)_2\text{CCl} \quad (\text{Me}_3\text{Si})_3\text{Si} \cdot \quad 4.0 \times 10^5 \quad 25 \, ^\circ\text{C} \quad 19 \\
\text{CH}_3(\text{CH}_2)_2\text{Br} \quad (\text{Me}_3\text{Si})_3\text{Si} \cdot \quad 2.0 \times 10^7 \quad 20 \, ^\circ\text{C} \quad 19 \\
(\text{CH}_3)_2\text{CBr} \quad (\text{Me}_3\text{Si})_3\text{Si} \cdot \quad 1.2 \times 10^8 \quad 20 \, ^\circ\text{C} \quad 19 \\
c\text{-C}_6\text{H}_{11}\text{I} \quad (\text{Me}_3\text{Si})_3\text{Si} \cdot \quad >4 \times 10^9 \quad 20 \, ^\circ\text{C} \quad 20 \\
\text{C}_6\text{H}_5\text{SC}_{10}\text{H}_{21} \quad (\text{Me}_3\text{Si})_3\text{Si} \cdot \quad <5 \times 10^6 \quad 21 \, ^\circ\text{C} \quad 21 \\
\text{C}_6\text{H}_5\text{SeC}_{10}\text{H}_{21} \quad (\text{Me}_3\text{Si})_3\text{Si} \cdot \quad 9.6 \times 10^7 \quad 21 \, ^\circ\text{C} \quad 21 \\
c\text{-C}_6\text{H}_{11}\text{OC}(=\text{S})\text{SMc} \quad (\text{Me}_3\text{Si})_3\text{Si} \cdot \quad 1.1 \times 10^9 \quad 21 \, ^\circ\text{C} \quad 21 \\
c\text{-C}_6\text{H}_{11}\text{NC} \quad (\text{Me}_3\text{Si})_3\text{Si} \cdot \quad 4.7 \times 10^7 \quad 21 \, ^\circ\text{C} \quad 21 \\
(\text{CH}_3)_2\text{CNO}_2 \quad (\text{Me}_3\text{Si})_3\text{Si} \cdot \quad 1.2 \times 10^7 \quad 21 \, ^\circ\text{C} \quad 21 \\

Table 1. Rate constants for radical formation by reaction of the tris(trimethylsilyl)silyl radical with simple organic molecules
D. Radical Reactions Are Highly Chemoselective and Regioselective and Often Highly Stereoselective.

1. Chemoselectivity

Chemoselectivity in most radical reactions is determined by how rapidly a tin- or silicon-centered radical reacts with a group or atom present in a molecule of starting material. Some simple organic compounds that form radicals by reacting with \((\text{Me}_3\text{Si})_3\text{Si}^·\) are shown in Table 1 along with the rates of their reactions. It is reasonable to expect similar reactivity from carbohydrates that contain these same substituents. Since a typical, carbohydrate-radical precursor contains only one reactive atom or group, radical formation from such a molecule is highly chemoselective.

2. Regioselectivity

Regioselectivity is primarily of concern when a carbon-centered radical is adding to a carbon–carbon double bond. The direction of this bimolecular addition is controlled by a combination of steric and polar effects. In most reactions these effects act in concert to cause addition of a nucleophilic radical to the more electron deficient, less substituted carbon atom of a multiple bond, a behavior that leads to highly regioselective reaction such as that shown in eq 4. When cyclization is taking place, ring strain at the transition state becomes the most significant factor; thus, in Schemes 1 and 2 less strained transition states lead to regioselective addition to the more highly substituted carbon atom of the double bond.

3. Stereoselectivity

Stereoselectivity in radical reactions is controlled by a combination of conformational, steric, stereoelectronic, and torsional effects. These effects often cause highly stereoselective reaction to take place; thus, in the radical addition shown in eq 4 (and other additions involving pyranos-1-yl radicals) stereoselective reaction is attributed primarily to the combination of conformational and stereoelectronic factors known as the kinetic anomeric effect. [A discussion of the kinetic anomeric effect is found in Section II (p 255) of Chapter 11 in Volume I.] When an addition reaction occurs that is not subject to the kinetic anomeric effect, steric interactions usually are
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Scheme 7

\[
\text{CA} \quad \text{O} \quad \text{CON} \quad \text{S} \quad \text{O} \quad \text{H} \quad \text{CH}_3 \quad \text{Spy} \\
\text{CA} \quad \text{O} \quad \text{AcO} \quad \text{HgOAc} \quad \text{Bu}_3\text{SnH} \quad 5\% \quad 56\%
\]

\[
\text{AcO} \quad \text{O} \quad \text{CH}_2 \quad \text{OAc} \quad \text{AcO} \quad \text{Br} \quad \text{AcO} \quad \text{AcO} \\
\text{AcO} \quad \text{CH}_2 \quad \text{OAc} \quad \text{AcO} \quad \text{CH}_2\text{OAc} \quad \text{AcO} \quad \text{Br} \quad \text{AcO} \quad \text{AcO} \\
\text{3 + 4} \hspace{1cm} 3/4
\]

- \( X = H, Z = \text{CN} \) \hspace{1cm} 67\% \hspace{1cm} 67/33
- \( X = H, Z = \text{CO}_2\text{CH}_3 \) \hspace{1cm} 55\% \hspace{1cm} 71/29
- \( X = Z = \text{CN} \) \hspace{1cm} 55\% \hspace{1cm} 90/10
- \( X = Z = \text{CO}_2\text{CH}_3 \) \hspace{1cm} 50\% \hspace{1cm} 97/3

\[
\text{CH}_2\text{OAc} \quad \text{AcO} \quad \text{O} \quad \text{CMe}_2 \quad \text{H}_{2}\text{Me} \quad \text{OAc} \quad \text{AIBN} \quad \text{Bu}_3\text{SnH} \quad \text{C}_6\text{H}_5\text{CH}_3 \quad 110\ \degree \text{C} \quad \text{AcO} \quad \text{CH}_2\text{OAc} \quad \text{(6)} \quad 29\%
\]
dominant; thus, in the reactions shown in eq 5, stereoselectivity increases as the size and number of the double bond substituents increase.\textsuperscript{24}

Carbohydrates affect stereoselectivity in reactions where the carbohydrate moiety is not directly attached to the reactive centers. In the reaction shown in Scheme 7, for example, highly stereoselective, carbon–carbon bond formation takes place due to the carbohydrate portion of the molecule functioning as a chiral auxiliary.\textsuperscript{25}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme_8.png}
\end{scheme}

E. Radical Reactions Can Form Carbon-Linked Disaccharides.

Radical addition and cyclization reactions are useful in linking saccharides together by carbon–carbon bonds. One such reaction is shown in eq 6,\textsuperscript{26} where radical addition joins two monosaccharide units. Radical cyclization is responsible for the new carbon–carbon bond in compound \textbf{5}, a product that then is converted into the \textit{C}-disaccharide \textbf{6} (Scheme 8).\textsuperscript{27}

F. Radical Reactions Can Be Part of Effective, Deoxygenation Sequences.

Radical-based replacement of a hydroxyl group with a hydrogen atom takes place when a partially protected sugar first is converted into the corresponding \textit{O}-thiocarbonyl compound and then this
carbohydrate derivative reacts with Bu₃SnH (Scheme 9). Deoxy sugars also can be synthesized by radical reaction of a halogenated carbohydrate (not a fluoride) with a tin or silicon hydride (Scheme 10).

G. Hydroxyl and Hydroxyl-Protecting Groups Are Stable During Radical Reactions.

Carbon-, tin-, and silicon-centered radicals typically do not react with hydroxyl groups; consequently, hydroxyl group protection during radical reaction is not necessary. The reaction shown in eq 7 provides an example of a simple reduction of a glycoside in which three hydroxyl
groups are unprotected. Potentially, then, using radical reactions can reduce the number of protection-deprotection steps in a synthetic scheme. If hydroxyl group protection is present because it was needed in earlier reactions or will be required for later ones, such protection normally is unaffected during radical reactions. In the cyclization process shown in Scheme 1, for example, the starting material contains ester, ether, and acetal linkages, all of which remain unchanged during radical reaction.

H. Radical Reactions Can Be Conducted Under Mild Conditions.

Although radicals are highly reactive species, drastic conditions are not required for their formation. Radicals are generated under conditions that typically involve inert solvents, the absence of added acids or bases, and low to moderate temperatures. If the sole purpose of heating a reaction mixture is to fragment the initiator, selecting a different initiator may permit reaction to occur under milder conditions. In the reaction shown in eq 8, for example, replacing AIBN by Et$_3$B–O$_2$ allows reaction to take place at room temperature.

I. Radicals Readily Undergo Sequential Reactions

Radicals are well suited for sequential transformations because each elementary reaction produces a new radical poised to continue the reaction sequence. Because in a sequential reaction
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two or more elementary reactions occur after the substrate radical is generated but before a product is formed, the substantial structural change possible from a sequential reaction offers a savings in time, effort, chemicals, and other materials. Sequential reactions, therefore, are capable of increasing synthetic efficiency and decreasing negative environmental impact. This increased efficiency can be seen in the reaction shown in Scheme 11 where two new rings are formed in a single reaction.34

Scheme 11

III. Disadvantages of Radical Reactions

In addition to the advantages associated with radical reactions, there also are disadvantages. Deciding whether to use a radical reaction depends, in part, on knowing what these disadvantages are. Problems with radical reactions are described in the next four sections.

A. Use of Tin Hydrides Creates Purification and Toxicity Problems.

Although tri-\(n\)-butyltin hydride is an effective hydrogen-atom donor and the tri-\(n\)-butyltin radical acts as a chain-carrying agent during reactions involving \(\text{Bu}_3\text{SnH}\), the use of tri-\(n\)-butyltin hydride (and other organotin hydrides) creates problems due to the toxicity of organotin compounds and the difficulty in separating tin-containing residues from other reaction products. These complications are most problematic in the synthesis of compounds destined for medical or biological applications. Considerable, imaginative effort has been devoted to devising procedures for removing tin-containing residues from reaction products or using reagents that are tin-free. These solutions to the “tin-hydride problem” are described in Appendix 1.
B. Hydrogen-Atom Transfer Competes With Radical Addition and Cyclization.

Most radical addition and cyclization reactions are conducted with a hydrogen-atom donor as one of the reactants. Such a compound typically provides a convenient source of chain-carrying radicals during reaction and a supply of hydrogen atoms for abstraction once addition or cyclization is complete; however, the hydrogen-atom donor also may participate in premature hydrogen-atom abstraction, a reaction that prevents addition or cyclization from taking place.\(^2\) The reaction shown in eq 9\(^{35-37}\) describes a situation in which simple reduction is in spirited competition with radical addition. In some reactions, but not most, this competition favors simple reduction [e.g., eq 9 (R=Bz) and eq 10\(^{38}\)].

C. Radical Addition and Cyclization Reactions Usually Are Accompanied by a Loss in Functionality.

Since the final step in most radical addition reactions is hydrogen-atom abstraction, the entire process results in a loss of functionality. In the reaction shown in Scheme 1, for example, a multiple bond and an iodine atom are eliminated during radical addition. Loss of these substituents can handicap further transformation of addition and cyclization products.

D. Radicals Combine with Other Radicals, Often at Diffusion-Controlled Rates.

Because two radicals typically combine rapidly (often at diffusion controlled rates), radical concentration must be kept low if combination is to be avoided. Reactions occurring by chain
mechanisms can maintain sufficiently low radical concentrations to minimize combination. Maintaining a low radical concentration during a reaction sometimes necessitates very slow reagent addition.\textsuperscript{8}

IV. Looking Ahead

The advantages of radical reactions discussed in this chapter provide an introduction to the possibilities these reactions bring to carbohydrate chemistry. The chapters immediately ahead are devoted to a systematic presentation of the various types of carbohydrate derivatives that are able to produce radicals and the reactions that these radicals undergo. Later chapters contain information about reactions that take place when radicals are generated by electron transfer from transition-metal complexes to various carbohydrate derivatives.

IV. References