I. Introduction

Aldehydes and, to a lesser extent, ketones participate in radical reactions of carbohydrates by generating intermediate, oxygen-centered and carbon-centered radicals. The radical addition pictured in eq 1 provides an example of conversion of a carbonyl compound into an oxygen-centered radical, while that in eq 2 involves transforming an aldehyde or ketone into a carbon-centered radical. [The radicals produced in the latter reaction (eq 2) are described as samarium ketyl in recognition of their partial radical-anion character.] Other reactions that generate radicals from
aldehydes and ketones are photochemical bond homolysis (eq 3) and fragmentation of \( \alpha \)-acyloxy ketones (eq 4). The discussion in this chapter centers on the types of compounds that can be produced by these reactions and the mechanisms for their formation.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CO} & \quad \cdot \text{SnBu}_3 \\
\text{R}_1\text{R}_2 & \quad \rightarrow \\
\text{C}_6\text{H}_5\text{CO} & \quad \text{SnBu}_3 + \text{R}_1\text{R}_2
\end{align*}
\]

(4)

II. Intramolecular Addition of Carbon-Centered Radicals to Aldehydo and Keto Groups

The possibility of isolating a product from intermolecular addition of a carbon-centered radical to an aldehyde or ketone is small due to the ready reversibility of this reaction (eq 1), but the possibility of product isolation increases considerably if the reaction becomes an intramolecular addition of a carbon-centered radical to an aldehydo or keto group to give a radical centered on an oxygen atom that is attached to a five- or six-membered ring.

An example of such a reaction is shown in Scheme 1, where the carbon-centered radical 2, generated from 6-bromohexanal (1), is converted reversibly into the cyclic alkoxy radical 3.
Hydrogen-atom abstraction by 3 from tri-n-butyltin hydride has a substantially larger rate constant than that for abstraction by 2; consequently, even though ring opening is more rapid than ring closure, reaction produces cyclohexanol as the major product and hexanal as a minor one.

Scheme 2

Intramolecular hydrogen-atom abstraction from the aldehyde group in 2 is a very minor process. The inability of this abstraction to compete with ring formation in a noncarbohydrate system is echoed in the reactions of carbohydrate radicals containing aldehyde groups. The reaction shown in Scheme 2 is one of several discussed in this chapter where hydrogen-atom abstraction from an aldehyde group is possible but does not take place.2

Even though ring opening always is a possibility for cyclic alkoxy radicals, this transformation sometimes does not take place; for example, the reaction producing the alkoxy radical 5 from the ring-open radical 4 is not reversible (Scheme 2).2,3 Failure of the cyclohexane ring in 5 to open is demonstrated by reaction of the nitrate ester 9 (Scheme 3).3 Treatment of 9 with Bu₃SnH pro-
duces 5 (and ultimately the product 7) but ring opening to give 4 does not happen. If the ring-open radical 4 were formed, the product 8 also would be produced in this reaction, but since no 8 could be detected, the conclusion is that the alkoxy radical 5 does not undergo ring opening.

![Scheme 3]

In contrast to cyclization of the aldehydo radical 4 (Scheme 2) the closely related keto radical 11 (Scheme 4) does not form a new ring system. Either the greater steric hindrance inherent in producing a tertiary alkoxy radical or rapid ring opening of such a strained intermediate or both are sufficient to prevent 11 from forming a new ring system. These reasons for failure to form a new ring draw support from the reactions of noncarbohydrate radicals 13 and 14 (Scheme 5). In the reaction shown in Scheme 5 where R is a methyl group, hydrogen-atom abstraction from tri-n-butyltin hydride is done exclusively by the open-chain radical 13. When R is a hydrogen atom, abstraction from Bu3SnH occurs only after conversion of the open-chain radical 12 into the cyclic alkoxy radical 14.

The reactivates of the aldehydo radical 4 (Scheme 2) and the keto radical 11 (Scheme 4) raise a number of questions (listed below) about participation of keto and aldehydo groups in radical cyclization reactions. Many of these questions have been answered by study of related compounds. Their answers provide insight into the factors that control the cyclization process. These questions and their answers are:
1. Is cyclization restricted only to aldehydes? The reaction of the ketone 16 to give the tertiary alcohol 17 shows that internal radical addition to a keto group can take place (Scheme 6).  

2. What size rings can be formed from internal radical addition to carbonyl groups? The reactions shown in Schemes 3 and 6 document the formation of five- and six-membered
rings. When the reaction shown in eq 5 is added to this pair, it indicates that formation of a product with a seven-membered ring, the next most probable ring structure, is too slow to be observable. Although firm conclusions cannot be drawn from these limited data, the possibility of forming a seven-membered or larger ring by internal addition to an aldehydo or keto group by a carbohydrate radical does not appear to be promising.

3. Are there aldehydes for which cyclization is possible but does not take place? Although there are many carbohydrate aldehydes for which radical cyclization occurs, the iodoaldehyde 18 fails to cyclize even though it produces a radical in which the radical center and the carbonyl carbon atom of the aldehydo group are 1,6-related (eq 6). Other factors (e.g., ring strain) must be preventing cyclization in this instance.
4. Are primary radicals needed for cyclization to take place? Among the reactions discussed thus far, the radicals adding to carbonyl groups all have been primary. The high reactivity and low steric requirements of these radicals make them well-suited for this type of reaction. Also, ring opening of a cyclic radical to regenerate a primary radical should be suppressed by the difficulty in forming this highly reactive species. Nonprimary radicals, however, do add to aldehydo groups. One might expect that other reactive radicals, such as vinyl radicals, would be good candidates for cyclization reactions. This expectation is fulfilled by the reaction shown in Scheme 7. Even secondary radicals can add internally to aldehydo groups (Scheme 8).

Scheme 7

5. Does complexation with a Lewis acid affect carbonyl group reactivity? The reaction shown in eq 7 illustrates the influence that a Lewis acid can have on radical addition to a carbonyl group. When Et3B complexes with such a group, it renders the already electron-deficient, carbonyl carbon atom even more so and, as a result, increases its rate of reaction with a nucleophilic, carbon-centered radical.

6. What factors affect radical cyclization of aldehydes and ketones? Anything that destabilizes a cyclic alkoxy radical or makes its formation more difficult will reduce or even prevent appearance of a product with a new ring system. Such factors include
forming a hindered alkoxy radical, creating a strained ring system, and forming a ring system that reopens to give a more stable radical.

III. Migration of Aldehydo Groups

A possible fate for an alkoxy radical formed by cyclization is ring opening to produce a radical different from the one that initially formed the ring. A new direction in ring opening is likely if it produces a more stable radical. In the reaction shown in Scheme 8 such a situation exists. Ring opening of the alkoxy radical 20 gives the resonance-stabilized, benzylic radical 21 rather than the unstabilized radical 19 that reacted to produce the ring system. This alternative
ring opening ($20 \rightarrow 21$) completes an addition-fragmentation sequence that causes migration of the aldehydo group.

IV. Addition of Tin- and Silicon-Centered Radicals to Aldehydes

Although the reactions discussed thus far have involved addition of carbon-centered radicals to carbonyl groups, other types of radicals, including tin- and silicon-centered ones, also add to
aldehydes and ketones. Reaction of the tri-\textit{n}-butyltin radical with a carbonyl group generates a tin ketyl, a radical with considerable negative charge on the oxygen atom. As the reaction in Scheme 9\textsuperscript{18} shows, tin ketyls undergo internal radical addition to electron-deficient, C–C multiple bonds.\textsuperscript{18-22} These ketylts also react with C–N double bonds,\textsuperscript{23} and they produce pinacols upon addition to carbonyl groups (eq 8).\textsuperscript{24} Internal addition also can occur when a silicon-centered radical adds to an aldehydo group, as happens in the reaction shown in eq 9.\textsuperscript{25}

![Scheme 9](image)

**Scheme 9**

V. Reaction of Samarium(II) Iodide with Aldehydes and Ketones

Reaction of an aldehyde or ketone with samarium(II) iodide produces a samarium ketyl.\textsuperscript{26-39} These ketylts add intramolecularly to appropriately positioned carbon–carbon\textsuperscript{25-33} (Scheme 10)\textsuperscript{26} and carbon–nitrogen\textsuperscript{34-37} (eq 10)\textsuperscript{34} double bonds. Such reactions are reminiscent of the addition of typical carbon-centered radicals to multiple bonds.

When samarium(II) iodide reacts with compounds containing two aldehydo groups, the first is converted into a samarium ketyl that then adds to the second. This addition depends upon proper separation between the reacting groups,\textsuperscript{40-53} accordingly, pinacols with five-membered\textsuperscript{40,49-53} (eq 11)\textsuperscript{40} and six-membered\textsuperscript{41-48} (eq 12)\textsuperscript{41} rings form easily. It is not necessary for both
interacting groups in a molecule to be aldehydo groups; pinacols also arise when one \(^{49-52}\) (eq 13, \(R = H\)) \(^{49}\) or both (eq 13, \(R = \text{CH}_2\text{SiMe}_2\text{C}_6\text{H}_5\)) \(^{53}\) are keto groups. Complexation of the ketyl and carbonyl oxygen atoms with SmI\(_2\) forces a cis relation between the hydroxyl groups in the products (Scheme 11). \(^{42}\) Pinacol formation and other reactions of aldehydes and ketones with samarium(II) iodide is revisited in Chapter 19, where a broader discussion of the interaction of SmI\(_2\) with carbohydrate derivatives takes place.

### VI. Ketone Photolysis

#### A. \(\alpha\)-Cleavage Reactions

When photolysis of ketones causes homolytic cleavage of a bond between the carbonyl group and one of the \(\alpha\) carbon atoms, either a pair of radicals or a diradical forms. (Such a reaction is known as an \(\alpha\)-cleavage or Norrish Type I reaction.) \(\alpha\)-Cleavage of simple ketones does not take place in solution, although it does occur in the gas phase. Cleavage in solution happens only when stabilized radicals are produced. This means that the reaction shown in eq 3 is successful for nonvolatile compounds such as carbohydrates only when the radical center in \(R^+\) is stabilized in some way (e.g., by having an oxygen or nitrogen atom attached). Most carbohydrates that contain
a keto group will have at least one pathway for forming an oxygen-stabilized radical by α-cleavage.\textsuperscript{54}

\begin{equation}
\text{BnO} \ 
\begin{array}{c}
\text{CHO} \\
\text{BnO} \ 
\text{CHO} \\
\text{OR} \\
\end{array} 
\xrightarrow{\text{SmI}_2} 
\text{BnO} \ 
\begin{array}{c}
\text{CHO} \\
\text{OH} \\
\text{OR} \\
\end{array} 
\quad \quad (12)
\end{equation}

\begin{align*}
R &= \text{SiMe}_2\text{-Bu} \\
42\%
\end{align*}

When the keto group in a carbohydrate is not part of a ring system, α-cleavage produces a radical pair. Most reactions of this type involve derivatives of nucleosides, nucleotides, or oligonucleotides.\textsuperscript{55–67} Scheme 12 describes such a reaction, one in which the nucleoside member (22) of the radical pair produced by α-cleavage undergoes two characteristic radical reactions, namely, hydrogen-atom abstraction (when an effective donor, such as a thiol, is present) and addition of O\textsubscript{2} (when molecular oxygen is one of the reactants).\textsuperscript{61}
Although α-cleavage in nucleotides produces radicals that undergo typical radical reactions, such as those shown in Scheme 12, many of these radicals also undergo a heterolytic cleavage to form radical cations and phosphate anions. An example of such a reaction is shown in Scheme 13, where the radical 23 cleaves its C-3′–O bond to generate the radical cation 24 and a phosphate anion. (Radical-cation formation of the type shown in Scheme 13 also is discussed in Section III of Chapter 9.)

α-Cleavage in a cyclic ketone, a reaction that occurs in many carbohydrates, is an internal process that produces a diradical. Diradicals of this type usually reform a ring system, but often after the loss of carbon monoxide. Scheme 14 describes formation of the diradical 25, a reaction that is followed by loss of carbon monoxide to give a second diradical, one that produces a new ring system by radical combination. The α-cleavage shown in Scheme 14 is driven, at least in part, by transition-state stabilization due to the developing radical center at C-6 being stabilized by an attached oxygen atom.
B. Hydrogen-Atom Abstraction Reactions

Ketones that do not undergo $\alpha$-cleavage have another option for diradical formation, namely, internal abstraction that occurs when a hydrogen atom comes with bonding distance of an excited
carbonyl group; thus, in the reaction is shown in Scheme 15, 1,6-hydrogen-atom abstraction produces a diradical that then forms a spiro compound by radical combination.\textsuperscript{70} If a 1,5-hydrogen-atom transfer takes place, the resulting 1,4-diradical fragments as shown in Scheme 16.\textsuperscript{71} (Many carbohyrates undergo this type of reaction, which is known as a Norrish Type II process.\textsuperscript{72})

\begin{center}
Scheme 15
\end{center}

\begin{center}
Scheme 16
\end{center}

If an excited ketone does not undergo internal abstraction or $\alpha$-cleavage, hydrogen-atom abstraction from another molecule sometimes takes place.\textsuperscript{73} Such abstraction requires a transition state in which there is considerable radical stabilization. Hydrogen-atom abstraction by excited benzophenone from the benzylidene acetal 26 meets this requirement by producing the highly stabilized radical 27 (Scheme 17).\textsuperscript{74} Radical combination completes this reaction.
Scheme 17

\[
(C_6H_5)_2C=O \xrightarrow{hv} (C_6H_5)_2C=O^*
\]

\[
(C_6H_5)_2C=O^* + \begin{array}{c}
\text{H} \\
\text{C}_6\text{H}_5
\end{array}
\xrightarrow{\text{AcO}} \begin{array}{c}
\text{O} \\
\text{Ac}
\end{array} \xrightarrow{\text{O}} \begin{array}{c}
\text{O} \\
\text{Ac}
\end{array}
\]

38%

Scheme 18

\[
\text{BnO} - \text{Br} \xrightarrow{\text{Bu}_3\text{Sn}} \text{O} \xrightarrow{\text{Bu}_3\text{Sn}} \text{Si}(C_6H_5)_2\text{Me} \\
\text{O} \xrightarrow{\text{Bu}_3\text{Sn}} \text{Si}(C_6H_5)_2\text{Me} \\
\text{Br} \xrightarrow{\text{Bu}_3\text{Sn}} \text{H} \xrightarrow{\text{Bu}_3\text{Sn}} \text{Si}(C_6H_5)_2\text{Me} \\
\text{O} \xrightarrow{\text{Bu}_3\text{Sn}} \text{Si}(C_6H_5)_2\text{Me}
\]

56% + 20%
VII. Cyclization of Acylsilanes

Acylsilanes undergo radical cyclization that involves addition of a carbon-centered radical to the carbonyl carbon atom in the acylsilyl group (Scheme 18). This reaction is unusual in that migration of the silyl group to the radical center on oxygen stops reaction that would reverse ring formation.

VIII. Reactions of α-Acyloxyketones

α-Acyloxyketones are compounds that undergo replacement of the acyloxy group with a hydrogen atom upon reaction with tri-n-butylin hydride. Reactions of these compounds are discussed in Section II.A of Chapter 8 along with other reactions of carboxylic acid esters.

IX. Summary

Aldehyde and keto groups in carbohydrates react internally with carbon-centered radicals to form cyclic alkoxy radicals. Most of these reactions involve aldehydes; both five- and six-membered rings can be formed. When ring opening of the newly formed alkoxy radical takes place, it does so to produce the more stable of the two possible, carbon-centered radicals. Such ring opening can be part of a process that causes aldehyde group migration.

Tin-centered radicals add to aldehydes to generate tin ketylts, intermediates that can add to multiple bonds. Samarium ketylts, more common than their tin counterparts, undergo similar reaction. Reaction of samarium(II) iodide with carbohydrates containing two appropriately placed aldehyde groups converts one group to a ketyl that then adds to the second in route to formation of a pinacol.

Ketone photolysis forms carbon-centered radicals by breaking the bond between the carbonyl carbon atom and one of the α carbon atoms (an α-cleavage). Typical radical reactions then take place; in addition, α-cleavage in some nucleotides and oligonucleotides is followed by radical cation formation. α-Cleavage and hydrogen-atom abstraction take place in cyclic ketones to produce diradicals.

X. References