Although oxygen-centered radicals are not formed in significant number by direct hydrogen-atom abstraction from carbohydrates, these radicals can be produced indirectly in high yield from carbohydrate derivatives. Since such radicals are capable of internal reaction, intramolecular abstraction provides a pathway for oxygen-centered radicals to produce specific, carbon-centered radicals and, in so doing, to participate in synthetically useful reactions. (Alkoxy and alkoxyl are both terms used in describing oxygen-centered radicals derived from alcohols. The alkoxy designation will be used here.)

A. Alkoxy Radical Precursors

The first step in forming an alkoxy radical from a partially protected carbohydrate is to synthesize an appropriate precursor. Carbohydrate hypoiodites, nitrates, and phthalimides are all effective in this role. Hypoiodites are too unstable to be isolated, although they have been observed by NMR spectroscopy. Nitrates and phthalimides are stable enough to be isolated and characterized.

1. Hypoiodites

Hydrogen-atom abstraction from carbohydrates often is done by alkoxy radicals that are formed from photochemical or thermal hypoiodite decomposition (eq 1). Traditional approaches to preparing hypoiodites call for reaction of partially protected carbohydrates with mercury(II) oxide–iodine\(^{1–3}\) or with lead(IV) acetate–iodine.\(^{1,3,4}\) The hypoiodites formed from these reactions are converted under the reaction conditions into alkoxy radicals and iodine atoms.

\[
\text{ROI} \xrightarrow{hv \text{ or } \Delta} \text{RO}^\bullet + \text{I}^\bullet \quad (1)
\]

More recent procedures for hypoiodite synthesis avoid compounds containing heavy metals. One approach uses acetyl hypoiodite, prepared from reaction of (diacetoxyiodo)benzene with iodine (eq 2), to convert an unprotected hydroxyl group into the corresponding hypoiodite (eq 3).\(^5,6\) Other reagents or reagent combinations that produce hypoiodites include \(N\)-iodosuccinimide,\(^5\) diphenylhydroxyselenium acetate–iodine,\(^7–10\) and iodosylbenzene–iodine.\(^11–13\) Where carbohydrates are concerned, however, (diacetoxyiodo)benzene–iodine is used most often.\(^4,8–10,14–28\)

\[
\text{C}_6\text{H}_5\text{I}(\text{OAc})_2 + I_2 \rightarrow 2 \text{CH}_3\text{COI} + \text{C}_6\text{H}_5\text{I} \quad (2)
\]

\[
\text{CH}_3\text{COI} + \text{ROH} \rightarrow \text{CH}_3\text{CH} + \text{ROI} \quad (3)
\]

2. Nitrates

Carbohydrate nitrates offer another option for forming alkoxy radicals. These compounds are prepared by reaction of partially protected carbohydrates with acetyl nitrate (eq 4)\(^29,30\) or by displacement of a nucleofuge from a carbohydrate derivative by the nitrate anion (eq 5).\(^30\) Alkoxy radicals form from carbohydrate nitrates by photolysis (eq 6)\(^30–32\) or by reaction with the tri-\(n\)-butyltin radical (eq 7).\(^33\)
3. Phthalimides

An alkoxy radical forms when an \( N \)-alkoxyphthalimide reacts with the tri-\( n \)-butyltin radical (Scheme 2).\(^{34} \) This type of reaction produces a variety of alkoxy radicals from phthalimide derivatives of carbohydrates.\(^{26,35–38} \) These derivatives are synthesized by reaction of partially protected carbohydrates with \( N \)-hydroxyphthalimide under Mitsunobu conditions (eq 8).\(^{34} \) A comparative study shows that the greater stability of \( N \)-alkoxyphthalimides makes them a better choice than nitrates for generating alkoxy radicals.\(^{38} \)

![Scheme 2](image)

B. Alkoxy Radical Reactions

1. Internal Hydrogen-atom abstraction

Intramolecular hydrogen-atom abstraction by an alkoxy radical is the first step in a variety of reactions useful in carbohydrate synthesis. These include formation of new ring systems,\(^{1,2,4,5,8,9,20,21} \) epimerization at chiral centers,\(^{4,39,40} \) incorporation of deuterium,\(^{39–42} \) and introducing new carbon–carbon double bonds.\(^{40–43} \) Internal reaction is attractive because even though alkoxy radicals are capable of abstracting most hydrogen atoms present in a typical molecule,\(^{44} \) internal reaction limits the number of possibilities and, in so doing permits hydrogen-atom abstraction to become part of synthetically useful transformations.
a. Transition-State Ring Size

(1). Six-Membered Rings

Because a six-membered-ring transition state usually minimizes ring strain, it is the most common arrangement for internal transfer of a hydrogen atom to an oxygen-centered radical; for example, the reaction shown in Scheme 3 begins with the alkoxy radical 1 internally transferring a hydrogen atom (H_a) via a six-membered-ring transition state (2) to produce the carbon-centered radical 3.\(^{23}\) [1,5-Hydrogen-atom transfer (1,5-HAT) and 1,5-radical translocation are both terms used to describe the conversion of 1 into 3.] Transformation of 3 into the corresponding iodide 4 ends the radical phase of the reaction, but the overall process continues when 4 ionizes to produce the cation 5, an intermediate that then completes the reaction by forming a new ring.

The possibility of 1,5-hydrogen-atom transfer does not insure that a particular abstraction will take place; rather, it indicates that such abstraction is likely unless some factor (e.g., a structural constraint) raises the energy for the transfer process. In the reaction shown in Scheme 3 the transition states for abstraction of H_a and H_b in compound 1 each involve a six-membered ring, but abstraction of H_b does not take place because the radical formed by abstracting the bridgehead hydrogen atom (H_b) from the [3.3.0] bicyclic system cannot easily adopt a planar or nearly planar configuration; that is, it cannot adopt the most stable configuration for an unrestricted, C-centered radical.\(^{23}\) The inability to move significantly toward the most stable configuration during radical formation is reflected in higher transition-state energy for H_b abstraction when compared to abstraction of H_a.

(2). Seven-Membered and Larger Rings

Forming a six-membered-ring transition state is not always possible during hydrogen-atom abstraction because sometimes the structure of a radical makes close approach of 1,6-related atoms too energetically demanding. This is the case in the reaction shown in Scheme 4, where H-1 and H-3 in the alkoxy radical 7 are 1,6-related to the radical center.
on oxygen, but because they are on opposite sides of the pyranoid ring, they do not come within bonding distance. The best option for hydrogen-atom abstraction in this case is via a seven-membered-ring transition state. In other radicals close approach of the reacting atoms can lead to hydrogen-atom abstraction via transition states with rings containing even more than seven members.35–37

The reaction shown in Scheme 5 is one in which the stability of the developing radical and the transition-state ring size compete for control of the reaction. On the basis of ring size the radical 8, which forms through a six-membered-ring transition state, should be produced more rapidly than the radical 9 (seven-membered-ring transition state), but if radical stability is the primary factor, 9 should form more readily. The result is that neither influence prevails; substantial yields of both products 10 (61%) and 11 (32%) are produced.36
b. Polarity Matching Between Reacting Atoms

Scheme 6 describes a reaction in which polarity matching affects the transition-state energy for hydrogen-atom transfer. In this reaction the alkoxy radical 13 internally transfers a hydrogen atom via a seven-membered-ring transition state even though a six-membered one is possible. The hydrogen atom that would be involved in the six-membered-ring transition state is less electron-rich than the one that actually is transferred; thus, the more electron-rich hydrogen atom is abstracted by the electrophilic oxygen atom bearing the radical center even though a normally less stable, seven-membered-ring transition state is involved.
A different, perhaps more striking, example of the importance of polarity matching during hydrogen-atom abstraction comes from comparing the reaction shown in eq 9 with that in eq 10. In each of these reactions two hydrogen atoms come within bonding distance of an electrophilic radical center on an oxygen atom. In the reaction shown in eq 9 the major product (15) forms via a six-membered-ring transition state and the minor product (16) arises from a seven-membered one. In compound 17 (eq 10) where the electron-withdrawing capacity of the protecting groups is greater than that in compound 14, H_b is affected more that H_a. Decreased electron density at H_b reduces its ability to react with an oxygen-centered radical to the point that only abstraction of H_a takes place; thus, the change in electron density causes reaction to occur entirely through an otherwise less favorable, seven-membered-ring transition state.
2. β-Fragmentation

In addition to hydrogen-atom abstraction, the other major reaction pathway for alkoxy radicals is β-fragmentation. When an alkoxy radical fragments, it produces a carbonyl group and a carbon-centered radical.\(^\text{38,45–48}\) If the oxygen atom in an alkoxy radical is not attached to a ring, β fragmentation breaks the radical into two parts (eq 11).\(^\text{49}\) If the oxygen atom is attached to a ring, fragmentation leads to an open-chain structure (Scheme 7).\(^\text{38,45,47,48}\) Sometimes rapid ring closure reforms the ring and regenerates an alkoxy radical (Scheme 8).\(^\text{33a}\) If ring closure regenerates the starting alkoxy radical, the process will go unnoticed, but in some reactions, such as the one shown in Scheme 8, epimerization, in this case at C-3, provides evidence for the fleeting existence of a ring-open radical.
3. Cyclization

An example of a cyclization reaction involving an alkoxy radical adding to a double bond is shown in eq 12.\(^{50}\) This type of reaction is rare because alkoxy radicals undergo either hydrogen-atom abstraction or radical fragmentation so readily. A significant factor in ring formation in this instance is having the oxygen atom bearing the radical center held in close proximity to the double bond.

4. Reactions of Carbon-Centered Radicals Produced From Alkoxy Radicals

Internal hydrogen-atom abstraction by an alkoxy radical to produce a carbon-centered radical often is followed by a second abstraction reaction. In this second reaction an iodine atom or hydrogen atom is transferred to the radical center on carbon. Although hydrogen-atom abstraction by an alkoxy radical usually is an internal (unimolecular) process, iodine-atom or hydrogen-atom abstraction by the resulting carbon-centered radical typically is bimolecular.

a. Iodine-Atom Abstraction or Capture

Examples of iodine-atom abstraction are found in the reactions shown in Schemes 3, 4, and 6. The reaction shown in Scheme 3 presents several ways in which the carbon-centered radical 3 can be converted into the corresponding iodide (4). The simplest of these is radical combination with an iodine atom produced during hypoiodite decomposition (eq 13).\(^{51}\) Another is by reaction of 3 with the I\(_2\) present in the reaction mixture (eq 14).\(^{52}\) A third involves abstraction of an iodine atom from a molecule of hypoiodite (eq 15).\(^{5,51}\) All of these reactions may be taking place or, as described in the next paragraph, a reaction is possible that does not involve iodide formation.

\[
\begin{align*}
R\cdot + I\cdot & \rightarrow RI \quad (13) \\
R\cdot + I_2 & \rightarrow RI + I\cdot \quad (14)
\end{align*}
\]
The mechanism shown in Scheme 3 includes the possibility that the radical 3 does not form a carbohydrate iodide at all but rather is oxidized by (diacetoxyiodo)benzene to the cation 5. Consistent with this pathway is the fact that in most reactions no carbohydrate iodide is isolated; however, lack of iodide isolation is not definitive because most such iodides (e.g., 4) would be expected to ionize to resonance stabilized cations (e.g., 5) so easily that no carbohydrate iodide would remain at the end of the reaction. Supporting iodide intermediacy is the observation that in reactions where cation formation is more difficult, iodides are isolated. Also favoring iodide intermediates is the fact that molecular iodine is present in the reaction mixture when (diacetoxyiodo)benzene is used, and reaction of I$_2$ with a carbon-centered radical is extremely rapid. [Iodine-atom abstraction from I$_2$ by the cyclohexyl radical takes place at or near diffusion control (k = 1.2 x 10$^{10}$ M$^{-1}$s$^{-1}$).]

b. Hydrogen-Atom Abstraction

When the reaction that follows internal hydrogen-atom abstraction in an alkoxy radical is an abstraction from a donor such as Bu$_3$SnH, it is not always possible to tell from the product structure that this second reaction has taken place. Often it is necessary to replace Bu$_3$SnH with Bu$_3$SnD in order to detect the second abstraction. For example, in the reaction shown in eq 16, internal abstraction of H-3 only becomes detectable when deuterium is incorporated at C-3 in the product. In the reaction shown in Scheme 5 epimerization provides evidence that 1,6-hydrogen-atom abstraction occurred during formation of compound 11. This abstraction is confirmed by deuterium incorporation, but since no epimerization takes place in the formation of compound 10, evidence that a 1,5-hydrogen-atom abstraction has occurred depends solely on deuterium incorporation.

c. Fragmentation of a Bond to a Substituent Group

When hydrogen-atom abstraction by an alkoxy radical produces a carbon-centered radical, loss of a substituent on an adjacent carbon atom becomes a possibility. Such a loss is likely if, as occurs in the reactions shown in Schemes 9 and 10, a carbon–sulfur or carbon–halogen (not fluorine) bond is being broken. In the reaction shown in Scheme 10 rapid, non-radical elimination of the nitrogenous base (BH) follows β-fragmentation and gives the α,β-unsaturated ketone.
Since the chloride 18 (Scheme 10)\textsuperscript{40} and the tosylate 21\textsuperscript{40,59} (Scheme 11) react to produce the same unsaturated ketone (20), it is reasonable to expect that the same mechanism is operative in both reactions; however, when Bu\textsubscript{3}SnD replaces Bu\textsubscript{3}SnH in these reactions, it becomes clear that they follow different pathways. The mechanism proposed in Scheme 10 adequately explains the lack of deuterium incorporation during conversion of 18 into 20, but the presence of deuterium in the product 20 when 21 reacts requires a different mechanism.
The mechanism shown in Scheme 11 rationalizes deuterium incorporation during reaction of the tosylate 21 by proposing formation of the radical 23, an intermediate that abstracts a deuterium atom from Bu₃SnD on route to the ketone 20. Two possible pathways leading to 23 are pictured in Scheme 11. One of these is a concerted loss of TsOH from 22, and the other is a stepwise process in which the acidic, α-hydroxy radical 22 deprotonates to give the radical anion 24, an intermediate that rapidly eliminates the tosylate anion.

The intermediacy of the radical anion 24 in the mechanism proposed in Scheme 11 draws support from the related reaction shown in Scheme 12. In the reaction in Scheme 12 the radical anion 26 forms when acetate ion abstracts a proton from the radical 25. Deprotonation by acetate ion is possible in this instance due to the considerable increase in acidity of a hydroxyl group attached to a carbon-centered radical. Proton loss is the rate-determining step in this general-base-catalyzed reaction (Scheme 12).
If the radical anion 24 forms in the reaction shown in Scheme 11, it must do so in the absence of a base such as acetate ion, but the reaction shown in Scheme 13 indicates that radical anion formation depends upon the presence of a proton-abstracting base. Even though internal hydrogen-atom abstraction in the radical 27 produces the required precursor 28 (i.e., a carbon-centered radical with a hydroxyl group attached), deprotonation to form a radical anion does not take place. Deuterium incorporation in the product 29 demonstrate that the radical 28 is produced; however, not only does 28 fail to deprotonate but it also fails to undergo β-fragmentation analogous to that taking place in the reactions shown in Schemes 9 and 10. β-Fragmentation that breaks a carbon–oxygen bond to produce the hydroxyl radical is too energy demanding to be observed.

d. Radical Addition

Although a carbon-centered radical produced by internal hydrogen-atom abstraction in an alkoxy radical is capable of adding to a compound with a carbon–carbon multiple bond, such reactions involving carbohydrates are rare. Part of the
reason for this is that when an alkoxy radical is generated from a hypoiodite, as is often the case, addition of the carbon-centered radical (formed by internal hydrogen-atom abstraction) to an unsaturated compound has difficulty competing with reaction of this radical with I-, I2, or RC(=O)OI. Addition of a carbon-centered radical is far more competitive when its alkoxy radical precursor is a nitrate.62,63 For example, the addition of the carbon-centered radical 30 (Scheme 14) to acrylonitrile is possible, in part, because the precursor alkoxy radical is generated from a carbohydrate nitrate.63

Contributors

Roger W. Binkley (Cleveland State University) and Edith R. Binkley (Cleveland Heights-University Heights school system)