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.\[^1\] 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.

Intramolecular hydrogen-atom abstraction from the aldehydo 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 aldehydo groups. The reaction shown in Scheme 2 is one of several discussed in this chapter where hydrogen-atom abstraction from an aldehydo 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). Failure of the cyclohexane ring in 5 to open is demonstrated by reaction of the nitrate ester 9 (Scheme 3). Treatment of 9 with Bu$_3$SnH produces 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.
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 reactives 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,

\[ \text{81%} \]

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).

\[ \text{no cyclic product} \]
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 aldehyde 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.\textsuperscript{11} Even secondary radicals can add internally to aldehydo groups (Scheme 8).
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.
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