Chemoselectivity, regioselectivity, and stereoselectivity are defining characteristics of radical reactions. Nowhere are they more important (particularly the latter two) than when a new ring is being formed. Understandably then when regioselectivity and stereoselectivity were broached in Chapters 10 and 11, discussion often turned to cyclization reactions. Some of the ideas and topics from these chapters are revisited here but now with an exclusive focus on their importance to new ring formation.

A. Chemoselectivity

Chemoselectivity enters into consideration at two places in radical cyclization reactions. The first is during radical formation, where it determines which atom or group in a molecule will react to form the radical that adds to a multiple bond. Chemoselectivity next is of consequence when a newly formed radical has the possibility of adding to more than one multiple bond. In the reaction shown in eq 4, for example, halogen-atom abstraction from the bromide 1 produces a radical that can add to either of two double bonds. Addition to one produces a five-membered ring while reaction with the other forms a six-membered ring. Although these two bonds are comparable in reactivity, the product with the five-membered ring forms more rapidly. (The reasons for usually forming a product with a five-membered ring are discussed in the next section.) If, however, the double bond for which reaction produces a six-membered ring, is decidedly more reactive (i.e., substantially more electron-deficient), as is the case in compound 2 (eq 5), the chemoselectivity of the cyclization process changes, and only the product with the larger ring forms. 6,7

![Chemoselectivity Diagram](image1.png)

B. Regioselectivity

Radical cyclization is nearly always a kinetically controlled process. Kinetic control often leads to regiospecific formation of the less stable cyclic radical. In the reaction shown in Scheme 1, for example, even though cyclization to give a six-membered ring is possible and would generate a more stable radical, the only reaction pathway followed leads to the smaller ring and the less stable radical. The reaction shown in Scheme 2, where the primary radical 3 forms in preference
to the tertiary radical 4, provides a particularly striking example of a kinetically controlled, radical cyclization.\(^{10}\)

There are cyclization reactions that take place under thermodynamic control when the proper conditions are met. In the reaction shown in eq 6 the major product contains a six-membered ring, when reaction is conducted in dilute Bu\(_3\)SnH solution,\(^{11}\) but at high Bu\(_3\)SnH concentration reaction regioselectivity changes to give a product with a five-membered ring.\(^{11,12}\) This concentration dependence can be explained by the more rapidly formed, but less stable, radical 5 having sufficient time and energy, when the concentration of Bu\(_3\)SnH is low, to be converted into the more stable radical 6, either by a rearrangement that involves a cyclic transition state or by a fragmentation-addition sequence (Scheme 3).\(^{13}\) At high Bu\(_3\)SnH concentration hydrogen-atom abstraction occurs before ring expansion can take place.
1. Five-Membered Versus Six-Membered Ring Formation

a. Five-Membered Rings

If a radical center and a multiple bond in a molecule are situated so that either a five- or six-membered ring is possible, the smaller ring generally will form. The reason for producing the smaller ring is that the strain engendered in reaching the transition state leading to a six-membered ring is greater than that necessary for forming a ring with five members. Both chair-like and boat-like transition-states are possible during five-membered-ring formation.
(Scheme 5). For the unsubstituted 5-hexenyl radical the chair-like transition state is calculated to be lower in energy than its boat-like counterpart, but only slightly so.\textsuperscript{16} (The “flagpole” and eclipsing interactions that contribute to making the boat conformation of cyclohexane much less stable than the chair conformation are not as severe in the boat-like transition state for radical cyclization.) Both transition states (boat-like and chair-like) leading to a five-membered ring (Scheme 5) are calculated to be lower in energy than any transition states leading to a six-membered ring. These calculations match well the experimental observation that cyclization of the 5-hexenyl radical gives a five-membered ring in a highly regioselective fashion (eq 7, R = H).\textsuperscript{14,20} They also are consistent with the reactions shown in Schemes 1 and 2, where five-membered rings form in preference to six-membered ones.
The greater ease of formation of five-membered rings when compared to six-membered ones is illustrated in a quantitative fashion by the approximately fifty-fold difference in rate constants for cyclization of the 5-hexenyl (eq 8) and 6-heptenyl (eq 9) radicals. A qualitative example of this type of difference in reactivity involving a pair of carbohydrates is found in the reactions shown in equations 10 and 11, where formation of a five-membered ring occurs in the normal manner, but cyclization to give a six-membered ring does not take place rapidly enough to compete with simple reduction.
b. Six-Membered Rings

Six-membered-ring formation takes place when structural features in a radical inhibit forming a five-membered ring. Possible inhibiting factors include: a) greater ring strain at the transition state for forming a five-membered ring as opposed to a six-membered one; b) steric hindrance that is sufficient to make bonding difficult at the carbon atom of the multiple bond needed to form a five-membered ring; c) structure and reactivity associated with the radical center that favors six-membered-ring formation.22

Reactions of the phenyl thionocarbonates 7 and 9 illustrate the importance of ring strain in determining the size of a ring being formed by radical cyclization. Compound 7 undergoes the expected cyclization to give a product (8) with a five-membered ring (eq 12), but similar reaction of 9 forms only a compound (10) with a six-membered ring (eq 13).22 Reaction producing the larger ring does so because forming a five-membered ring would introduce the substantial strain at the transition state inherent in a reaction leading to a product (11) with a pair of trans-fused, five-membered rings.

Steric effects can have a powerful, modifying influence on the cyclization of simple organic radicals; thus, the 5-hexenyl radical preferentially forms a five-member ring (eq 7, R = H), but 5-methyl-5-hexenyl radical, more hindered at C-5, regioselectivity generates a product with a six-membered ring (eq 7, R = CH₃).14,16 Steric effects do not exercise the control shown in eq 7 in determining ring size in the cyclization reaction pictured in eq 12, where the C-5 substituents do not force formation of any product with a new six-membered ring; in fact, study of 7 and similar compounds shows that the steric effects associated with C-5 substitution are unable, by themselves, to promote any six-membered-ring formation.22

Clear examples of steric effects controlling radical cyclization in the reactions of carbohydrates are lacking, but the reactions shown in Scheme 6 suggest a steric component to regioselectivity. Formation of the spiro compound 15 takes place when R=CH₃ or OBz, but when R is a hydrogen atom, products 16 and 17 are formed (Scheme 6).23 One proposal is that larger substituents favor formation of the spironucleoside 15 by sterically hindering reaction at C-2′, but when the
C-2' substituent is a hydrogen atom, reaction takes place to form products 16 and 17, compounds with new six-membered rings. Regioselectivity in this reaction also could be explained by product-radical stability; that is, compound 15 forms only when the intermediate radical 12 has stabilizing substituents at C-2'.

The nature of the radical center also can have an effect on the regioselectivity of ring formation. The intermediate primary radical in the reaction shown in eq 12 forms a product with a new, five-membered ring, but the analogous vinylic radical cyclizes to form products with new six-membered rings (Scheme 7). The possibility exists that, as shown in Scheme 7, a five-membered ring does form, but it then rearranges to a more stable six-membered-ring radical. If such a transformation takes place, it would be reminiscent of the silyl-ether rearrangement pictured in Scheme 3.
2. Six-Membered Versus Seven-Membered Ring Formation

When constructed from carbon, nitrogen, and oxygen atoms, six-membered rings form more rapidly than seven-membered ones, but sometimes ring formation is not fast enough to prevent hydrogen-atom abstraction prior to cyclization. The reaction shown in eq 11 is one in which internal radical addition to a multiple that is not electron-deficient is too slow for ring formation to compete with simple reduction. In contrast, cyclization involving a similar double bond (i.e., one that also is not electron-deficient) does take place in the reaction shown in eq 3 because the rate of competing hydrogen-atom abstraction is reduced to an insignificant level by maintaining a low Bu₃SnH concentration during the reaction.⁵

As long as the only atoms in the ring are second row elements, radical cyclization typically produces a six-membered, rather than a seven-membered ring (eq 3). If an atom of the third-row element silicon is present, a seven-membered ring can be produced (eq 14).²⁴ This change in regioselectivity can be explained, at least in part, by longer bond lengths to silicon making approach of the radical center to the terminal carbon atom in the double bond the lower energy pathway.²⁵ Seven-membered ring formation depends upon the terminal carbon atom in the double bond being unsubstituted; otherwise, steric effects raise the transition-state energy sufficiently to favor formation of a six-membered ring.²⁵
3. Three- and Four-Membered Ring Formation

Forming a three-membered ring is not a promising beginning for radical cyclization because the strained, cyclic radical produced would open readily to its more stable, acyclic counterpart (eq 15). Although ring strain also hinders formation of products with four-membered rings, the lesser magnitude of the strain increases the possibility for isolating a cyclic product; thus, the reaction shown in Scheme 8 produces a compound with a four-membered ring. This reaction is kinetically controlled; otherwise, it would lead to a less strained, five-membered ring, one that contains an oxygen-stabilized radical.

Radical philicity, which often is a significant factor in determining regioselectivity in kinetically controlled reactions, rationalizes the direction of ring closure in the reaction shown in Scheme 8. The nucleophilic, carbon-centered radical adds to the electron-deficient, β-carbon atom in the α,β-unsaturated ester portion of the molecule. Frontier-orbital interactions, also useful in explaining kinetically controlled reactions, make the same prediction; that is, reaction should occur at the β carbon atom in an α,β-unsaturated ester (see Section II.B.2 of Chapter 18).

4. Seven-Membered and Larger Ring Formation

Radical cyclization can be surprisingly effective in forming rings with seven, eight, nine, ten, or
even eleven\textsuperscript{45} members. Generating these larger rings from carbohydrates often is associated with the linking together of two monosaccharide units by a tether containing silicon and oxygen atoms.\textsuperscript{31–36,37–42} An example of such a reaction is shown in Scheme 9, where cyclization produces an eight-membered ring.\textsuperscript{35} Although the most common method for joining a radical forming group and a multiple bond is by a silicon–oxygen tether, other connecting linkages are possible. These other tethers include phosphoramidic\textsuperscript{43} (nine-membered ring formed) and ketal\textsuperscript{46} (nine-membered ring formed) connectors, as well as bridging units consisting of pyranoid\textsuperscript{45} (eleven-membered ring formed) and furanoid\textsuperscript{37} (eight-membered ring formed) rings.

C. Stereoselectivity

1. Five-Membered Ring Formation

a. Chair-Like Transition States

Even though the complex substitution patterns present in many carbohydrates introduce a variety of possibilities for steric and polar interactions, the chair-like, transition-state model typically predicts the primary stereochemical outcome of a cyclization reaction forming a five-membered ring (Scheme 10).\textsuperscript{14,47,48} The lowest energy transition state for such a reaction has as many pseudoequatorial “ring substituents” as possible. An example is shown in Scheme 11,\textsuperscript{49} where if one assumes the reaction passes through a chair-like transition state that maximizes pseudoequatorial substituents, it is possible to explain the stereochemistry in the final product.
b. Boat-Like Transition States

Although chair-like, transition-state structures can be used to rationalize the stereoselectivity in most radical cyclization reactions, calculations indicate that boat-like structures should be included as possibilities. In the reaction shown in Scheme 12, for example, the minor product can be explained by invoking a boat-like transition state. With the structural complexity of carbohydrates and the general similarity in energies between boat-like and chair-like transition states, it is not surprising to find that the major stereoisomer in the cyclization reaction pictured in Scheme 13 appears to arise from a boat-like transition state.
c. Factors Affecting Transition-State Stability

(1.) Pseudo-1,3-Diaxial Interactions

In the reaction shown in Scheme 13 it is possible to identify a pseudo-1,3-diaxial interaction in the intermediate radical 19 and the associated, chair-like transition state 21. In the conformationally isomeric radical 18 and its associated, boat-like transition state 20 this destabilizing interaction is absent. The stereochemistry of the product from ring formation indicates that 1,3-diaxial interaction is the primary factor causing reaction to occur by the pathway passing through the boat-like transition state 20 (Scheme 13).
(2.) Allylic Strain

Another phenomenon that is credited with affecting transition-state stability is allylic strain, which can be defined in terms of the partial structures shown in eq 16.53 Conformation 23 is favored energetically over 22 because the destabilizing steric interaction between R1 and R3 in 22 is greater than the corresponding interaction between H and R3 in 23. Such interaction also affects the transition-state energies for reactions from these two conformers; thus, reaction occurs preferentially, sometimes exclusively, from 23. In the reaction shown in Scheme 14 allylic strain destabilizes conformation 24, but bond rotation to give conformer 25 relieves this strain.54,55 In a similar manner strain relief causes the reaction shown in Scheme 15 to occur primarily via a boat-like transition state derived from 26.54,55
(3.) Hydrogen Bonding$^{56,57}$

The energies of the transition states in the reactions shown in Scheme 16 depend upon whether R is a hydrogen atom or a trimethylsilyl group. When the trimethylsilyl group is in place, the chair-like transition state 28 is preferred because it places all substituents in pseudoequatorial positions.$^{56}$ If the trimethylsilyl groups are replaced by hydrogen atoms, a different, chair-like transition state (27), one that has two pseudoaxial substituents but is stabilized by hydrogen bonding, has lower energy. The reactions described in Scheme 16, therefore, illustrate the power of hydrogen bonding in influencing reaction stereoselectivity.
(4.) Conformation of an Existing Ring

The reactions shown in eq 17 illustrate the effect that the stereochemistry of a remote ring substituent can have on reaction stereoselectivity. It is unlikely that the C-4 benzyloxy groups in the radicals formed from the allyl ethers 29a and 29b are close enough to the radical center or the multiple bond to influence reaction directly. A more likely possibility is that substituent stereochemistry affects pyranoid-ring conformation in the intermediate radicals and that differences in conformation (or in the mixture of accessible conformations) determine reaction stereoselectivity. The idea that inversion of configuration at C-4 can change intermediate-radical conformation in these reactions (eq 17) is supported by the observation that other pyranos-1-yl radicals that are epimeric at C-4 adopt quite different radical conformations.
2. Six-Membered Ring Formation

Chair-like transitions states also provide a basis for understanding stereoselectivity in six-membered ring formation. In the cyclization reaction shown in Scheme 17, product formation can be explained by assuming that two chair-like transition states (30 and 31) are accessible during reaction. The difference in energy between these two depends primarily on steric interactions involving the CH₂CO₂CH₃ group. The transition state 31 with its pseudo-1,3-diaxial interaction would be expected to be higher in energy than the transition state 30, which avoids such interaction. The highly stereoselective formation of 32 is consistent with this proposed difference in transition-state energies (Scheme 17).

![Diagram of six-membered ring formation](image)

3. Seven-Membered and Larger Ring Formation

In the reaction shown in Scheme 18 the size of the t-butyldimethylsilyl groups causes the pyranoid ring in the phenyl selenide 34 to adopt a ¹⁴C₄ conformation. If this conformation is maintained during cyclization, as appears to be the case, radical addition to the vinyl group will occur exclusively from the α face of the pyranoid ring in the radical 35 to give, after hydrogen-atom abstraction, the cyclic silyl ether 36. When protection is provided by the less sterically demanding benzyl groups, more conformational flexibility exists in the pyranoid ring (⁴C₁ and ¹⁴C₄ interconvert more easily) and radical
addition occurs from either face of the ring system (Scheme 19).\textsuperscript{24,29b}
Further indications exist of the importance of radical conformation in forming rings with seven or more members. In the reaction shown in eq 18 the rigidity of the radical derived from the iodide 37 reduces the number of conformations possible but includes one that holds the radical center and the double bond in close enough proximity that cyclization gives the major product; in contrast, in the reaction shown in eq 19 the greater flexibility of the radical generated from the iodide 38 changes the opportunity for interaction between reactive centers to the point that a complex mixture of products is formed.\(^{61}\)
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