A. Five- and Six-Membered Rings

1. Factors Determining Ring Size

When a radical center and a double bond are situated so that formation of either a five- or a six-membered ring is possible, the smaller ring generally is produced.\textsuperscript{25,26} The reason for forming the smaller ring is that the strain engendered in reaching the transition state for a six-membered ring is greater than that required for reaching a five-membered one (Scheme 7).\textsuperscript{27–29} In the reaction shown in Scheme 2, for example, even though radical cyclization producing a six-membered ring is possible and generates a more stable intermediate radical than five-membered ring formation, the only pathway followed is the one leading to the smaller ring.

For formation of a five-membered ring the calculated angle of approach of the atom bearing the radical center to the multiple bond is 106°, an angle similar to the 104° calculated for the transition state in the strain-free addition of the methyl radical to propene (Figure 5).\textsuperscript{27} For six-membered ring formation the transition state has a calculated angle of approach of 94° (Figure 5). This considerable angle deformation away from a strain-free situation is a major factor in raising the energy of the transition state leading to a six-membered ring.
In addition to describing cyclization reactions by the size of the ring produced, the terms exo and endo indicate the way in which the ring is formed. The meaning of these terms is illustrated in the reactions shown in Scheme 8. When the exo/endo terminology is used to describe ring formation from reaction of the 5-hexenyl radical, the five-membered ring is seen as arising from exo closure and the six-membered one from endo closure (Scheme 7).

**2. Transition-State Structure**

Transition-state structures for radical addition and radical cyclization are given in Figure 6 in a general form. For cyclization reactions not only ring size but also ring conformation affect transition-state energy; thus, both chair-like\(^{25,27}\) and boat-like\(^ {27,30}\) structures are possible during five-membered ring formation. For the unsubstituted 5-hexenyl radical the chair-like transition state leading to a five-membered ring is calculated to be lower in energy, but only slightly so, than the boat-like transition state (Scheme 9).\(^ {27}\) (The “flagpole” interactions that contribute to making the boat conformation of cyclohexane much less stable than the chair conformation are less 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 9) 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 14, \(R = H\)).\(^ {25,31}\)
3. Altering Normal Regioselectivity

a. Steric Interactions and Adduct-Radical Stability

Although ring size is the primary factor affecting regioselectivity in cyclization reactions, other factors sometimes have a modifying effect; for example, in the reaction of the 5-methyl-5-hexenyl radical the presence of the methyl group increases the amount of six-membered-ring formation (eq 14, \( R = \text{CH}_3 \)).\(^{25,27}\) In this reaction steric effects and adduct-radical stability both favor a six-membered ring. The transition state in this reaction presumably is reached late enough that either steric effects or adduct-radical stability or both have a substantial impact on regioselectivity. Predicting when the transition state in this type of reaction will be early enough to cause highly regioselective, five-membered-ring formation is
not easy. In the reaction shown in Scheme 10, where steric interactions and adduct-radical stability favor six-membered-ring formation at least as much as they do in the reaction shown in eq 14 (R=CH₃), only a product with a five-membered ring forms.³²

b. Thermodynamic Control

Although kinetically controlled reaction is the norm in radical cyclization, thermodynamic control is observed in the reaction shown in eq 15 where the substrate is an unsaturated silyl ether and the hydrogen donor (Bu₃SnH) is maintained at a low level.³³ When this reaction is conducted with a high Bu₃SnH concentration, kinetically controlled, five-membered ring formation is the major reaction pathway. An explanation for this dependence on hydrogen-donor concentration begins with the radical 18 cyclizing to form 19, a radical with a new five-membered ring (Scheme 11). If the concentration of Bu₃SnH is high, hydrogen-atom abstraction rapidly completes the reaction, but if the donor concentration is low, rearrangement to the more stable radical 20, via the transition state 21, takes place before hydrogen-atom abstraction can occur.³⁴ Hydrogen-atom abstraction by 20 then gives the thermodynamically favored product. An alternative mechanism for this reaction, also shown in Scheme 11, is that ring opening of 19 produces a silicon-centered radical that undergoes ring closure to give the intermediate radical 20.³⁵
c. Reversal Due to Stereochemistry

One situation where six-membered ring formation is favored consistently over reaction producing a five-membered ring is when cyclization would produce a pair of trans-fused, five-membered rings. Reactions of iodides 22 and 23 illustrate the effect that stereochemistry can have on radical cyclization. The acyclic iodide 22 undergoes an expected cyclization to give a five-membered ring (Scheme 12), but reaction of the iodide 23 forms a six-membered ring (Scheme 13). Since a trans fusion between two five-membered rings would produce the highly strained radical 25, the stereochemistry of the radical 24 dictates the regioselectivity of the cyclization reaction. Six-membered-ring formation also occurs in the reaction shown in Scheme 14, again, because the other option would force the formation of trans-fused, five-membered rings.
Scheme 12

Scheme 13

Scheme 14
B. Three- and Four-Membered Rings

Radical cyclization to form a three-membered ring is a rare event because cyclization does not compete well with ring opening of the cyclized radical. Although competitive ring opening remains a possibility during four-membered-ring formation, the reaction pictured in Scheme 15 shows that it is possible to obtain a cyclic product with a four-membered ring. Even though formation of a larger ring would produce a less strained radical (Scheme 15), the transition state in this reaction must be reached before ring strain becomes a significant factor. This result is not a general one. A reaction discussed later in this Chapter (Section V.A.2.b) describes forming a five-membered ring by radical cyclization even though a four-membered one is possible.

C. Larger Rings

Radical cyclization can be effective in producing rings with more than six members. In forming a larger ring (seven or more members) not only must the radical center be able to react rapidly with the multiple bond but the reacting radical also needs to be able to adopt a conformation that brings the reactive centers within bonding distance often enough for detectable reaction to take place. The ability of the iodide 26 to form an eight-membered ring in 50% yield (eq 16) while the iodide 27 gives a complex mixture of products (eq 17) seems likely to be a matter of the rigidity and ring fusion of the radical derived from 26 causing it frequently to adopt a suitable conformation for ring formation.
Normal formation of the smaller of the two rings when the choice is between a five-membered or six-membered ring no longer is adhered to where larger rings are involved. Examples of reactions of carbohydrates that regioselectively produce the larger of the two possible rings are found in the reactions shown in eq 16 and eq 18. Larger ring formation frequently is associated with reaction between parts of a molecule, often two monosaccharide units,\textsuperscript{42,43} linked together by a silicon–oxygen tether.\textsuperscript{42–45} An example of such a reaction is shown in Scheme 16, where cyclization involves formation of an eight-membered ring.\textsuperscript{45}
A terminology for categorizing cyclization reactions expands on endo-exo designations. In this description each term consists of three parts: (a) a number identifying the size of the ring system being formed, (b) an “exo” or “endo” designation that tells whether one (exo) or both (endo) of the atoms in the multiple bond become part of the ring system, and (c) a tetra (sp$^3$), trig (sp$^2$), or dig (sp) term to describe the hybridization of the atom bonding to the radical center. The reaction shown in Scheme 2, for example, is 5-exo-trig, while that in eq 19 is 5-exo-dig. Schemes 15 and 16 describe 4-exo-trig and 8-endo-trig cyclizations, respectively.

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