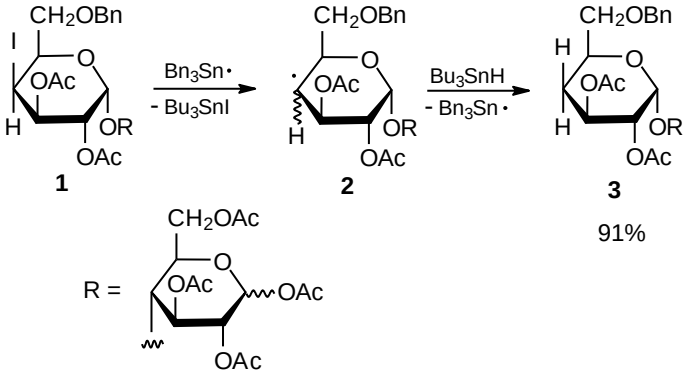
# Chapter 6
# Radical Structure



## I. Introduction

Establishing the structure of a free radical is a prerequisite for understanding its reactivity. Structural determination for a radical requires the same type of information needed to establish the structure of any reactive intermediate or stable molecule. The process begins by identifying the constituent atoms and their connectivity. Since radicals normally are generated from known compounds, connectivity information usually comes directly from the substrate structure. The configuration at ever carbon atom, except the one where the radical is centered, ordinarily is unchanged from that in the substrate. With this basic, structural information in hand, one can turn to investigating the remaining unknowns, that is, radical-center configuration and radical conformation. Although reactive intermediates, such as radicals, present special problems in structural determination due to their transient nature, the basic information needed is the same for both intermediates and stable molecules.

Scheme 1



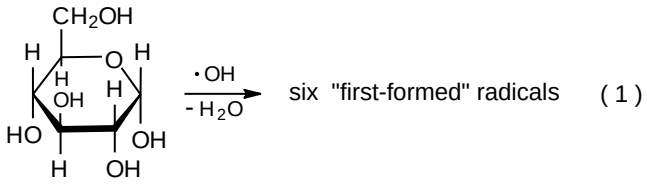

## II. Structural Formulas

The structural formula for a radical often, but not always, can be deduced from a combination of different types of information. This information includes the structure of the radical precursor, the method of radical formation, and the identity of the reaction products. For example, in the reaction shown in Scheme l the structure of the deoxyiodo sugar **1**, the known reactivity of alkyl iodides with the tri-*n*-butyltin radical, and the structure of the product **3** together provide enough information to assign the basic structural formula **2** to the intermediate radical.[1] At this point, the configuration at the radical center in **2** and the conformation of this radical remain to be determined. The way in which radical configuration and conformation are assigned is discussed in Sections III and IV, respectively, in this chapter.

The same type of information that effectively establishes the structure of the radical **2** (Scheme 1) is insufficient for determining the structures of the radicals produced by hydrogen-atom abstraction from simple sugars. Due to the large number of hydrogen atoms present in even simple sugars, knowing the structure of the starting material has limited value in establishing the identity of any particular intermediate radical. Product structures also are of limited usefulness due to the large number of compounds generated by hydrogen-atom abstraction (at least twenty-five from D-glucose[2]), and the probability that molecular rearrangement has occurred during formation of some of these products.[2,3] Proposing structures for the radicals generated by hydrogen-atom abstraction from even a simple sugar, such as D-glucose, can involve a good deal of speculation, but such speculation can be reduced by using electron spin resonance (ESR) to observe radicals directly.

It is possible to identify six, first-formed radicals in the ESR spectrum of the mixture produced by reaction of α-D-glucopyranose (**4**) with the hydroxyl radical (eq 1).[3] These six radicals are the ones generated by hydrogen-atom abstraction from of the six carbon atoms present in **4**. (Hydrogen-atom abstraction from the oxygen-hydrogen bonds is too slow to be competitive.)

Identification of first-formed radicals is possible because when the structure of the radical precursor is combined with information from its ESR spectrum, the combination provides a basis for assigning a structural formula to each radical.




**4**

Whenever a radical reaction is encountered for the first time, the structure of any intermediate radical is naturally a topic of primary interest. Once the basic structure of a radical has been established, the unknowns that usually remain are the configuration at a radical center and conformation of the radical. Establishing this configuration and determining radical conformation often involve both experimental findings and molecular-orbital calculations.

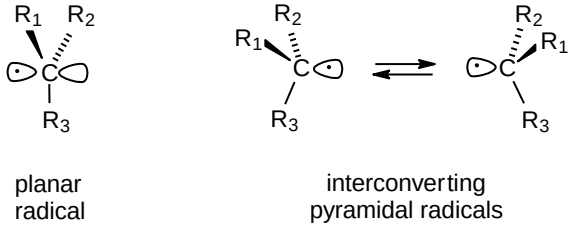



Figure 1. Possible configurations for carbon-centered radicals

## III. Radical-Center Configuration

### A. Planar and Pyramidal Structures

The configuration of a radical defines the location in space of the atoms directly attached to the radical center. When three such atoms are bonded to the carbon atom upon which a radical is centered, the configuration is either planar or pyramidal.[4] A planar configuration is one in which the atoms directly attached to the radical center and the center itself all exist in the same plane (Figure 1). For pyramidal radicals the plane defined by these directly attached atoms no longer includes the central atom (Figure 1).

Nearly every carbon-centered radical has a pyramidal configuration at the radical center, but these radicals vary widely in how close their configurations are to being planar.[5]A terminology has arisen that is designed to indicate approximate radical configuration. If a radical center has a nearly planar arrangement of attached atoms, the radical is described as being π-type.[6] (Since in a π-type radical the orbital in which the electron is centered is close to being a *p* orbital, this orbital often is

referred to as being *p*-type.) If a radical has a decidedly pyramidal configuration (i.e., one approaching that corresponding to $sp^3$ hybridization), the radical is described as being σ-type.

Pyramidal, carbon-centered radicals with no electronegative substituents attached to the radical center tend to have a small distortion from planarity;[5] that is, they usually are considered to be π-type radicals. (It is worth noting that the magnitude of the angle of distortion can be deceptive. The relatively small 6.2° distortion from planarity reported for the ethyl radical means that this radical is actually about 1/3 of the way to being $sp^3$ hybridized.[7]) The distortion from planar arrangement increases as electron-withdrawing substituents replace other groups attached to the radical center. The change in configuration that accompanies replacement of the hydrogen atoms in the methyl radical by fluorine atoms provides a clear example of the effect of electronegative substituents on radical geometry.[5,8,9] The methyl radical is either planar, or nearly so,[10] but progressive replacement of hydrogen atoms with fluorine atoms produces pyramidal radicals with structures increasingly further from planarity until the trifluoromethyl radical is reached, in which case the F–C–F bond angles are similar to those found in tetrahedral structures.[11]

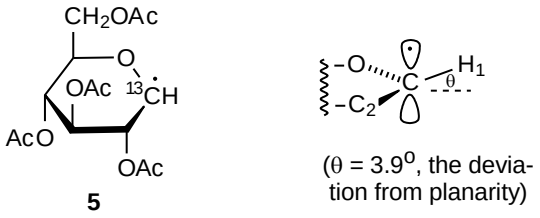


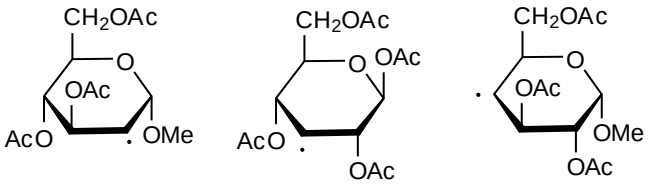

Figure 2. The D-glucopyranos-1-yl radical **5** and its configuration at C-1

## B. Configurational Determination from α-$^{13}$C Hyperfine Coupling Constants

Information about radical configuration can be obtained from analysis of α-$^{13}$C hyperfine coupling constants. These coupling constants, obtained from the ESR spectra of $^{13}$C-enriched radicals, provide a sensitive measure of the hybridization at a radical center.[12,13] The configuration of a pyranos-1-yl radical is naturally of considerable interest due to the unique role of the anomeric carbon atom in carbohydrate chemistry. The α-$^{13}$C hyperfine coupling constants, obtained from the ESR spectrum of the $^{13}$C-enriched D-glucopyranos-1-yl radical **5**, show the deviation from planarity for this radical to be 3.9° (Figure 2).[6,14] Since an $sp^3$-hybridized σ radical would have a deviation 19.5°, the D-glucopyranos-1-yl radical **5** is considered to be π-type.[6] Radicals centered at C-2 (**6**), C-3 (**7**), and C-4 (**8**) in pyranoid rings also have π-type configurations.[15]

Since organic radicals with no electronegative substituents attached to the radical center have π-type configurations, finding that radicals **6**-**8** have this type of configuration is not surprising. Because radical centers with electronegative atoms attached become more pyramidal, it is surprising to discover that the radical **5**, which has an oxygen atom bonded to the radical center, also

has a π-type configuration. To understand why this configuration is adopted, it is helpful to analyze the stability of **5** as determined by frontier-orbital interactions.




**6** **7** **8**

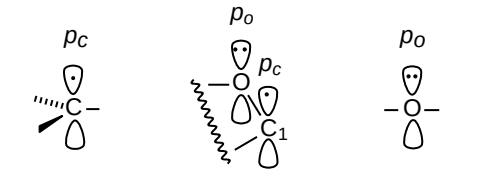
## C. Theoretical Explanation of Observed Configurations

### 1. Frontier-Orbital Interactions

Frontier-orbital interactions are based on an approximate, quantum-mechanical method that assumes that all interactions between occupied orbitals in a bimolecular reaction can be neglected and that the only interactions that need to be considered are between the highest occupied molecular orbital (HOMO) of one reactant and the lowest unoccupied molecular orbital (LUMO) of the other. A small energy difference between the HOMO and the LUMO (the frontier orbitals) translates into a large stabilizing interaction. In radical reactions the singly occupied molecular orbital (SOMO) can be either a HOMO or a LUMO.[16] Although frontier-orbital interactions are intended to be applied to bimolecular reactions, they can be used for understanding radical structure. In making such an application the radical is formally split into two fragments and fragment recombination is treated as a bimolecular reaction.[16] This approach, which has enjoyed widespread application and success in explaining radical structure,[17] will be used to rationalize the π-type configuration at C-1 adopted by the D-glucopyranos-1-yl radical **5** (Figure 2).

### 2. $p_c/p_o$ Orbital Interaction

Experimental and theoretical studies show that the two unshared pairs of electrons on an oxygen atom in a pyranoid ring, do not have the same energy.[18,19] The higher energy pair exists in a *p*-type orbital while the lower energy pair is in a hybrid orbital that has considerable *s* character. As pictured in Figure 3, stabilization should result from interaction of the electrons in a *p*-type orbital on a ring oxygen atom ($p_o$) with the electron in the singly occupied, *p*-type orbital on an adjacent carbon atom ($p_c$). The increase in energy of the electron in the singly occupied molecular orbital (SOMO) is more than offset by the combined decrease in energy of the two electrons in the doubly occupied orbital. Because a nonparallel alignment of orbitals would exist in a pyranos-1-yl radical with a σ-type configuration, stabilizing orbital interaction for such a radical would be less than that for a radical with a π-type configuration; thus, there is a gain in radical stabilization to be had from having a *p*-type orbital at C-1 even though this atom has an electronegative oxygen atom attached.




**9**

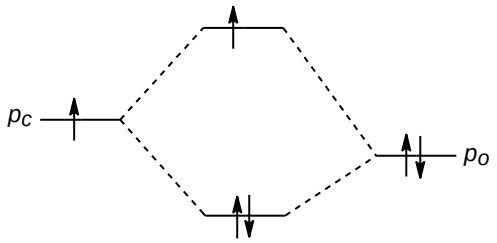



Figure 3. Change in energy levels from $p_O/p_C$ orbital interaction

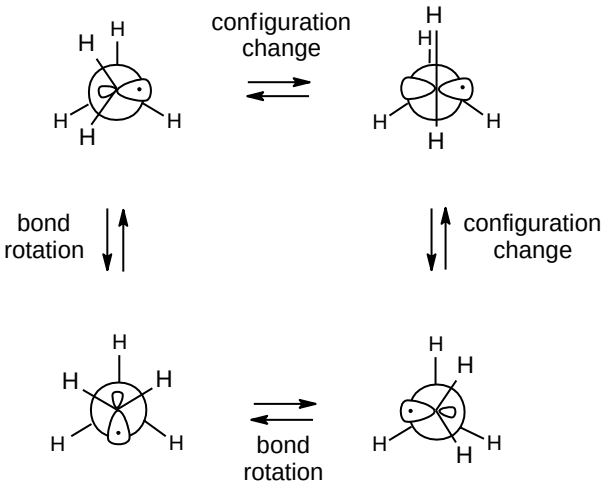



Figure 4. Interconversion of ethyl radical conformations by bond rotation and change of configuration

## IV. Radical Conformation

Conformations of a molecule are usually viewed as arrangements of atoms that differ only by rotation about one or more single bonds. This view needs to be expanded where radicals are concerned because in some instances radicals with pyramidal configurations change from one conformation to another by inversion of configuration at the radical center. Consider the case of the ethyl radical (Figure 4). This radical is reported to have a pyramidal configuration with a 6.2° distortion from planarity and an extremely low (0.15 kcal/mol) energy barrier between confor-

mations.[20–22] For the ethyl radical bond rotation and inversion of configuration both can contribute to conversion of one conformation into another (Figure 4).[20]

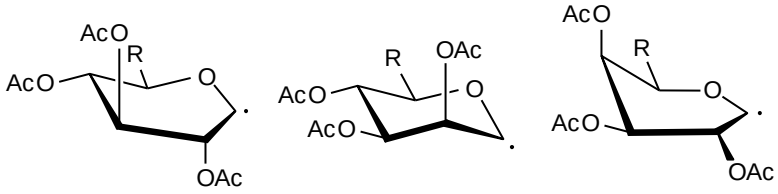
The intriguing complications associated with changes in conformation of alkyl radicals are not a major focus for conformational analysis of carbohydrates. The primary objective where carbohydrate radicals are concerned is to determine why a particular conformation is preferred and then to understand how conformation influences reactivity. ESR spectroscopy is an essential tool in achieving these objectives because it enables direct observation of radicals and, in so doing, provides valuable information about their conformation.


**10** **11** ( 2 )

## A. Pyranos-1-yl Radicals

### 1. Experimentally Observed Conformations

The conformational analysis of pyranos-1-yl radicals is an extensively studied topic that contains surprising results.[6,14,23–26] The most striking of these is that conversion of some protected D-glucopyranosyl derivatives, such as the bromide **10**,[6] into the corresponding D-glucopyranos-1-yl radicals causes the conformation of the system to change from a $^4C_1$ chair to a distorted $B_{2,5}$ boat (eq 2).[6,14,24] Evidence from low temperature studies suggests that a chair conformation initially forms but rapidly converts to a boat as the temperature rises.[25]




**11** R = $CH_2OAc$ **13** R = $CH_2OAc$ **15** R = $CH_2OAc$

**12** R = H **14** R = H

Perhaps as surprising as the observation that a D-glucopyranos-1-yl radical such as **11** adopts a distorted boat conformation is the finding that the conformations of pyranos-1-yl radicals depend upon the C-2 substituent and its configuration. For example, the 2,3,4,6-tetra-*O*-acetyl-D-glucopyranos-1-yl radical (**11**) and the 2,3,4,6-tetra-*O*-acetyl-D-mannopyranos-1-yl radical (**13**) differ from each other only in their configurations at C-2; yet, this difference causes them to adopt $B_{2,5}$ boat and $^4C_1$ chair conformations, respectively. The 2,3,4-tri-*O*-acetyl-D-xylopyranos-1-yl radical

(**12**) and 2,3,4-tri-*O*-acetyl-D-lyxopyranos-1-yl radical (**14**), which also differ only in C-2 configuration, echo the behavior of **11** and **13** by assuming primarily $B_{2,5}$ boat and $^4C_1$ chair conformations, respectively.[6,14,24] The complexity of this situation is increased further by the 2,3,4,6-tetra-*O*-acetyl-D-galactopyranos-1-yl radical (**15**), which adopts a $^4H$ half-chair conformation. In an effort to understand why these radicals adopt the conformations they do, researchers have turned to frontier-orbital interactions[6,14,15,24,27] and to ab initio molecular-orbital calculations.[23,28,29]

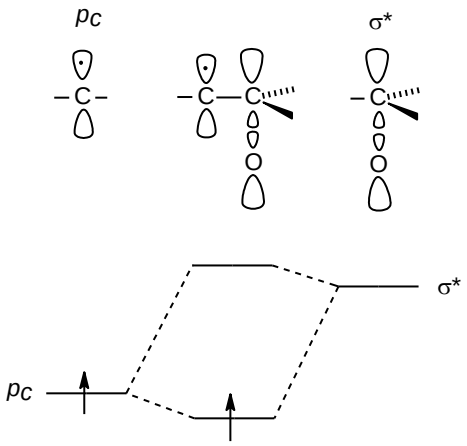



Figure 5. Change in energy levels from $p_C/\sigma*$ orbital interaction

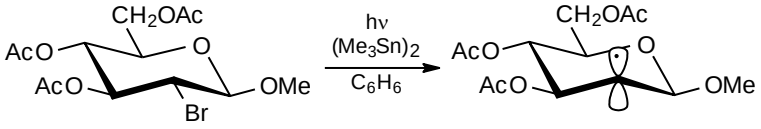
2. Radical Conformation Explained by Frontier-Orbital Interactions

a. $p_c/\sigma*$ Orbital Interaction

In attempting to understand the orbital interactions controlling the conformations of pyranos-1-yl radicals, it is reasonable to begin with some simple possibilities. One of these is that interaction between a *p*-type orbital on a ring carbon atom ($p_c$) and the σ* orbital of a substituent C–O bond on an adjacent carbon atom (Figure 5) could provide the stabilization needed to determine radical conformation. If this were the case, the 2-deoxypyranos-2-yl radical **16** would adopt a distorted boat (**17**) or ring-inverted chair (**18**) conformation to maximize the benefit from orbital interaction (eq 3). Such conformational change does not take place. The radical **16** retains the chair conformation of its precursor.[15]

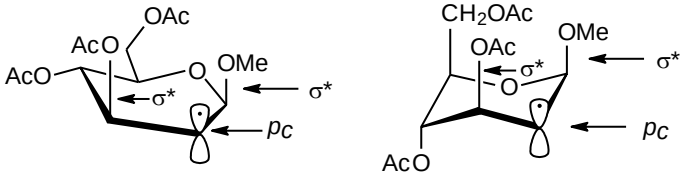
Deciding upon the significance of $p_c/\sigma*$ interaction based on the relative population of conformers **16**-**18** is open to question because substantial differences in steric interactions should exist among these conformations. Doubts raised by these differences are reduced when comparing conformations **19** and **20** of the cyclohexyl radical that has an acyloxy group attached to a carbon atom adjacent to the radical center. Stabilization due to $p_c/\sigma*$ interactions should increase the population of the conformer **20**. Based on the relative conformational populations indicated in eq 4, one can conclude that if a stabilizing interaction exists between a *p*-type orbital on a carbon atom

and a σ* orbital associated with a neighboring C–O bond, this stabilization is not sufficient to cause a radical to undergo conformational change.[26] Such a conclusion is supported by the observation that other 2-deoxypyranos-2-yl radicals, as well as 3-deoxypyranos-3-yl and 4-deoxypyranos-4-yl radicals, all assume $^4C_1$ chair conformations even though some of these radicals would adopt a boat-like conformation if the stabilization needed could be provided by coplanar $p_c$ /σ* orbital interaction.[15]



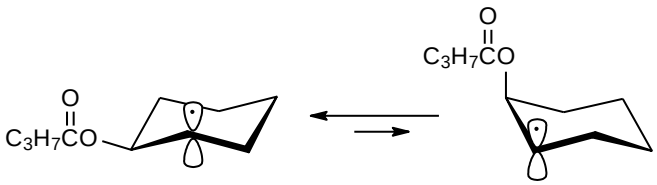

( 3 )

**16**




**17** **18**

Conformations **17** and **18** have parallel $p_c$/σ* orbital alignment but only conformation **16** is observed. (Arrows indicate positions of interacting orbitals.)




( 4 )

**19** **20**

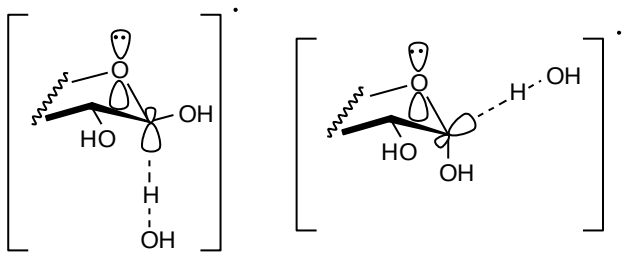
major minor

conformation favored by $p_c$/σ* interaction

b. $p_c$ /$p_o$ Orbital Interaction

As mentioned in discussing radical configuration (Section III.C.2.), stabilization results from frontier-orbital interaction of the electrons in a *p*-type orbital on a ring oxygen atom ($p_o$) with the singly occupied, *p*-type orbital on an adjacent carbon atom ($p_c$) (Figure 3). Experimentally supporting this view of $p_c$ /$p_o$ interaction is the observation that H-1 is abstracted more easily by the hydroxyl radical from β-D-glucopyranose than from its α-anomer.[30] This difference in reactivity

can be attributed to an orbital alignment that provides transition-state stabilization for reaction of the β-anomer that is greater than the stabilization for the α-anomer (Figure 6).[30] Difference in rates of hydrogen-atom abstraction, therefore, support the idea that $p_c$ /$p_o$ orbital interaction does stabilize a developing radical.




stabilized transition state for abstraction from the β-anomer

nearly unstabilized transition transition state for abstraction from the α-anomer

Figure 6. Possible transition states for hydrogen abstraction from C-1

Stabilization of the type pictured in Figure 3 cannot, by itself, explain the different conformations adopted by various pyranos-1-yl radicals because $p_c$ /$p_o$ interaction is basically the same for all radicals of this type, but further analysis shows that this interaction is part of a broader effect that does control conformational selection. In preparing to discuss this broader effect, it is useful first to consider orbital interactions responsible for the anomeric effect.

c. The Anomeric Effect

The anomeric effect is described as "the tendency of an electronegative substituent at C-1 in a pyranoid ring to assume an axial rather than equatorial orientation".[31] Two explanations have been proposed for the anomeric effect. One of these depends on dipole-dipole repulsions and the other on orbital interactions. Although there is evidence supporting both,[32,33] the discussion below is based on the orbital-interaction explanation.

The α anomer (**21**) in a typical compound containing a pyranoid ring has the bond between C-1 and its attached substituent aligned so that the σ* orbital associated with the $C_1$–O bond is parallel to the *p*-type orbital ($p_o$) on the ring oxygen atom (Figure 7). The parallel alignment of these orbitals optimizes their interaction and, as a result, maximizes the electron stabilization this interaction produces. These same orbitals ($p_o$ and σ*) in the β anomer (**22**) cannot interact as effectively because they are not nearly parallel; thus, little stabilization occurs. This difference in orbital interactions can be linked to the difference in stability between α and β anomers; therefore, these orbital interactions provide an explanation for the anomeric effect.

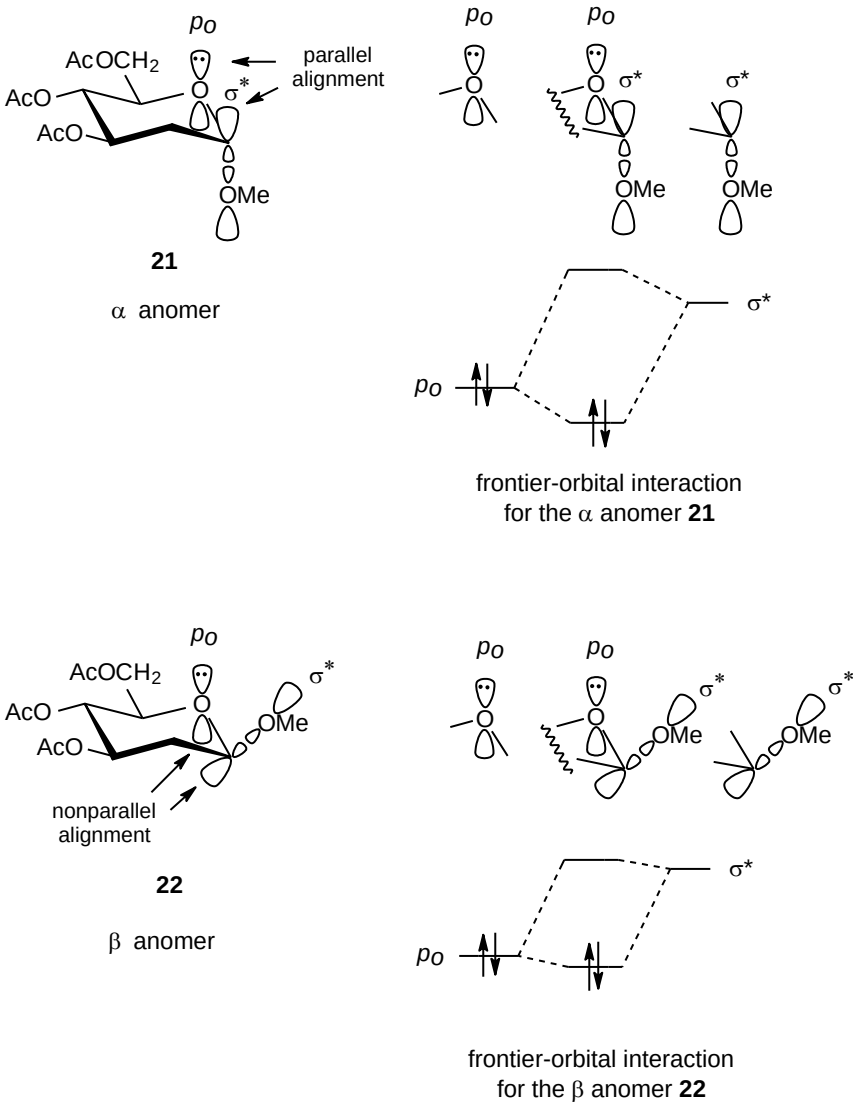



Figure 7. Orbital interactions responsible for the anomeric effect

d. The Quasi-Anomeric Effect

An explanation for the conformations adopted by pyranos-1-yl radicals comes from interaction among the *p*-type orbital on the ring oxygen atom ($p_o$), the singly occupied, *p*-type orbital on C-1 ($p_c$), and the antibonding (σ*) orbital associated with the carbon–oxygen bond at C-2.[14] Since stabilizing interaction is greatest when these orbitals are parallel to each other, there is an energetic advantage to adopting a conformation that has parallel orbital alignment.

When analyzing the interaction among $p_o$, $p_c$, and σ* orbitals, it useful to consider the process as occurring in two steps. The first step, one already discussed in Section III.C.2. and pictured

in Figure 3, involves the *p*-type orbital on C-1 and the *p*-type orbital on the ring oxygen atom. Interaction between these two orbitals has a net stabilizing effect on the system because the rise in energy of the electron in the singly occupied molecular orbital (SOMO) is more than offset by the combined decrease in energy of the two electrons in the doubly occupied orbital. Raising the energy level of the SOMO also brings it closer in energy to the σ* orbital associated with the bond between C-2 and O-2. Having these two orbitals closer together in energy increases their interaction and, consequently, increases radical stabilization (Figure 8). (Since an SOMO can function as both a HOMO and a LUMO, interactions of the SOMO with both σ (HOMO) and σ* (LUMO) orbitals are included in Figure 8.[16,34]) The conclusion that can be drawn from the frontier-orbital interactions is that a pyranos-1-yl radical (**23**) is more stable when the bond to an electronegative group at C-2 is parallel to the *p*-type orbitals at C-1 and the ring oxygen atom. Due to the similarity between the interactions described in Figure 8 and those pictured in Figure 7 for the anomeric effect,[31] the stabilization shown in Figure 8 is described as arising from a quasi-anomeric effect.[14]

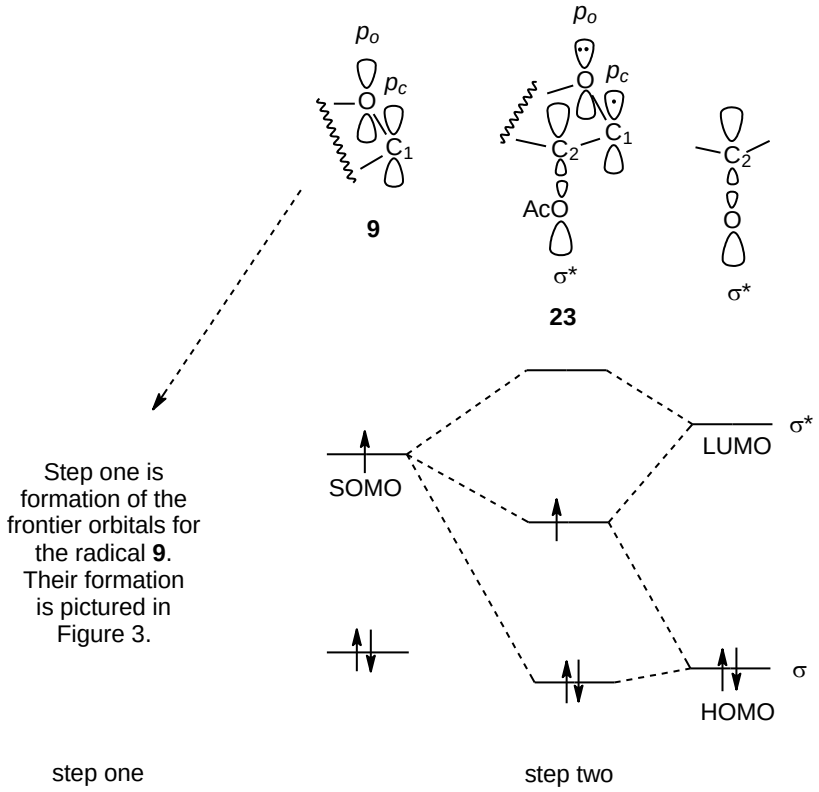


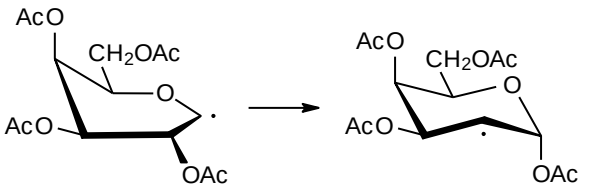

Figure 8. Frontier-orbital interactions causing the quasi-anomeric effect

e. Radical Conformation Explained by the Quasi-Anomeric Effect

The quasi-anomeric effect provides a basis for understanding the various conformations adopted by pyranos-1-yl radicals.[6,14,24,35] For each of these radicals the stereochemistry at C-2 is

critical in determining which conformation provides the needed, parallel alignment among the interacting orbitals. It is possible to understand the conformations of the pyranos-1-yl radicals **11**-**15** based on the way in which they achieve this orbital alignment. For the 2,3,4,6-tetra-*O*-acetyl-D-glucopyranos-1-yl and the 2,3,4-tri-*O*-acetyl-D-xylopyranos-1-yl radicals (**11** and **12**, respectively) parallel alignment is attained by adopting a distorted $B_{2,5}$ boat conformation. For the 2,3,4,6-tetra-*O*-acetyl-D-mannopyranos-1-yl and 2,3,4-tri-*O*-acetyl-D-lyxopyranos-1-yl radicals (**13** and **14**, respectively) the orbital alignment needed for stabilization by the quasi-anomeric effect is realized in a $^4C_1$ chair conformation.

The D-galactopyranos-1-yl radical **15** exists in a $^4H$ half-chair conformation in order to achieve an orbital alignment as close as possible to that needed for quasi-anomeric stabilization without creating substantial eclipsing interactions between the C-3 and C-4 substituents. The half-chair conformation for **15**, therefore, represents a compromise in which the energetic benefit realized from quasi-anomeric stabilization is balanced against the expense of introducing the destabilizing interactions inherent in a half-chair conformation. Due to these destabilizing interactions it is reasonable to assume that the radical **15** is relatively unstable, that is, more reactive than comparable pyranos-1-yl radicals. Indirect support for this assumption exists in the finding that **15** undergoes acyloxy group migration (eq 5) under conditions where similar pyranos-1-yl radicals (**11**-**14**) are stable.[14] (Acyloxy group migration is discussed in Chapter 8 of Volume II.)




**15** ( 5 )

f. Substituent-Atom Electronegativity and Radical Conformation

The electronegativity of an atom linking C-2 to an attached substituent in a pyranos-1-yl radical plays a critical role in determining radical conformation. The experimental evidence for the 2,3,4,6-tetra-*O*-acetyl-D-glucopyranos-1-yl radical **11** is that it adopts the "now familiar", distorted $B_{2,5}$ boat conformation, but when the oxygen atom attached to C-2 in **11** is replaced by a less electronegative atom, such as carbon or nitrogen, a $^4C_1$ chair conformation is more stable (Figure 9).[35,36] Finally, when a fluorine atom becomes the C-2 substituent, the $B_{2,5}$ boat conformation returns. The quasi-anomeric effect offers an explanation for this connection between atom electronegativity and radical conformation.

Because the electronegative atom X lowers the energy of the σ* orbital associated with the $C_2$-X bond, this orbital moves closer in energy to the SOMO as the electronegativity of X increases (Figure 9).[35,37] Since stabilizing SOMO-σ* interaction is greatest when these orbitals are parallel, achieving proper orbital alignment takes place when the radical assumes a $B_{2,5}$ boat conformation.

If the atom attached to C-2 is highly electronegative (oxygen or fluorine), the stabilization gained from SOMO-σ* interaction is large enough to cause the radical to adopt a boat conformation, but if this attached atom is less electronegative (carbon or nitrogen), the radical retains the normally more stable $^4C_1$ chair conformation because the energy levels of the σ* and SOMO orbitals are too far apart for stabilizing interaction to be sufficient to cause conformational change (Figure 9).

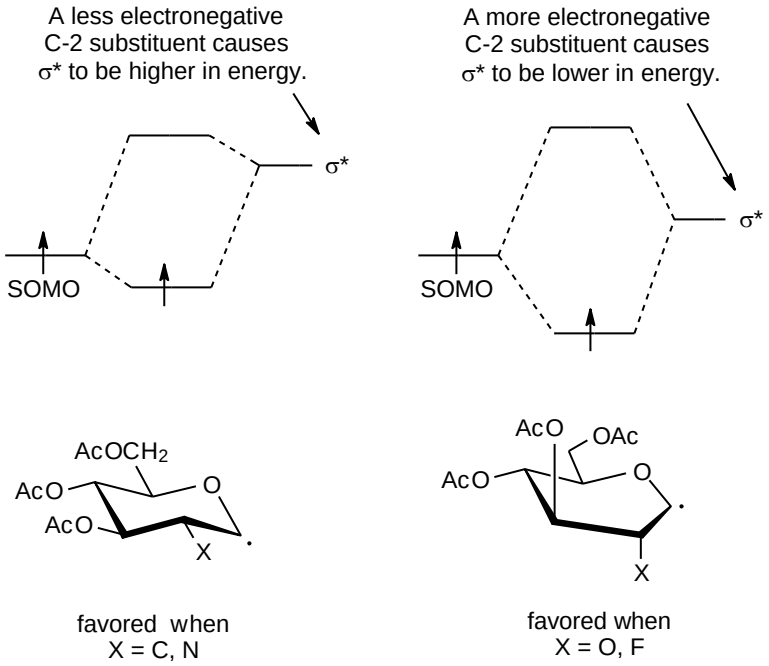



Figure 9. The effect of electronegativity of a C-2 substituent on frontier-orbital interactions

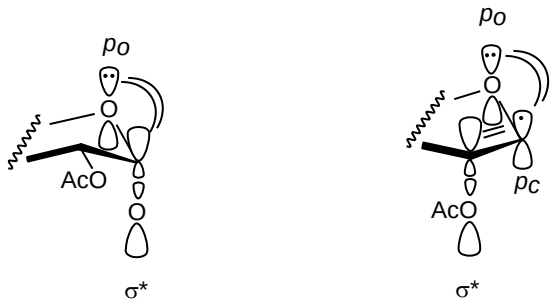



Figure 10. A comparison of orbital interactions in the anomeric effect with those in the quasi-anomeric effect

g. The Similarity between Orbital Interactions in the Anomeric and Quasi-Anomeric Effects

The explanation provided by the quasi-anomeric effect for the dependence of pyranos-1-yl radical conformation on the electronegativity of the atom bonded to C-2 is reminiscent of that given by the anomeric effect for explaining why an α anomer with an electronegative atom bonded to C-1 is more stable that the corresponding β anomer.[31] In the anomeric effect, stabilization of a molecule comes from electron delocalization made possible by parallel alignment of the *p*-type orbital on the ring oxygen atom and the σ* orbital of the $C_1$–O bond (Figure 10). This interaction determines the favored configuration (α rather than β) of the group attached to C-1. For the quasi-anomeric effect this same type of interaction is believed to be occurring, but it is "transmitted" from the *p*-type orbital on the ring oxygen atom through the *p*-type orbital on C-1 to the σ* orbital of the $C_2$–O bond (Figure 10).

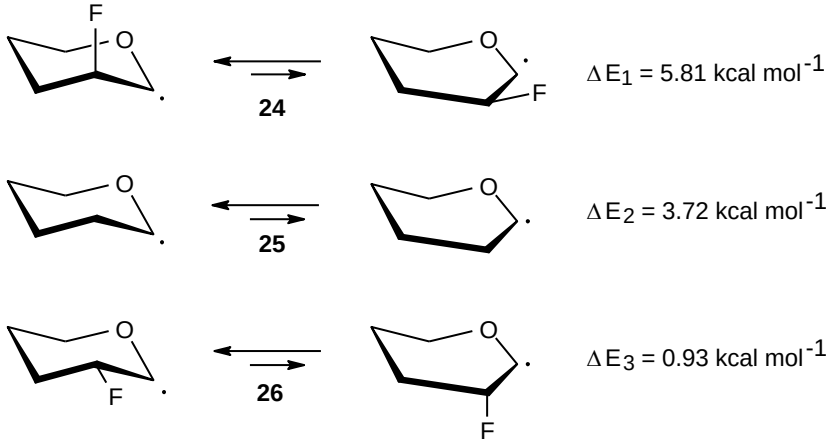


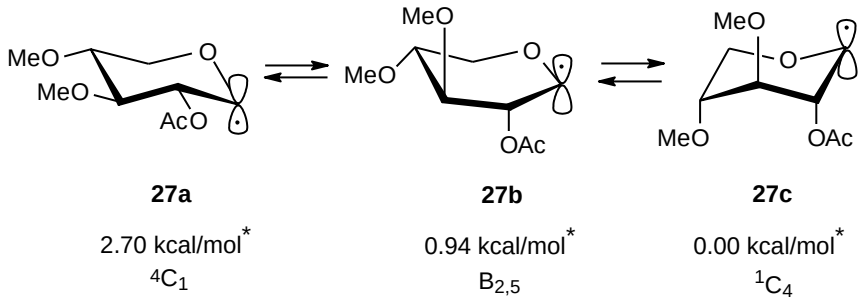

Figure 11. Stabilities of model, pyranosy-1-yl radical conformations

3. Radical Conformation Determined from Ab Initio Molecular-Orbital Calculations

Molecular-orbital calculations at various levels of complexity on model, pyranos-1-yl radicals reinforce the idea that both stereochemistry and electronegativity of a C-2 substituent affect radical conformation. Comparing the differences in calculated energies of the chair and boat conformations of the radicals **24** and **25** leads to the conclusion that an axial C–F bond in **24** stabilizes the chair conformation of this model pyranos-1-yl radical by 2.09 kcal $mol^{-1}$ (Figure 11).[23] A similar comparison of the radicals **25** and **26** indicates that the axial C–F bond in **26** stabilizes the boat conformation by 2.79 kcal $mol^{-1}$ (Figure 11). The calculated stabilization energies for these

model radicals (**24**-**26**) indicate a reliance of conformation on substituent configuration at C-2 that is similar to that predicted by the quasi-anomeric effect.

Scheme 2




**27a** 2.70 kcal/mol* $^4C_1$

**27b** 0.94 kcal/mol* $B_{2,5}$

**27c** 0.00 kcal/mol* $^1C_4$

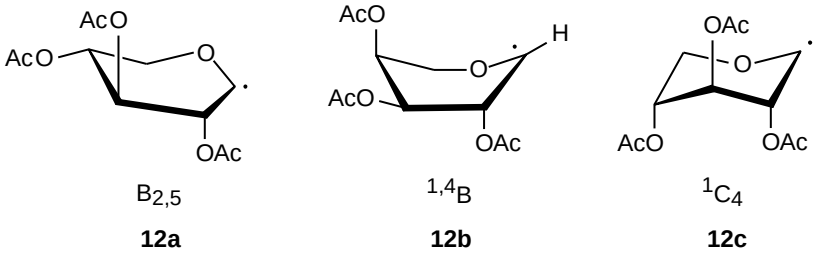
* relative energies

Although molecular-orbital calculations on the model systems **24**-**26** support experimental findings concerning the effect of C-2 substituents on the conformation of pyranos-1-yl radicals, these calculations do not predict a distorted $B_{2,5}$ boat to be the most stable conformation for the radical **26** (Figure 11). Although this radical (**26**) is a rough model for the 2,3,4,6-tetra-*O*-acetyl-D-glucopyranos-1-yl radical (**11**), the model radical (**26**) does adopt a distorted $B_{2,5}$ boat conformation (eq 2). Making the model system more like a pyranos-1-yl radical by adding electronegative substituents to the ring could bring calculated structures more "in line" with ones based on experimental observation.[23] Indeed, this appears to be the case because when ab initio molecular-orbital calculations are performed on the D-xylopyranos-1-yl radical shown in Scheme 2, the $B_{2,5}$ boat conformation (**27b**) is found to be decidedly more stable than the $^4C_1$ chair (**27a**).[29] The calculated energies for conformations **27a-c** support the idea that an axial bond to an electronegative atom at C-2 increases stability in conformations with this bonding arrangement (**27b** and **27c**) when compare to those where it is lacking (**27a**).[29]

## 4. Influence of Steric Effects on Radical Conformation

Although C-2 substituents clearly have a vital role in determining pyranos-1-yl radical conformation, other ring substituents have distinct, sometimes equally dramatic, effects. If the $CH_2OAc$ substituent at C-5 in a pyranos-1-yl radical is replaced by a hydrogen atom, the conformational preference for having this substituent in an equatorial position disappears and the resulting radical becomes more conformationally mobile. This change has its greatest impact on radicals that exist primarily in boat and distorted boat conformations because for such radicals other conformations often are similar in energy; for example, the only detectable conformation for the D-glucopyranos-1-yl radical **11** is a distorted $B_{2,5}$ boat, but for the more flexible D-xylopyran-

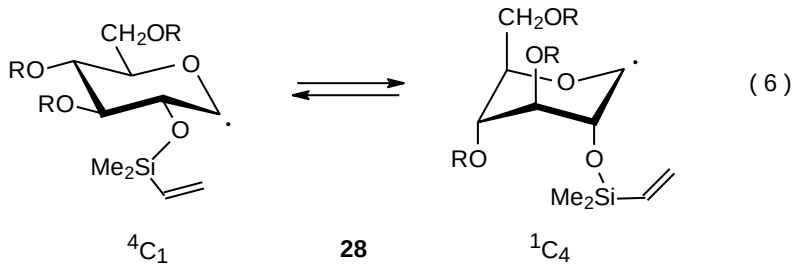
os-1-yl radical **12** ($CH_2OAc$ group at C-5 replaced by a hydrogen atom) $^{1,4}B$ (**12b**), and $^{1}C_4$ (**12c**) conformations also can be detected in its ESR spectrum.[35,38]




$B_{2,5}$ $^{1,4}B$ $^{1}C_4$

**12a** **12b** **12c**

The steric size of groups attached to the 3- and 4-positions in a pyranoid ring also affects radical conformation. If *trans*-related protecting groups at O-3 and O-4 are sufficiently large, steric interactions will force them apart and cause the usually more stable $^{4}C_1$ conformation to change to a $^{1}C_4$ conformation (eq 6).[39,40] Such a change occurs when the *O*-benzyl groups in the radical **28** are exchanged for the sterically more demanding *O*-*t*-butyldimethylsilyl groups.[41,42]

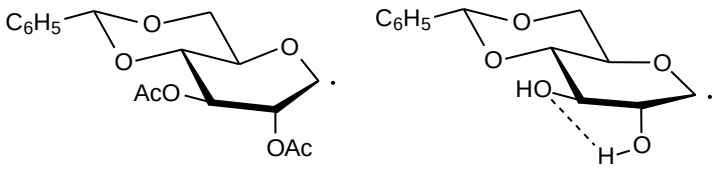



( 6 )

$^{4}C_1$ **28** $^{1}C_4$

major ← R = Bn

R = SiMe$_2$*t*-Bu → major

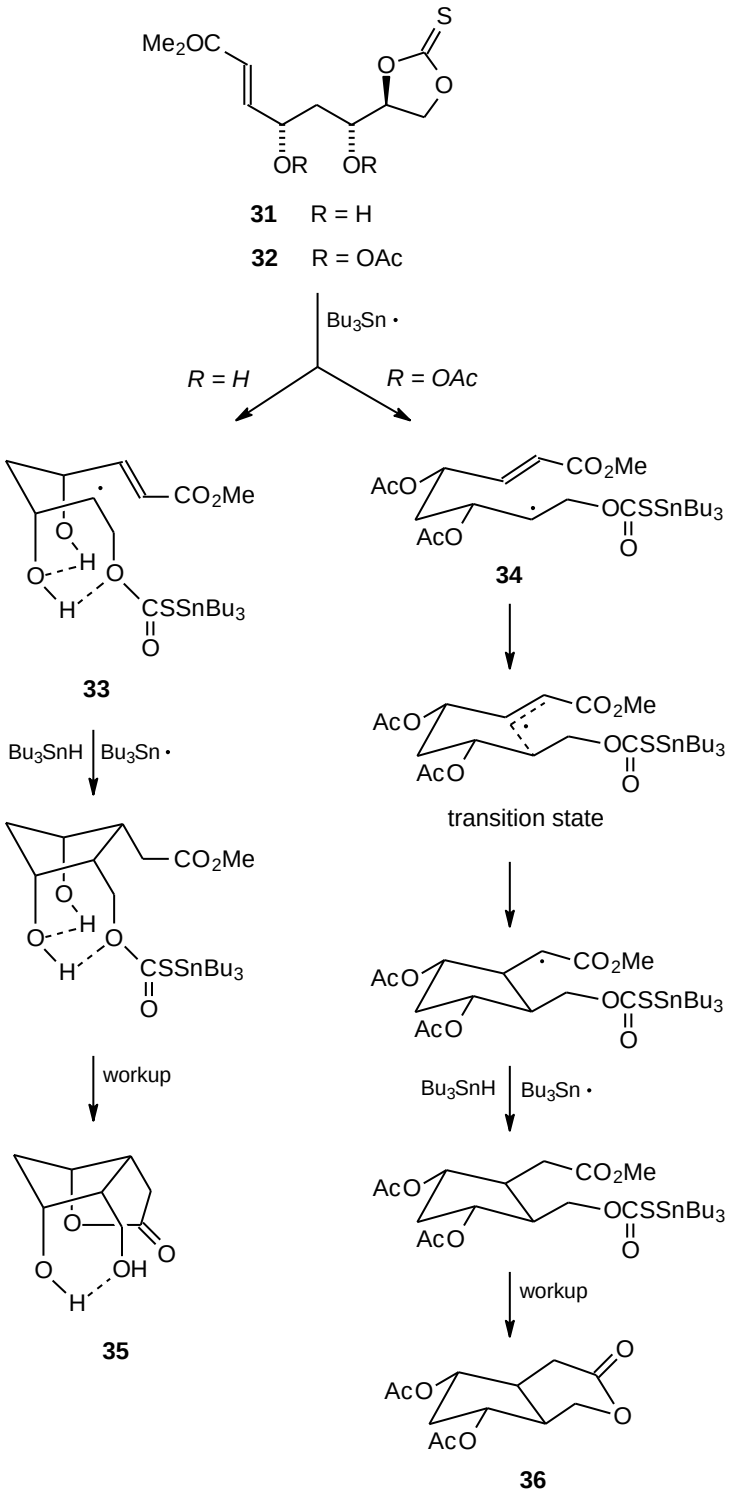



**29** **30**

## 5. Effect of Hydrogen Bonding on Radical Conformation

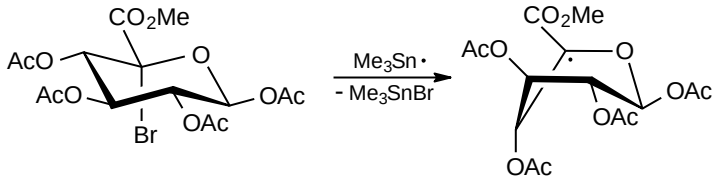
The conformational changes discussed thus far all have been related to protected sugars. Removing protecting groups, a change that allows hydrogen bonding to take place, can have a significant, sometimes controlling, effect on conformation. Comparing the radicals **29** and **30** provides an illustration of the importance of hydrogen bonding to radical conformation. The fully protected D-glucopyranos-1-yl radical **29** adopts a $B_{2,5}$ boat conformation, but removing the acetyl

Scheme 3

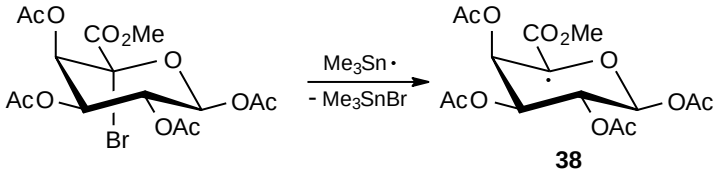

Me2OC
S
O
O
OR
OR
31 R = H
32 R = OAc
Bu3Sn·
R = H
R = OAc
CO2Me
O
H
O
O
H
CSSnBu3
O
33
AcO
CO2Me
OCSSnBu3
AcO
O
34
Bu3SnH
Bu3Sn·
transition state
workup
OH
35
Bu3SnH
Bu3Sn·
workup
36

protection from O-2 and O-3 causes a change to a half-chair conformation (**30**).[6,14] Since this new conformation permits internal hydrogen bonding,[6,43] its formation shows that hydrogen bonding is another powerful force in determining the conformation of a radical.

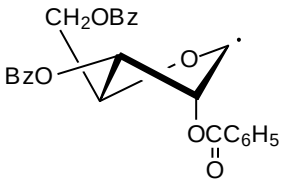
Changes in conformation caused by hydrogen bonding can be reflected in the products from a reaction. The difference in radical cyclization of compounds **31** and **32**, for example, is attributed to hydrogen bonding in the intermediate radical **33** that does not exist in the radical **34** (Scheme 3).[44] The stereochemistry in the product **35** is determined in large part by the control that hydrogen bonding exercises on the conformation of the intermediate radical **33**. Since hydrogen bonding does not exist in the radical **34**, stereochemistry in the product **36** is due to **34** reacting from a chair-like transition state that maximizes the number of pseudoequatorial substituents. (Formation of five-membered rings via chair-like transition states is discussed in Section IV.A. of Chapter 11 and Section III.C.1.a. of Chapter 19 in Volume II.)




**37** ( 7 )




**38** ( 8 )



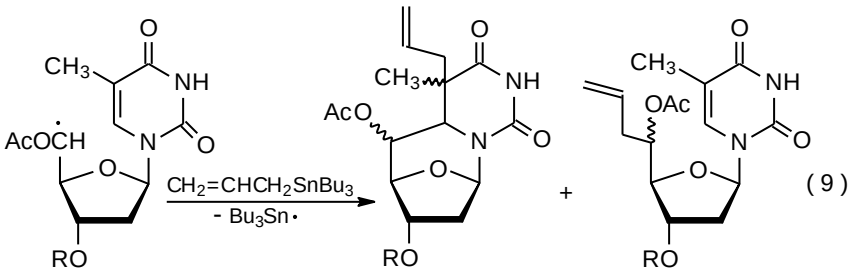

$_2$E

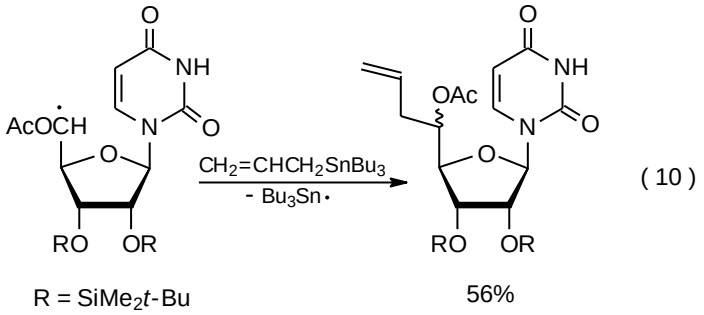
**39**

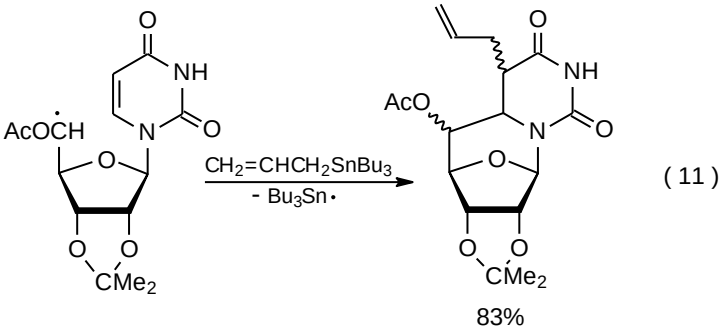
## B. Pyranos-5-yl Radicals

The influence of the quasi-anomeric effect naturally extends to pyranos-5-yl radicals. For these radicals the stereochemistry at C-4 is a key element in determining radical conformation. The radical **37** adopts a boat conformation to place the C-4 acetoxy group in the proper orientation for

quasi-anomeric stabilization (eq 7), but the radical **38** retains a chair conformation because the C-4 acetoxy group is already in the needed, axial orientation (eq 8).[27]




## C. Furanosyl Radicals

ESR studies[45] and ab initio molecular-orbital calculations[28] indicate that furanos-1-yl radicals usually adopt the envelope conformation characteristic of many cyclopentane derivatives. The ESR spectrum of the D-ribofuranos-1-yl radical **39** indicates that it adopts a $_2$E conformation. Such a conformation maximizes stabilization from the quasi-anomeric effect.[45] Calculations on radicals centered at C-1, C-2, C-3, and C-4 in 2-deoxy-D-*erythro*-furanosyl systems predict two stable conformations for each radical. Seven of the eight calculated conformations are envelopes.[28]

The reactions shown in equations 9-11 indicate that radical conformation has a pronounced effect on reactivity of furanos-1-yl radicals.[46] Internal addition of a radical centered at C-5' to the double bond between C-5 and C-6, the major pathway for the reaction shown in eq 9, only can occur if the two reactive centers readily come into close proximity. When puckering caused by sterically demanding ring substituents moves the reactive centers too far apart, intramolecular addition no longer can take place (eq 10). The addition pathway can be restored if structural rigidity, such as that imposed by a 2',3'-*O*-isopropylidene group, reestablishes a conformation with the reactive centers within bonding distance (eq 11).

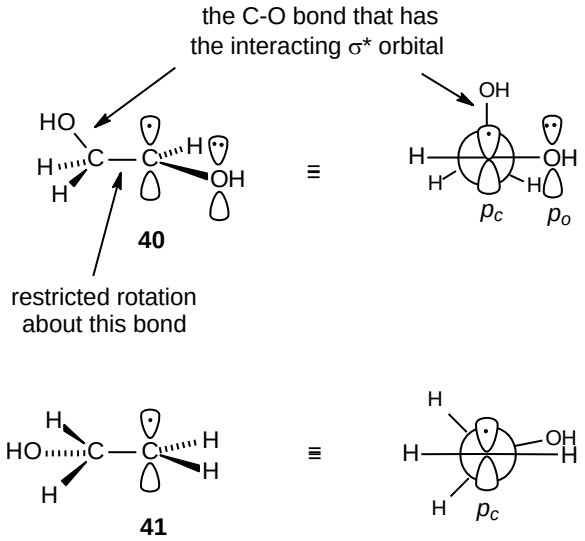



Figure 12. Preferred conformations for the radicals **40** and **41**.

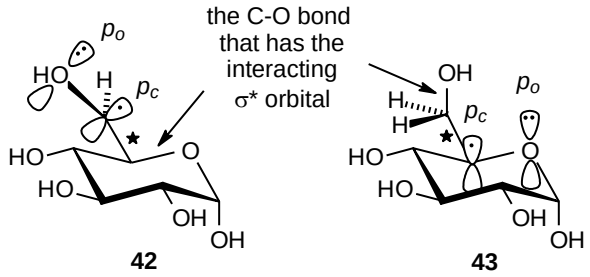



Figure 13. Two radicals each of which has restricted rotation (a "locked conformation") about the single bond indicated by a star.

## D. Radicals in "Locked" Conformations

The quasi-anomeric effect usually is invoked to explain conformations of cyclic structures, but the type of orbital interaction responsible for this effect can be found in acyclic systems as

well. The preferred conformation of the radical **40** (Figure 12) has an orbital alignment identical to that associated with the quasi-anomeric effect; that is, the singly occupied, *p*-type orbital on a central carbon atom is flanked by an oxygen atom with an electron pair in a *p*-type orbital and a carbon atom that is part of a C–O bond with a σ* orbital that is parallel to the *p*-type orbitals.[47] The conformation for **40** shown in Figure 12 has a significant barrier to rotation about the $C_1$–$C_2$ bond and, consequently, is described as a "locked" conformation.[48,49] When the oxygen atom with the interacting, *p*-type orbital is removed from the system, the lock is "broken" and the resulting radical (**41)** assumes a different conformation (Figure 12). The carbohydrate radicals **42** and **43** (Figure 13) each have locked conformations; that is, for these two (**42** and **43**) rotation about the carbon–carbon bond between C-5 and C-6 is restricted.[45]

## V. Quasi-Anomeric Radical Stabilization

Radicals centered at various carbon atoms in a pyranoid ring can be divided, on the basis of their stability, into two groups. The first group includes the pyranos-1-yl and pyranos-5-yl radicals, intermediates that are stable enough to be generated and observed in toluene or tetrahydrofuran. The second group, pyranosyl radicals centered at C-2, C-3, and C-4, cannot be observed in toluene or tetrahydrofuran because they abstract hydrogen atoms from these solvents too rapidly.[15] Since only the pyranos-1-yl and pyranos-5-yl radicals are capable of experiencing stabilization from the quasi-anomeric effect (Figure 8), the special stability of these radicals provides further support for the existence of quasi-anomeric stabilization.

## VI. Summary

Determining the structure of a radical is essential to understanding its reactivity. The process begins by establishing the structural formula for the radical, that is, by identifying the constituent atoms, their connectivity, and elements of stereochemistry. Remaining unknown at this point typically are radical-center configuration and radical conformation.

The structural formula of a radical often can be determined reliably from knowledge of the structure of the radical precursor, the method of radical formation, and the reaction products. In instances where this information is insufficient, direct observation of the radical by ESR spectroscopy sometimes is possible and can provide the additional information needed to establish a structural formula.

The configuration at a radical center defines the location in space of the atoms directly attached to this central atom. Nearly every carbon-centered radical has a pyramidal configuration, but these radicals vary widely in how close their configurations are to being planar. If a radical is nearly planar, it is described as being π-type. If, on the other hand, a radical is much more pyramidal, it is considered to be a σ-type radical. Information about radical structure is obtained from molecular-orbital calculations and from observation of α-$^{13}$C hyperfine coupling constants (determined from ESR spectra of the $^{13}$C-enriched radicals).

A conformation of a radical is one of the arrangements of atoms that can be formed by rotation about one or more single bonds. Pyranos-1-yl radicals have been extensively studied and some have been found to favor unexpected conformations. Perhaps most striking among these is the 2,3,4,6-tetra-*O*-acetyl-D-glucopyranos-1-yl radical, which exists in a distorted $B_{2,5}$ boat conformation.

Information about radical conformations is derived from both experimental and theoretical studies. Experimental information comes from analysis of ESR spectra. Study of pyranos-1-yl radicals has led to the identification of the quasi-anomeric effect as a general, controlling influence in determining conformations in many radicals. Understanding of radical conformation comes both from simple and complex applications of molecular-orbital theory. Frontier-orbital interactions offer a simple, theoretical means for rationalizing radical conformation. The far more sophisticated ab initio molecular-orbital calculations also provide understanding of the reasons for a radical adopting a particular conformation.

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