

Chapter 7

Radical Philicity

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I. Introduction

A. The Evans-Polanyi Relation

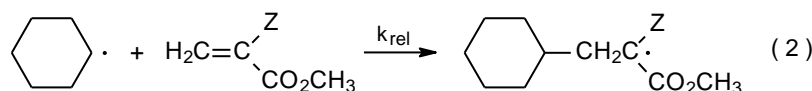
For many radical reactions there is a simple relation between the energy of activation for the reaction and its enthalpy. This relation, which is referred to by several, similar names¹⁻³ (a common being Evans-Polanyi), is given in eq 1. Equation 1 expresses in a quantitative fashion the notion that in a group of closely related reactions the enthalpy for a particular reaction should be related to its energy of activation; specifically, energies of activation should decrease in a linear fashion as reactions become more exothermic.

$$E_a = \text{constant} + \alpha H_r \quad (1)$$

E_a = activation energy

H_r = reaction enthalpy

Once the two constants in eq 1 have been determined, it is possible to predict the energy of activation for reaction of any member of the group from knowledge of the reaction enthalpy. The numerical value of the constant α represents the fraction of the overall enthalpy change that exists at the transition state. The value of α can be viewed as a measure of how far a reaction has proceeded along the reaction coordinate when the transition state is reached. The later a transition state occurs in a reaction the closer α will be to unity.

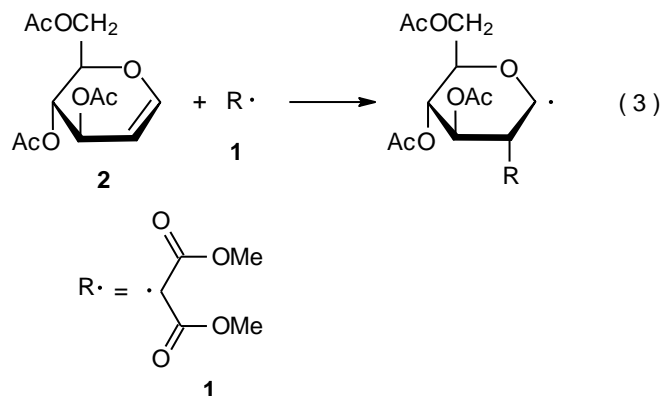


Z	k_{rel}	Z	k_{rel}
CN	1940	H	6
CO ₂ CH ₃	940	CH ₃	5
Cl	75	CH ₃ O	1

B. Nucleophilic and Electrophilic Radicals

Although radicals are neutral species, they often exhibit behavior characteristic of either nucleophilic or electrophilic intermediates.^{4,5} This behavior facilitates certain types of reaction; for example, in the addition reactions shown in eq 2, the carbon-centered, cyclohexyl radical behaves as a nucleophile by adding more rapidly to compounds with more electron-deficient double bonds than to ones in which the double bonds are less electron-deficient.⁶ In contrast, the malonyl radical **1** can be viewed as electrophilic because it adds to electron-rich double bonds such as that in the

D-glucal **2** (eq 3).⁷ A good beginning point for discussing radical philicity is examining some hydrogen-atom abstraction reactions.



	$\delta^{\ominus} \delta^{\oplus}$ H—Sn	$\delta^{\ominus} \delta^{\oplus}$ H—Si	$\delta^{\oplus} \delta^{\oplus}$ H—S	$\delta^{\oplus} \delta^{\oplus}$ H—Se	$\delta^{\oplus} \delta^{\oplus}$ H—C
Pauling's electronegativity values	2.1 1.8	2.1 1.8	2.1 2.5	2.1 2.4	2.1 2.5
bond energies (kcal/mol) ⁸	78.0 (Bu ₃ SnH)	95.0 (Me ₃ SiH)	88.6 (Me ₃ CSH)	78 (C ₆ H ₅ SeH)	95 (Me ₃ CH)
		83.7 ((Me ₃ Si) ₃ SiH)	83.5 (C ₆ H ₅ SH)		
rate constants (M ⁻¹ s ⁻¹)	2 × 10 ⁶ (Bu ₃ SnH)	7.0 × 10 ³ (Et ₃ SiH)	8.0 × 10 ⁶ (Me ₃ CSH)	2.1 × 10 ⁹ (C ₆ H ₅ SeH)	---
		3 × 10 ⁵ ((Me ₃ Si) ₃ SiH)	1 × 10 ⁸ (C ₆ H ₅ SH)		

(References to these rate constants are found in Table 2.)

Table 1. Bond polarities, bond dissociation energies, and rate constants for hydrogen abstraction

II. Bond Polarities, Bond-Dissociation Energies, and Rate Constants for Hydrogen-Atom Abstraction Reactions

Bond polarities, bond-dissociation energies, and rate constants for abstraction of hydrogen atoms bonded to tin, silicon, sulfur, selenium, or carbon atoms all are given in Table 1. Based on Pauling's electronegativity values, hydrogen has a small negative charge when bonded to tin or silicon and a small positive charge when bonded to sulfur, selenium, or carbon. The information in

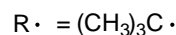
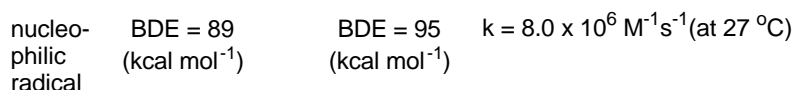
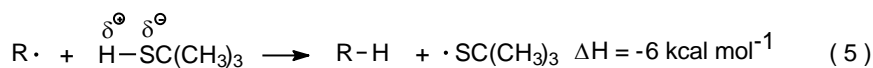
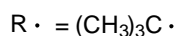
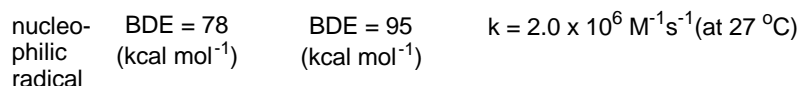
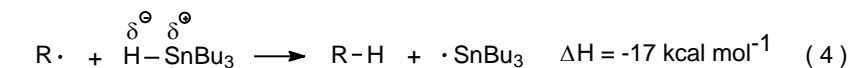
Table 2 shows that for each type of bond, the rate constant for hydrogen-atom abstraction by simple primary, secondary, and tertiary, carbon-centered radicals is nearly the same.

abstracting radical	hydrogen donor	reaction rate, $M^{-1}s^{-1}$	temp	ref
ethyl	Bu ₃ SnH	2.4×10^6	27 °C	9
<i>iso</i> -propyl	Bu ₃ SnH	1.5×10^6	27 °C	9
<i>tert</i> -butyl	Bu ₃ SnH	1.8×10^6	27 °C	9
general rate constant for abstraction by alkyl radicals		Bu ₃ SnH	2×10^6	
primary	Et ₃ SiH	7.0×10^3	50 °C	10
primary	(Me ₃ Si) ₃ SiH	3.8×10^5	25 °C	11
secondary	(Me ₃ Si) ₃ SiH	1.4×10^5	25 °C	11
tertiary	(Me ₃ Si) ₃ SiH	2.6×10^5	25 °C	11
general rate constant for abstraction by alkyl radicals		(Me ₃ Si) ₃ SiH	3×10^5	
primary	Me ₃ CSH	8.0×10^6	25 °C	12
ethyl	C ₆ H ₅ SH	1.36×10^8	25 °C	13
<i>iso</i> -propyl	C ₆ H ₅ SH	1.05×10^8	25 °C	13
<i>tert</i> -butyl	C ₆ H ₅ SH	1.47×10^8	25 °C	13
general rate constant for abstraction by alkyl radicals		C ₆ H ₅ SH	1×10^8	
primary	C ₆ H ₅ SeH	2.1×10^9	25 °C	14, 15

Table 2. Rate constants for hydrogen abstraction by simple, carbon-centered radicals from common hydrogen-atom donors

When the bond dissociation energies in Table 1 are used to calculate reaction enthalpies, they show that the reaction in eq 4 is more exothermic than that in eq 5. If the Evans-Polanyi relation is obeyed, the first reaction (eq 4) should have a lower energy of activation than the second (eq 5), but the opposite appears to be true. The rate constants for these reactions, when related to activa-

tion energies through the Arrhenius equation (eq 6), show that, unless the frequency factors for these two reactions are quite different, the reaction given in eq 4 actually has a higher energy of activation. Clearly, something in addition to reaction enthalpies must have a significant role in determining energies of activation for these two reactions.



$$k = A e^{-E_a/RT} \quad (6)$$

A = the frequency factor

E_a = the energy of activation

k = the reaction rate constant

The identification of a likely candidate for this additional factor can be made by returning to the reactions pictured in equations 2 and 3 and recalling that these reactions show some carbon-centered radicals to be nucleophilic and others electrophilic. If one assumes that the *tert*-butyl radical is similar in its philicity to the nucleophilic cyclohexyl radical, then in the reaction in eq 5 there is a polarity match between the nucleophilic radical and the electron-deficient hydrogen atom being abstracted. Since a similar match does not exist in the slower reaction (eq 4), radical philicity becomes a prime candidate for the factor that joins with reaction enthalpy in explaining the rate constants for hydrogen-atom abstraction reactions.

III. Determining Radical Philicity

Since radical philicity appears to have an important role in radical reactivity, it is valuable to be able to determine easily whether a particular radical is electrophilic or nucleophilic. A procedure that accomplishes this task would be especially useful if it could be implemented simply by inspecting the structure of the radical in question. Fortunately, two such procedures exist. One is

based on atom electronegativity¹⁶ and the other on cation and anion stability.¹⁷ More sophisticated techniques for determining radical philicity also are known. One of these, principal component analysis,^{18,19} extracts information about nucleophilicity and electrophilicity of radicals from experimentally determined rate constants. A second, based on ab initio molecular orbital calculations, determines radical philicity from the extent and direction of charge transfer between a radical and an alkene at the transition state for an addition reaction.^{3,20-23} These different approaches to determining radical philicity are described in the next four sections.

A. Atom Electronegativity

Atom electronegativity provides a basis for assigning radical philicity. Radicals such as $\text{RO}\cdot$, $\text{RCO}_2\cdot$, $\text{R}_2\text{N}\cdot$, $\text{Cl}\cdot$, and $\text{F}\cdot$, where the radical center is on an atom more electronegative than carbon, are considered to be electrophilic, and those with the radical centered on an atom less electronegative than carbon (e.g., $\text{R}_3\text{Ge}\cdot$, $\text{R}_3\text{Sn}\cdot$, and $\text{R}_3\text{Si}\cdot$) are classified as nucleophilic.¹⁶ Carbon-centered radicals themselves are considered to be electrophilic if the carbon atom bearing the radical center also contains at least one powerful electron-withdrawing group (e.g., NO_2 , CN , CO_2R , COR). Alkyl radicals and carbon-centered radicals bonded to an atom that can donate electron density to the radical center (e.g., an oxygen or nitrogen atom with an unshared pair of electrons) are taken to be nucleophilic.

B. Cation and Anion Stability

Another approach to assigning radical philicity depends upon knowledge of ion stability.¹⁷ According to this method, a nucleophilic radical is one that leads more easily to a cation by electron loss than to an anion by electron gain. Such an assessment allows alkyl radicals and carbon-centered radicals bearing electron-donating groups (e.g., $\cdot\text{CH}_2\text{OH}$) to be identified as nucleophilic. In a similar fashion, radicals such as $\text{RO}\cdot$, $\text{RCO}_2\cdot$, $\text{R}_2\text{N}\cdot$, $\text{Cl}\cdot$, $\text{F}\cdot$, and $\text{RS}\cdot$, which form anions by accepting electrons more easily than cations by electron loss, are designated as electrophilic.

C. Principal Component Analysis

Principal component analysis is a procedure that extracts nucleophilic and electrophilic components from experimentally determined rate constants for radical addition reactions.^{18,19} Application of this procedure to the problem of radical philicity shows that most carbon-centered radicals range from being strongly to weakly nucleophilic. For example, the hydroxymethyl radical is strongly nucleophilic, but the methyl radical itself is only moderately so. (There are different views about exactly where the methyl radical resides on the nucleophilicity-electrophilicity continuum.^{3,18,20,21,23}) Replacement of one hydrogen atom in the methyl radical with a carbonyl group

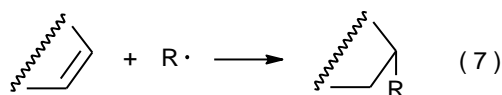
leaves the radical weakly nucleophilic, but replacement of two hydrogen atoms with carbonyl groups produces an electrophilic radical.¹⁸

D. Ab Initio Molecular Orbital Calculations

Studies that use ab initio molecular orbital calculations to investigate radical-addition reactions define radical philicity in terms of electron transfer at the transition state; for example, in radical addition to an alkene a nucleophilic radical is one in which there is transition-state, electron transfer from the radical to the alkene.^{22,23} For an electrophilic radical the reverse situation holds; that is, electron transfer is from the alkene to the radical. Determining the nucleophilicity or electrophilicity of simple radicals (e.g., $\text{CH}_3\cdot$, $\text{Me}_3\text{C}\cdot$, $\text{HOCH}_2\cdot$, $\text{CNCH}_2\cdot$) in addition reactions by ab initio molecular orbital calculations is accomplished in conjunction with a processes known as curve-crossing analysis. (Curve-crossing analysis is a technique for determining the extent of mixing of charge-transfer configurations into the wave function describing the transition state for a reaction.²¹⁻²³)

E. Comparing Procedures for Assigning Radical Philicity

Since there is more than one way in which the nucleophilicity and electrophilicity of radicals can be assigned, the question naturally arises as to whether all procedures make the same assignment. It turns out that the agreement is good but not perfect. Carbon-centered radicals that are decidedly nucleophilic [e.g., $(\text{CH}_3)_3\text{C}\cdot$ or $\text{HOCH}_2\cdot$] or electrophilic [$\cdot\text{CH}(\text{CN})_2$] are classified as such by all approaches. For radicals that are closer to the borderline between nucleophilicity and electrophilicity, (e.g., $\text{CH}_3\cdot$ and $\cdot\text{CH}_2\text{CN}$) there is some disagreement about the proper assignment.^{18,20-23}



IV. Explaining Radical Philicity

A. Valence Bond Theory

One way to explain the existence of radical philicity begins with the addition reaction shown in eq 7. The transition-state structure in this reaction can be represented as a hybrid of valence-bond structures. If there is no separation of charge, the transition state can be represented by the contributors **3** and **4** shown in Figure 1. Unequal electron distribution at the transition state can be taken into account by including additional resonance contributors. If in the transition state there is a transfer of electron density from $\text{R}\cdot$ to the C–C double bond, this transfer can be represented by adding contributors **5** and **6** (Figure 2). If electron transfer is in the other direction, resonance

contributors **7** and **8** (but not **5** and **6**) make a significant contribution to the transition state structure (Figure 2).

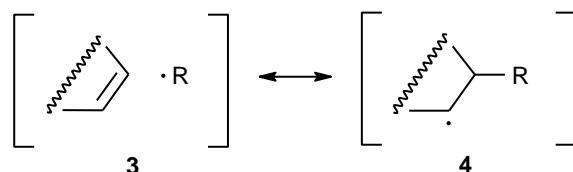


Figure 1. Valence-bond contributors to a nonpolar transition state for radical addition

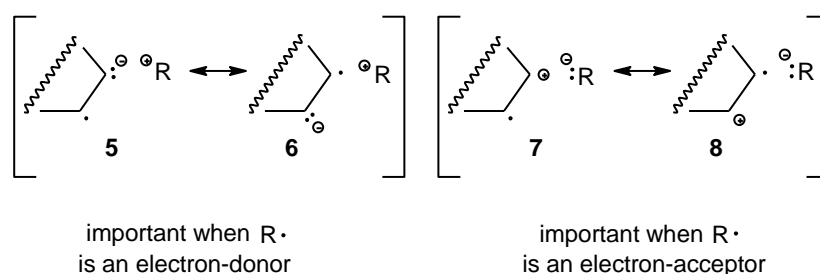
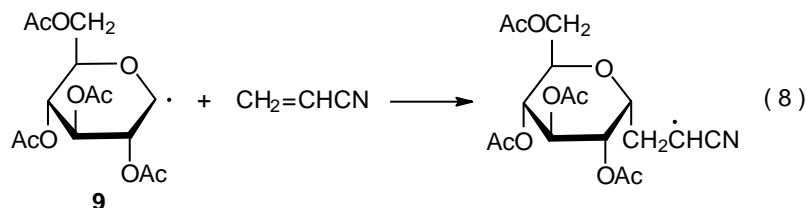


Figure 2. Significant valence-bond contributors when a transition state is polar



1. Nucleophilic Radicals

To illustrate the way in which valence bond theory explains radical nucleophilicity, it is instructive to examine the reaction shown in eq 8. In this reaction the D-glucopyranosyl radical **9** is considered to be nucleophilic because it adds to the electron-deficient double bond in acrylonitrile.²⁴ The valence-bond structures **10-14** (Figure 3) all potentially contribute to the transition-state structure in this reaction. Structures **10** and **11** are major contributors that have no separation of charge. Structures **12** and **13** are minor but significant contributors, minor because they involve separation of charge but significant because they stabilize either negative charge (**12**) or positive and negative (**13**) charges effectively. Structure **14** is not significant because it has charge-separation and the charges are not effectively stabilized. Since structures **12** and **13** make a

greater contribution than does **14** to the transition state in this reaction (eq 8), the radical **9** becomes a net electron-donor at the transition state and, thus, is considered to be nucleophilic.

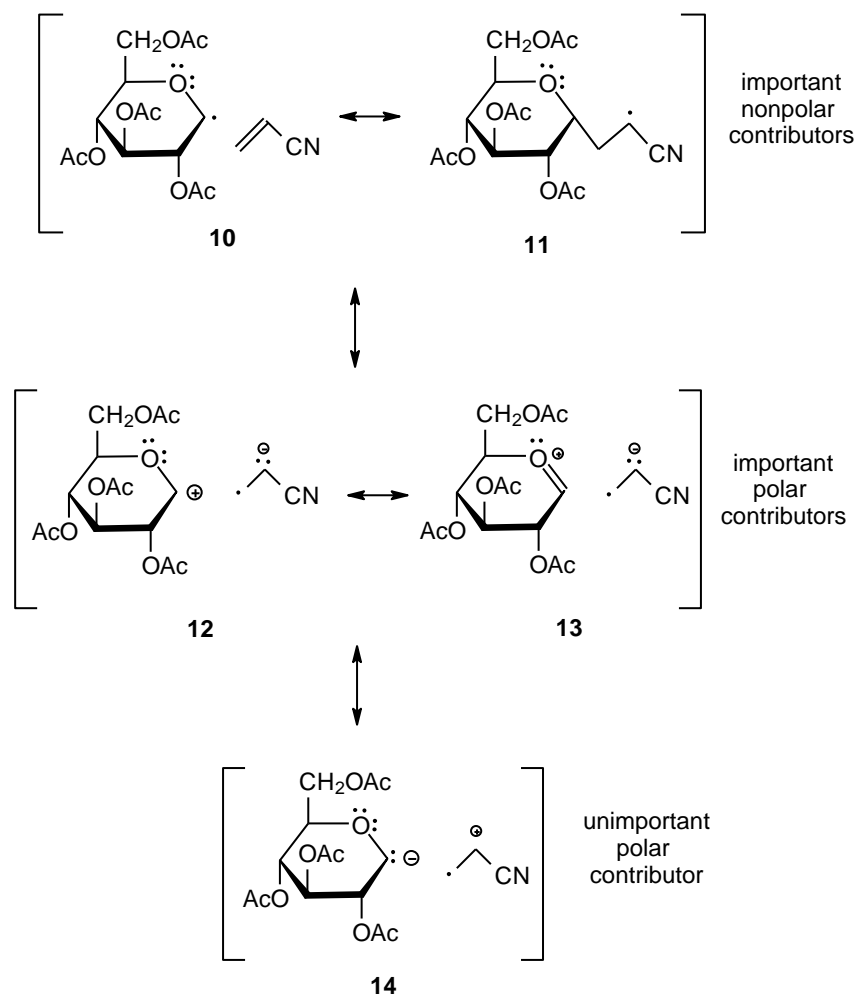


Figure 3. Resonance contributors to the transition-state for addition of a pyranos-1-yl radical to acrylonitrile

2. Electrophilic Radicals

If a radical center has a sufficiently strongly electron-withdrawing substituent (or substituents) attached, the inherently nucleophilic character of a carbon-centered radical is reduced to the point that the radical becomes electrophilic.¹⁸ For example, the malonyl radical **1**, which has two electron-withdrawing groups attached to the radical center, is considered to be electrophilic because it adds to the electron-rich double bond in the D-glucal **2** (eq 3).⁷ The electrophilicity of **1** can be understood primarily in terms of the importance to the transition-state structure of the charge-transfer contributor **15**, a structure in which the electron-withdrawing methoxycarbonyl groups stabilize the negative charge and the ring oxygen atom stabilizes the positive charge (Fig-

ure 4). Together these stabilizing interactions increase the contribution at the transition state from a structure in which the radical **1** is acting as an electrophile by accepting electron density from the D-glucal **2**. The resonance structure **16** is not an important contributor at the transition state because within **16** there is a destabilizing shift of electron density away from a radical center that contains electron-withdrawing, methoxycarbonyl substituents.

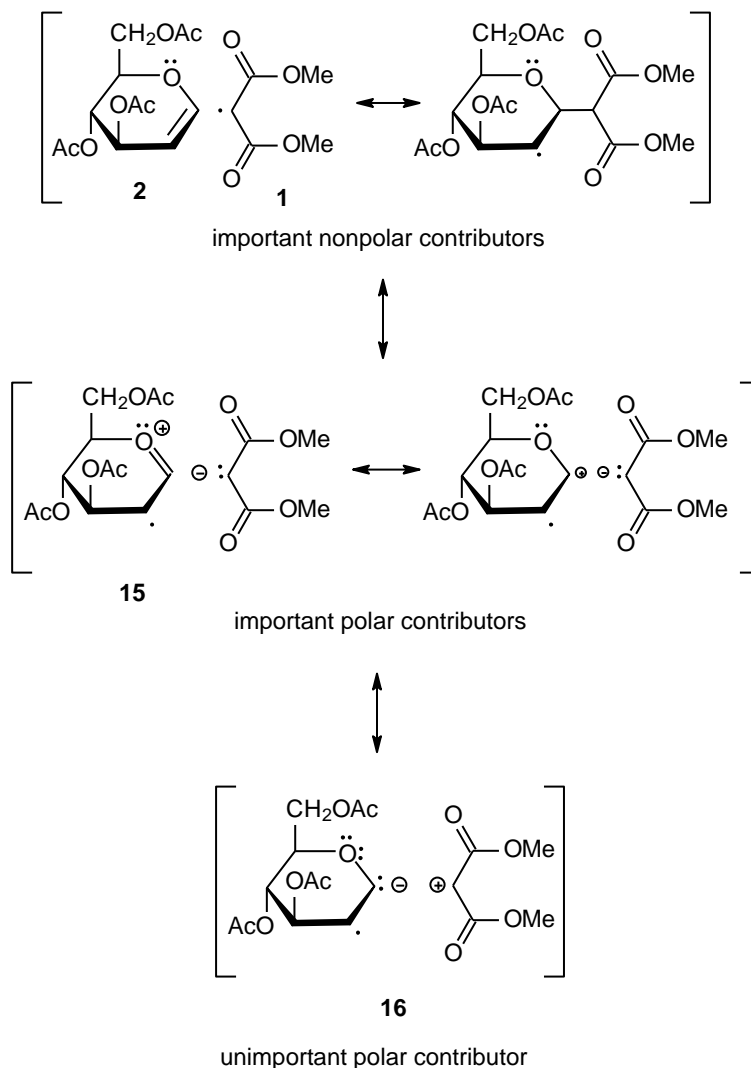


Figure 4. Polar resonance contributors to the transition state during addition of the malonyl radical **1** to the D-glucal **2**

3. Ambiphilic Radicals

Inherent in defining radical philicity in terms of electron-transfer is the idea that the philicity of a radical is a function of the reaction in question. This means that instead of describing a radical as nucleophilic, it should be described as nucleophilic in a particular reaction. It is fair to say, however, that radicals that are moderately or strongly electrophilic or nucleophilic in one reaction are

likely to have the same philicity in all reactions, but radicals that are weakly nucleophilic or electrophilic in one reaction are better candidates for a philicity change in a different reaction. Radicals that are nucleophilic in one reaction but electrophilic in another are classified as ambiphilic.

B. Molecular Orbital Theory: Frontier-Orbital Interactions

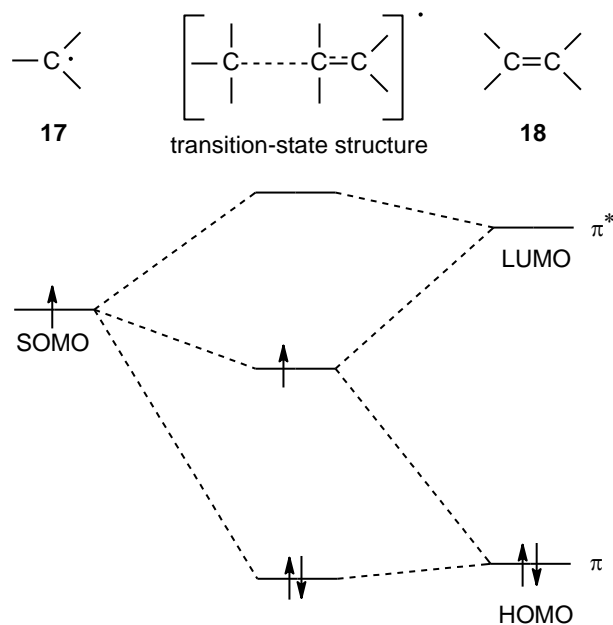


Figure 5. Frontier-orbital interactions for addition of an unsubstituted, carbon-centered radical to a compound with a carbon-carbon double bond

When a transition-state structure for a reaction resembles the structure of the starting materials, frontier-orbital interactions provide qualitative information about energy changes taking place at the transition state. (Since frontier orbitals are based on the structures of the starting materials, the further the transition state is along the reaction pathway the less reliable frontier-orbital interactions will be in predicting or rationalizing reactivity.) According to Hammond's postulate,²⁵ an exothermic reaction should have an early transition state with a structure resembling that of the starting materials; therefore, such a reaction should be suitable for analysis by frontier-orbital interactions. A reaction involving addition of a carbon-centered radical to a carbon-carbon double bond is a prime candidate for this type of analysis because such a reaction replaces a π bond with a more stable σ bond, a change that should produce a decidedly exothermic reaction.^{1,3,6,26}

1. Nucleophilic Radicals

A beginning point for explaining radical nucleophilicity in terms of frontier-orbital interactions is found in Figure 5, which pictures the singly occupied molecular orbital (SOMO) in the

radical **17** interacting with both the π^* (LUMO) and the π (HOMO) orbitals of the alkene **18**. Identifying the most important interaction is critical to determining the nucleophilicity of the adding radical. When the SOMO of **17** interacts with the alkene **18**, the greater interaction is with the π^* orbital of the alkene (Figure 5).⁶ Convincing evidence supporting this position comes from plotting calculated HOMO and LUMO energies of substituted alkenes against the natural logarithm of the relative rate constants ($\ln k_{\text{rel}}$) for addition of a carbon-centered radical (the *tert*-butyl radical was used) to these alkenes.²⁷ A linear correlation exists between $\ln k_{\text{rel}}$ and LUMO energies, but no such correlation exists between $\ln k_{\text{rel}}$ and HOMO energies. The correlation with LUMO energies then is consistent with the dominant frontier-orbital interaction being between the SOMO of the radical **17** and the π^* orbital of the alkene **18** (Figure 5).

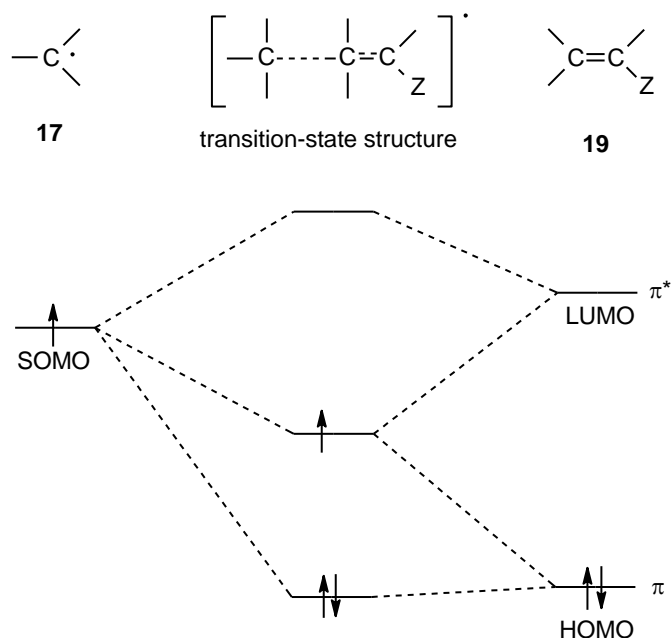


Figure 6. Frontier-orbital interactions for addition of a carbon-centered radical to a compound with an electron-deficient double bond

The next step in understanding how frontier-orbital interactions can explain radical nucleophilicity involves the addition of the radical **17** to the alkene **19**, a compound in which the double bond contains the electron-withdrawing substituent Z (Figure 6). When Z replaces one of the hydrogen atoms attached to a doubly bonded carbon atom, the π^* orbital is stabilized and the associated energy level moves closer to that of the SOMO of **17**.²⁸ This change in energy level position increases the interaction between the SOMO and the π^* orbital (Figure 6). Greater interaction translates into a lower transition-state barrier for reaction; therefore, the radical **17** will add more

rapidly to the alkene containing the electron-withdrawing Z group than to an unsubstituted alkene. This preferential reaction with electron-deficient alkenes makes the radical **17** nucleophilic.

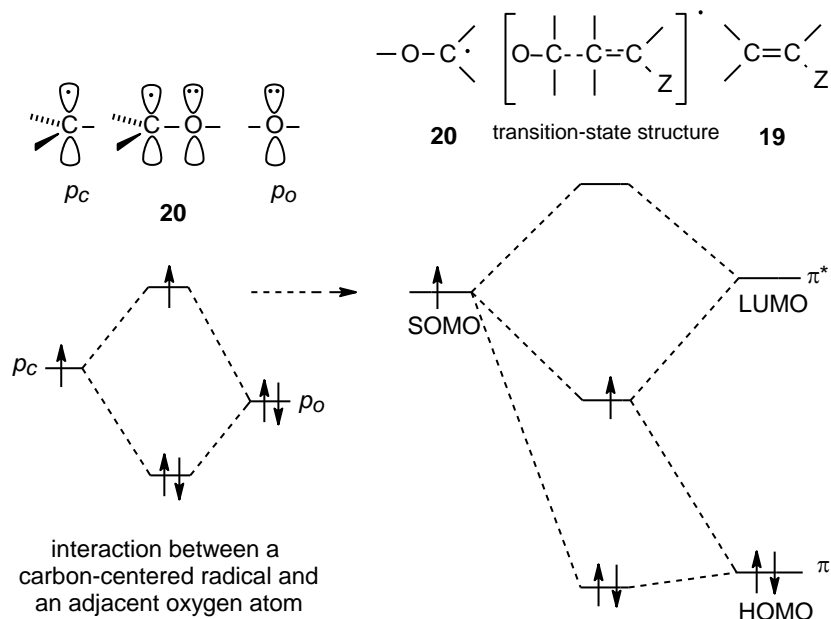


Figure 7. Frontier-orbital interaction for addition of an oxygen-substituted radical to a compound with an electron-deficient double bond

It is possible to increase the nucleophilicity of a carbon-centered radical still further if its SOMO energy level moves even closer to that of the π^* orbital of an alkene. This type of change occurs when an oxygen atom is attached directly to the radical center because interaction between the p -type orbital on the carbon atom and the p -type orbital on the adjacent oxygen atom raises the SOMO energy level in the resulting radical (**20**) (Figure 7). This higher energy level places the SOMO closer energetically to the π^* orbital of the reactant alkene. Such a change further increases orbital interaction and in so doing causes greater transition-state stabilization. The enhanced reactivity, due to the presence of the attached oxygen atom, means that the radical **20** will be even more nucleophilic than **17**; thus, this oxygen-substituted radical (**20**) is considered to be strongly nucleophilic.

There is an additional way of viewing the frontier-orbital interaction between an alkene and a carbon-centered radical. Understanding this alternative view begins by recalling that the major, frontier-orbital interaction between a carbon-centered radical and an unsaturated compound is between the SOMO of the radical and the π^* orbital (LUMO) of the alkene (Figures 5-7). Since SOMO-LUMO interaction is the most important and since any electron donation at the transition state resulting from this interaction must involve electron transfer from the SOMO (the LUMO has

no electrons to transfer), the radical is acting as an electron donor and, therefore, is behaving as a nucleophile.²⁹

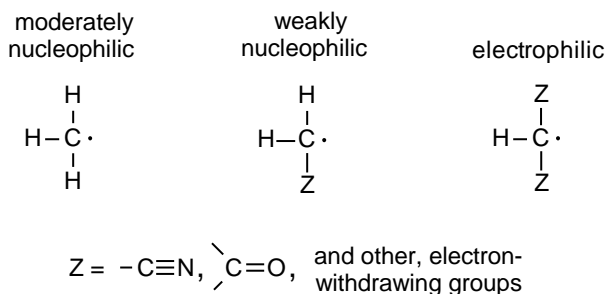


Figure 8. Replacement of the hydrogen atoms in the methyl radical with electron-withdrawing substituents

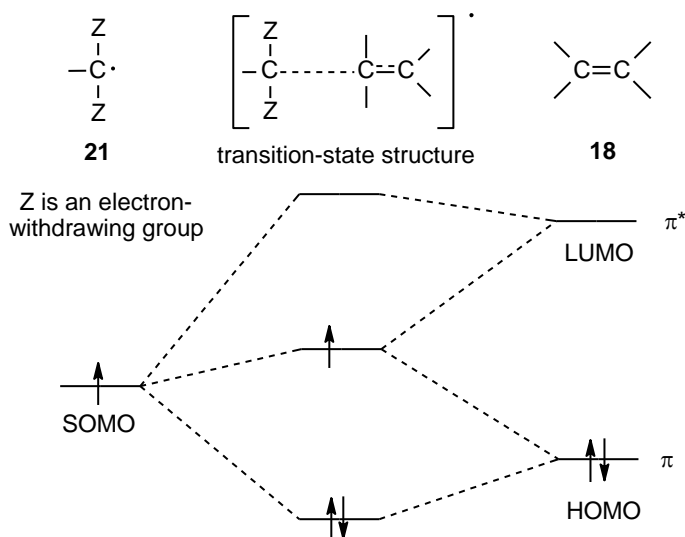


Figure 9. Frontier-orbital interactions for addition of an electron-deficient, carbon-centered radical to an unsaturated compound

2. Electrophilic Radicals

If a hydrogen atom attached to a carbon-centered radical is replaced by an electron-withdrawing substituent (e.g., a cyano or carbonyl group), the resulting radical becomes more electrophilic.^{6,18,30,31} Additional substitution of this type further increases radical electrophilicity (Figure 8). The electron-withdrawing group causes the energy level associated with the singly occupied molecular orbital of the substituted radical to move to a position lower in energy; that is,

the radical becomes more stable.^{6,32} When the energy level of an SOMO in a carbon-centered radical becomes sufficiently low, the major, frontier-orbital interaction with an alkene changes; that is, the primary interaction is no longer with the π^* orbital of the alkene but rather with its π orbital (Figure 9). When this change occurs, the primary shift in electron density at the transition state is away from the filled HOMO toward the partially filled SOMO; thus, the radical is electrophilic.

Figure 10 pictures the frontier-orbital interaction of the radical **21** with an alkene that has an electron-donating substituent. Since the HOMO for the substituted alkene (Figure 10) is higher in energy than the HOMO of the unsubstituted alkene (Figure 9),²⁸ transition-state stabilization from SOMO-HOMO interaction will be greater for reaction involving the substituted alkene (Figure 10). Due to this greater stabilization, the radical **21** reacts more rapidly with the more electron-rich alkene, a behavior expected from an electrophilic intermediate.

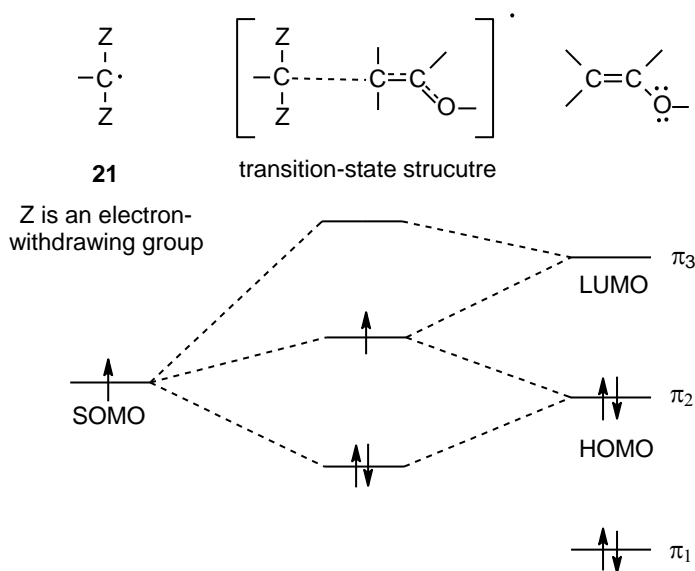


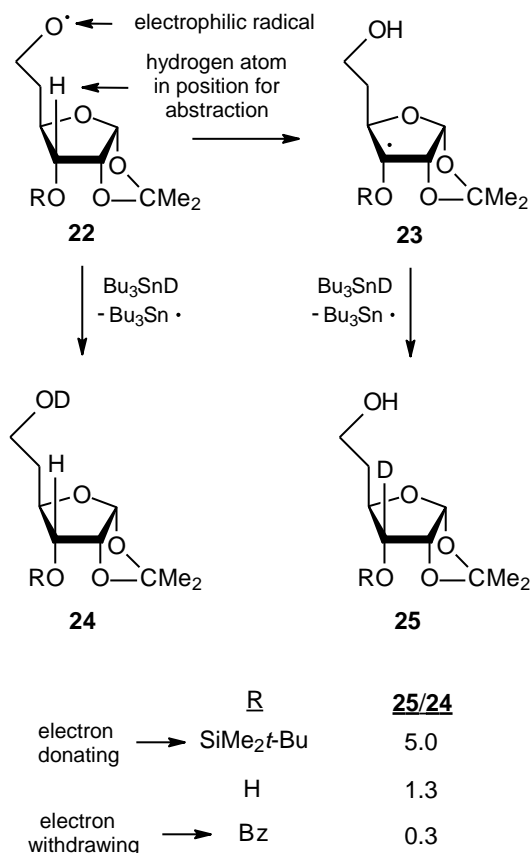
Figure 10. Frontier-orbital interactions for addition of an electron-deficient, carbon-centered radical to a compound with an oxygen-substituted double bond

C. Balancing Polar and Enthalpy Effects

The discussion at the beginning of this chapter focused on groups of similar reactions that obey the Evans-Polanyi relation, that is, reactions in which the energies of activation can be determined from reaction enthalpies using eq 1. Attention then turned to reactions where this simple relation (eq 1) does not hold. The energies of activation for reactions that do not obey the Evans-Polanyi relation are influenced by polar effects operative at the transition state. Since some reactions are more subject to enthalpy effects and others to polar effects, the question naturally arises as to what the balance is between these two. Principal component analysis answers this

question with the finding that “the dominant factors influencing radical addition reactions are polar effects alone for strongly nucleophilic or strongly electrophilic radicals...and enthalpy effects alone for weakly nucleophilic or weakly electrophilic radicals”.¹⁸ For moderately nucleophilic or moderately electrophilic radicals both polar and enthalpy effects are important.¹⁸

Scheme 1



V. Examples of Radical Philicity in Reactions of Carbohydrates

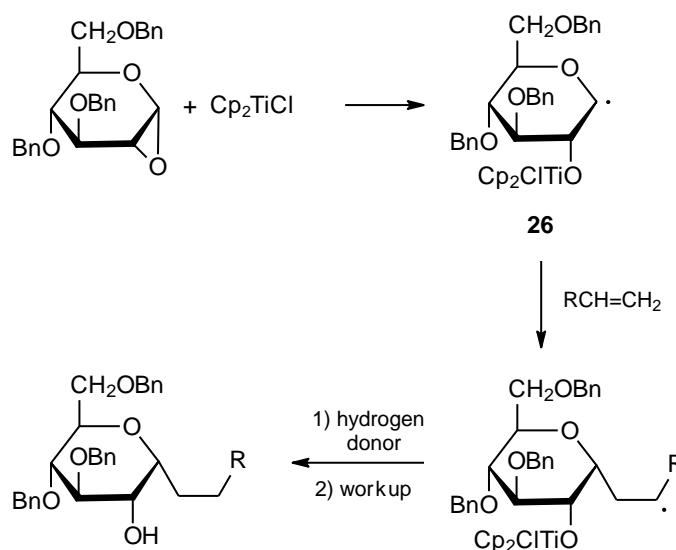
A. Hydrogen-Atom Abstraction

The reactions shown in equations 4 and 5 illustrate the importance of radical philicity in hydrogen-atom abstraction reactions by showing that the nucleophilic radical R \cdot abstracts the electron-deficient hydrogen atom attached to sulfur (eq 5) more rapidly than the electron-rich hydrogen atom bonded to tin (eq 4).^{33–35} The differences in rate constants and enthalpies for these two reactions underscore the fact that radical philicity affects the stability of the transition-state structure in a reaction but not the overall energy changes due to bond breaking and bond formation.

Comparing the three reactions pictured in Scheme 1 draws attention to the effect of radical philicity on hydrogen-atom abstraction from carbohydrates. In each of these reactions the

oxygen-centered radical **22** either abstracts a deuterium atom from Bu_3SnD to give the deuterated alcohol **24**, or it reacts internally with H-3 to generate the carbon-centered radical **23**.³⁶ After the radical **23** forms, it then abstracts a deuterium atom for Bu_3SnD to give the second reaction product (**25**). The relative amounts of products **24** and **25** provide a measure of external (deuterium-atom) versus internal (hydrogen-atom) abstraction. As H-3 becomes less electron rich, internal reaction (**22**→**23**) becomes less competitive. External abstraction (**22**→**24**), on the other hand, should not be noticeably affected by changes in substituents at C-3. If, as expected, the transition states for the internal hydrogen-atom abstraction reactions shown in Scheme 1 are early, these reactions support the idea that polarity matching has a critical role in determining the favored reaction pathway for the radical **22**.

Scheme 2



<u>R</u>	<u>reduction potential (V)</u>	<u>product yield</u>
CN	-2.83	61%
CO ₂ Me	-2.93	56%
C ₆ H ₅	> -3.3	no reaction
C ₄ H ₉	> -3.3	no reaction

B. Radical Addition

Pyranos-1-yl radicals add readily to electron-deficient, carbon-carbon double bonds but are much less reactive toward double bonds lacking electron-withdrawing substituents.^{37,38} A group of reactions that illustrates this difference in reactivity is found in Scheme 2.³⁷ The ability of the pyranos-1-yl radical **26** to add to the unsaturated compounds shown in Scheme 2 correlates with the reduction potentials of these compounds; that is, addition to compounds with less negative

reduction potentials occurs more rapidly than addition to compounds with more negative reduction potentials.³⁷

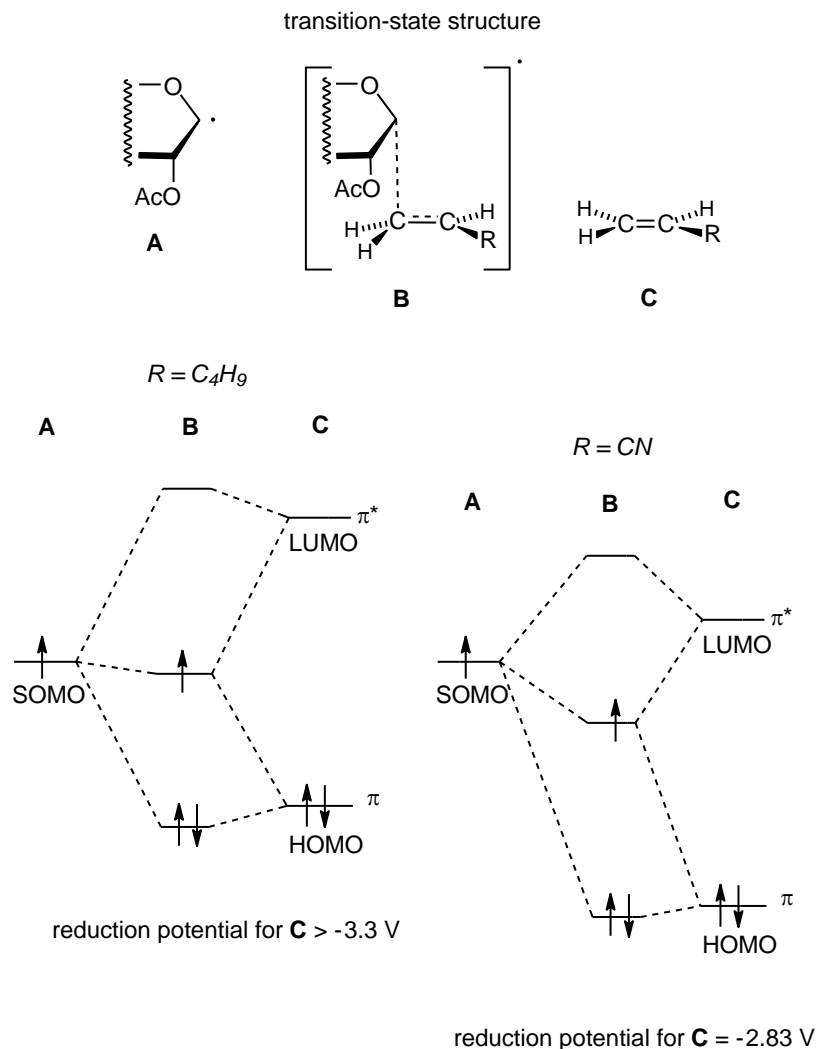


Figure 11. Reaction of a nucleophilic radical with substituted alkenes

Since the reduction potential in a substituted alkene is a measure of the ease of introducing an electron into a π^* orbital, this potential becomes an indicator of energy-level positioning. When comparing two reduction potentials, the less negative one has a lower energy level for the π^* orbital. Because this lower energy level causes the π^* orbital (LUMO) to interact more effectively with the SOMO of the adding radical, transition-state stabilization due to frontier-orbital interaction increases as the reduction potential for the substituted alkene becomes less negative (Figure 11).

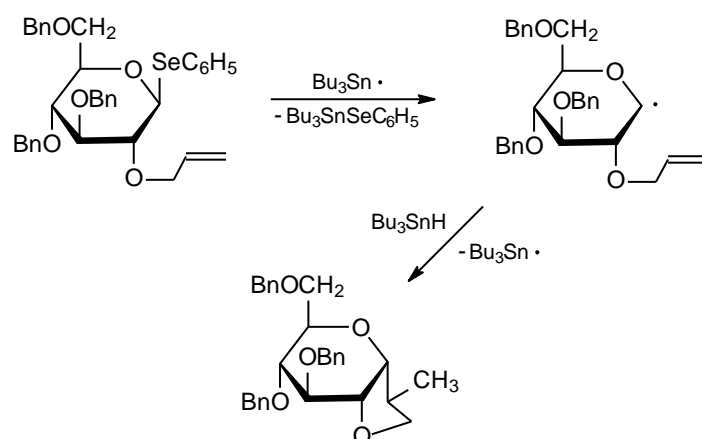
Although the addition of a nucleophilic radical to a π bond that is not electron-deficient is too slow to be observed in the reactions shown in Scheme 2, the situation changes when reactions

become intramolecular. For π bonds that are 1,5- or 1,6-related to a radical center, intramolecular addition can take place even if the π bond is not decidedly electron-deficient (Scheme 3).³⁹ As far as overall reaction rate is concerned, forced, close proximity of the radical center to the π bond can compensate for a small transition-state stabilization caused by a large separation in energy levels of interacting, frontier orbitals.

C. Polarity-Reversal Catalysis

The philicity of radicals involved in hydrogen-abstraction reactions provides the basis for a phenomenon known as polarity-reversal catalysis.^{4,33–35,40} This type of catalysis, which is responsible for the effect that thiols have on the reactions of carbohydrate acetals and ethers, is discussed in Section III of Chapter 5 in Volume II.

Scheme 3

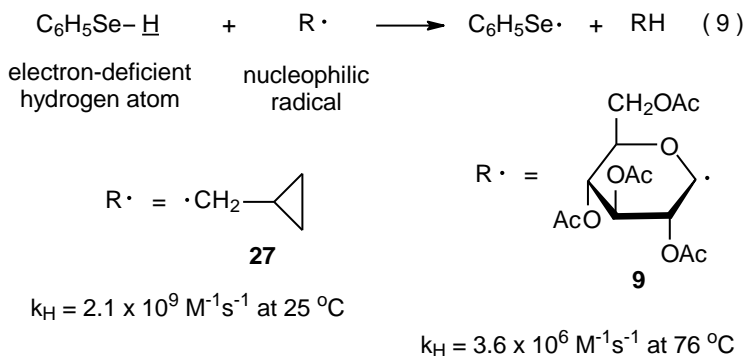


VI. Rate Constants for Hydrogen-Atom Abstraction by Carbohydrate Radicals

A. Extrapolating Results from Model Radicals

Radical philicity first was encountered in this chapter in the reactions of simple organic compounds (Section I.B). The assumption was that information about the reactivity of these compounds could be extrapolated to more complex ones, specifically, carbohydrates. Experimental data supported the validity of this assumption by providing examples of reactions of carbohydrate radicals that qualitatively paralleled those of simpler radicals. For instance, the reactions in eq 2 showed the cyclohexyl radical (a carbohydrate model) to be nucleophilic because it added more rapidly to electron-deficient multiple bonds than to electron-rich ones.⁶ A similar, nucleophilic behavior was seen in the reactions of the carbohydrate radical **26** (Scheme 2). In another example, the reactions described in equations 4 and 5 for simple organic molecules showed that polarity

matching increased the rate of hydrogen abstraction. Extending polarity matching to carbohydrate radicals offered a rationale for the electrophilic radical **22** abstracting an electron-rich hydrogen atom more rapidly than an electron-deficient one (Scheme 1). There is, of course, a limitation to extrapolation of results obtained from simple radicals to radicals that are more complicated. Identifying a limitation, as is done in the following section, can be useful and can lead to increased understanding of the reactivity of the more complicated radicals.



B. A Limitation on Extrapolating Alkyl Radical Reactivity to Carbohydrate Radicals

Extrapolating results from reactions of structurally simple intermediates sometimes provides the only information available for judging reactivity of more complex ones. Successful extrapolation builds confidence in the models selected, but since model systems by their very nature have limitations, such extrapolation is always subject to some uncertainty. The reaction shown in eq 9 illustrates the need for caution in projecting reactivity from a simple to a more complex radical. The data in Table 2 show that rate constants for hydrogen-atom abstraction from compounds with H–Sn, H–S, and H–Si bonds are essentially independent of whether the abstracting radical is primary, secondary, or tertiary. (Steric factors have little effect on rate constants for hydrogen-atom abstraction.⁴¹) Extending this reactivity pattern to compounds with H–Se bonds and knowing that the rate constant for hydrogen-atom abstraction from C₆H₅SeH by the primary radical **27** is 2.1 × 10⁹ M⁻¹s⁻¹ at 25 °C¹⁴ leads to the prediction that the rate constant for reaction of the pyranos-1-yl radical **9** with C₆H₅SeH should have a similar value. It does not; the value is far smaller (3.6 × 10⁶ M⁻¹s⁻¹ at 78 °C).¹⁵

C. An Explanation for Unsuccessful Extrapolation: Loss of Transition-State Stabilization

In attempting to understand the smaller-than-expected rate constant for hydrogen-atom abstraction by the radical **9**, it is useful to recall from Chapter 6 (Section IV.A.2.c) that the conformation of pyranos-1-yl radicals depends on the quasi-anomeric effect, that is, on the

stabilizing interaction of the σ^* orbital of the C₂-O bond with the p -type orbitals on the ring oxygen atom and C-1. This effect is sufficiently powerful to cause **9** to adopt the otherwise unstable, boat conformation shown in Figure 12. Since quasi-anomeric stabilization can only exist in structurally complex systems, simple radicals are limited in their ability to model pyranos-1-yl radicals. The quasi-anomeric effect provides a basis for understanding the smaller-than-expected value for the rate constant for hydrogen-atom abstraction by the radical **9**.

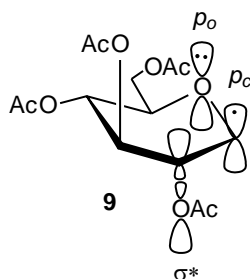


Figure 12. p_C , p_O , and σ^* orbitals that undergo stabilizing interaction in a pyranos-1-yl radical

As the hydrogen-atom abstraction reaction shown in eq 9 ($R\cdot = \mathbf{9}$) moves toward the transition state, the orbital interactions (Figure 12) that cause the electron delocalization that stabilizes the radical **9** are disappearing. (They are totally gone when the product is reached.) This loss of stabilization means that the energy of activation for hydrogen-atom abstraction by **9** will be greater than that for the radical **27**, for which there is no comparable reduction in electron delocalization as the reaction progresses.¹⁵ Hydrogen-atom abstraction, in effect, forces an electron localization that causes a loss of stabilization for the delocalized radical **9** but not for the localized one **27**. This decrease in stabilization at the transition state for reaction of a pyranos-1-yl radical reduces its rate constant for hydrogen-atom abstraction.

The proposal that transition-state loss of quasi-anomeric stabilization in pyranos-1-yl radicals is responsible for their reduced hydrogen-atom-abstracting ability carries with it the prediction that carbohydrate radicals that are not so stabilized should have larger rate constants for hydrogen-atom abstraction. The quantitative information needed to evaluate this prediction does not exist, but there is qualitative information that supports the basic idea. As mentioned in Section V of Chapter 6, pyranos-1-yl radicals can be generated and observed in toluene or tetrahydrofuran but radicals centered on C-2, C-3, or C-4 (with no oxygen atom attached to the radical center and, hence, no quasi-anomeric stabilization possible) cannot be observed in these solvents because such radicals rapidly abstract hydrogen atoms from the solvent. (Only α -tetrahydrofuryl radicals are observed in reactions conducted in tetrahydrofuran and only benzyl radicals are detected in reactions in toluene.⁴²)

The possibility that a loss of transition-state stabilization due to diminishing delocalization is responsible for a smaller-than-expected rate constant for hydrogen-atom abstraction by a pyranos-1-yl radical leads to the proposal that a similar loss of stabilization should have a similar effect on hydrogen-atom abstraction by other radicals. Rate constants for abstraction from C₆H₅SH have a bearing on this proposal. Simple primary, secondary, and tertiary radicals all have rate constants for hydrogen-atom abstraction from C₆H₅SH near $1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ at 25 °C (Table 2), but the rate constant for abstraction from this thiol by the benzyl radical is far smaller ($3.13 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ at 25 °C).¹³ Because the benzyl radical loses resonance stabilization as hydrogen-atom abstraction takes place, it would be expected to parallel the pyranos-1-yl radical in having a smaller rate constant for hydrogen-atom abstraction than the $1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ observed for unstabilized radicals. The fact that the rate constant for hydrogen-atom abstraction by the benzyl radical ($3.13 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$) is a substantially smaller than $1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ strengthens the diminishing-delocalization explanation for reduced reactivity of the pyranos-1-yl radical **9**.

VII. Summary

Radicals often exhibit reactivity characteristic of either nucleophilic or electrophilic species. An electrophilic radical reacts more rapidly with an electron-rich center in a molecule, and a nucleophilic radical is more reactive toward an electron-deficient one.

A number of procedures exist for determining the philicity of a radical. These range from simple ones that involve assignment based on inspection of radical structure combined with a general knowledge of organic chemistry to complicated ones based on ab initio molecular orbital calculations. All procedures lead to the conclusion that nearly every carbohydrate radical is nucleophilic.

Most quantitative information about rates of reaction of carbohydrate radicals comes from extrapolation of data obtained from reaction of model radicals. Although this information is useful in understanding the philicity of carbohydrate radicals, it must be treated with caution when pyranos-1-yl radicals are under consideration. Simple radicals are unable to model the stereoelectronic effects that are critical to radical stability in pyranos-1-yl radicals and, consequently, do not always provide a good measure of their reactivity.

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