JOC Article

Calculated Effect of Substitutions on the Regioselectivity of Cyclization of α-Sulfenyl-, α-Sulfinyl-, and α-Sulfonyl-(5*R*)-5-hexenyl Radicals

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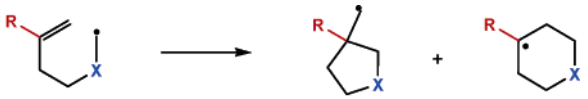
Received August 3, 2006



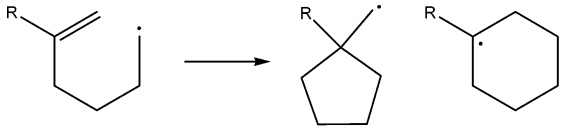
X = S, SO, SO_2
R = H, CN, NO_2, CH_3, NH_2

Calculations of the activation energy of cyclization of α-sulfenyl-, α-sulfinyl-, and α-sulfonyl-5-hexenyl radicals and their respective 5-methyl-5-hexenyl counterparts at the G3MP2B3 level agree quite well with experimental data. The α-sulfinyl-5-hexenyl radical exhibits unexpected regioselectivity (93.99:6.01) via the 5-exo mode, whereas the α-sulfenyl- and α-sulfonyl-5-hexenyl radicals show increasing branching ratios of the 6-endo product. In contrast, the cyclization of the α-sulfur-based 5-methyl-substituted counterparts yields essentially the 6-endo products in all cases; in particular, the α-SO_2-5-CH_3-5-hexenyl radical gives high regioselectivity (98.85:1.15) via the 6-endo mode. Several other 5-substituted moieties, including the electron-withdrawing (CN and NO_2) or electron-donating substituents (NH_2), also proceed preferentially to 6-endo closure. The α-sulfonyl-5-amine-5-hexenyl radical is calculated to proceed to exclusively the 6-endo product, a demonstration of the high synthetic value of this reactant.

Introduction

Several procedures have been proven to be viable for the synthesis of organic and bioorganic compounds that contain *n*-member rings.[1−9] One common procedure is intramolecular radical cyclization, especially for five- or six-membered rings.[10] For example, the 5-hexenyl radical, **1** (shown in Scheme 1), undergoes ring closure to form (over 97%) a 5-exo primary product, **2**, as opposed to a 6-endo product, **3** (less than 3%), which is supposed to be thermodynamically more stable.[6,11] The plausible explanation referred to the so-called stereoelectronic control.[6a] However, it is still possible to achieve a reaction yielding a six-membered ring by substituted radicals of various kinds.[12−16] In general, the regiochemistry of cyclization is governed by not only a stereoelectronic factor but also polar and steric effects. One illustration involves the cyclization of

SCHEME 1. Cyclization of the 5-Hexenyl Radical



1, R=H
4, R=Me

2, R=H
5, R=Me

3, R=H
6, R=Me

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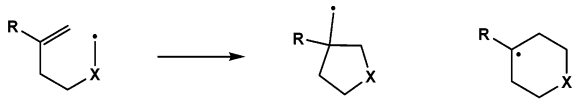
10.1021/jo061614a CCC: $33.50
Published on Web 11/29/2006

SCHEME 2. Cyclization of α-Sulfur-Based 5-Hexenyl Radicals



7. X = S, R = H **8.** X = S, R = H **9.** X = S, R = H
10. X = SO, R = H **11.** X = SO, R = H **12.** X = SO, R = H
13. X = SO_2, R = H **14.** X = SO_2, R = H **15.** X = SO_2, R = H

5-methyl hexenyl radical **4** that yields 5-exo **5** (40%) and 6-endo products **6** (60%), due to an unfavorable steric effect in the 5-exo mode of cyclization.[6,11,17,18] Another illustration of the increased endo/exo product ratio, 6:1, in the ring closure of the 5-carbomethoxy(CO_2Me)-5-hexenyl radical is attributed to the combined polar and steric effects of the substituent.

In the cyclization of 5-hexenyl radicals that contain an α-heteroatom, the nature and reactivity of a radical center can be altered significantly by an adjacent heteroatom such as nitrogen and oxygen.[19] For example, when the heteroatom was N, in α-ammonio-5-hexenyl radicals, cyclization proceeded with high regioselectivity to the 5-exo mode as a major product, whereas the 6-endo mode was not detected. Similarly, when the heteroatom N was in the β-position, a 5-exo product was formed exclusively; a heteroatom O in the β-position likewise favored the 5-exo product (5-exo/6-endo = 98/2).[20] The ring closure of α-sulfenyl-, α-sulfinyl-, and α-sulfonyl-5-hexenyl radicals is reported with the sulfonyl group located external to the 5-hexenyl chain.[21,22] Della et al.[23] conducted experiments on the cyclization of α-sulfur-based 5-hexenyl radicals in which the hetero group constitutes part of the hexenyl chain (including α-sulfenyl, sulfinyl, and sulfonyl functional groups), shown in Scheme 2; their purpose focused on the effect of the longer C−S bond on the cyclization and the presence of these groups that might influence the regiochemistry of the ring closure.

SO and SO_2, in radicals **10** and **13**, respectively, are strongly inductive electron-withdrawing groups that might destabilize an electron-deficient radical center, whereas the S atom in radical **7** exerts a stabilizing influence through the mesomeric interaction of the lone pair with the radical center. Radicals **10** and **13** exhibit a more electrophilic character, whereas **7** has a more nucleophilic nature. According to frontier molecular orbital (FMO) theory,[24] electrophilic radicals such as **10** and **13** (sulfinyl and sulfonyl, with σ_I values as the inductive component 0.52 and 0.53,[25] respectively) have a lower SOMO energy level that allows a more attractive interaction with the alkene HOMO. The terminal carbon (C_6) has a larger HOMO coefficient than that at C_5, providing a larger orbital overlap interaction with SOMO and thus increasing the probability of 6-endo closure. For a nucleophilic radical such as sulfenyl **7** ($\sigma_I = 0.23$), a more favorable orbital interaction in the transition structure occurs between the radical SOMO (due to the elevation of the SOMO energy level) and the π-bond LUMO. The greatest overlap is the radical center with the larger LUMO coefficient at C_5, which leads to a 5-exo closure. These outcomes are thought to be dominated mainly by two factors—a stereoelectronic effect, for which a particular geometric relationship is required to maximize the stabilizing interaction,[26] and a polar effect. A schematic orbital diagram of the interaction of the SOMO with HOMO or LUMO appears in Figure 1.

For the cyclization of the 5-methyl-5-hexenyl radical, in which no heteroatom is involved and the C_5 position carries a substituted methyl group, the product ratio shifts from almost absolute 5-exo[17] (5-exo/6-endo = 99:1 for the nonsubstituted 5-hexenyl radical) to 40:60 of a 5-exo/6-endo mixture.[11] A steric effect is ascribed at the C_5 position such that the methyl group hinders the formation of 5-exo; a 6-endo closure is thus preferred. Our interest is the ring closure of substituents CH_3, NH_2, CN, and NO_2 at the C_5 position of α-sulfur-based 5-(R)-5-hexenyl radicals, including α-sulfenyl-, α-sulfinyl-, and α-sulfonyl-5-substituted-5-hexenyl radicals. We calculated the activation energies, transition structures, rate coefficients, and branching ratios for the formation of 5-exo and 6-endo products, examined the influence of the substituents on the activation energies, and rationalized the attributes to an intrinsic activation energy and thermodynamic contribution based on the Marcus theory.[27,28] Understanding the origin of these rate effects in the radical cyclization of substituted α-sulfur-based 5-hexenyl radicals assists the understanding of substituent effects on other radical cyclization reactions.

Computational Methods

The geometries of all reactants, products, and transition structures that involve radical cyclization were optimized using density functional theory[30−33] with the hybrid UB3LYP[34−36] functional in

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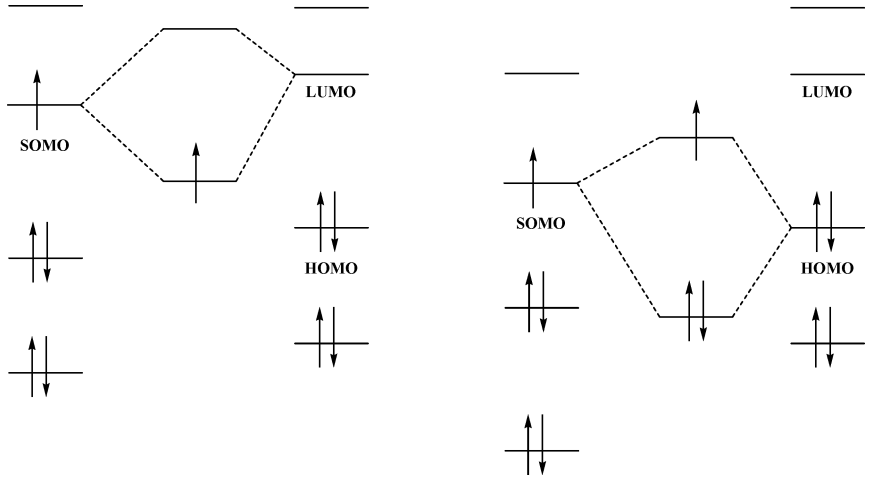

(a) ***A nucleophilic radical*** **(b)** ***An electrophilic radical***

FIGURE 1. Frontier orbital interactions for radicals: (a) LUMO with high-energy SOMO, and (b) HOMO with low-energy SOMO.

conjunction with the 6-31G(d) basis set in the Gaussian 03 package.[37] Each stationary point as an energy minimum or a saddle point was verified by calculation of the harmonic vibrational wavenumbers. Zero-point energies were included in the evaluation of activation energies and heats of reactions. Calculations of intrinsic reaction coordinate (IRC)[38] were performed on all transition structures to confirm the connection between the reactants and products. Single-point calculations at two levels—UB3LYP/6-311++G(d,p)//UB3LPY/6-31G(d) and CCSD(T)/cc-pVDZ//UB3LPY/ 6-31G(d)—were performed. Furthermore, for the calculation of the energies of all structures using the G3-MP2 method at the UB3LYP/6-31G(d) geometries (G3MP2B3),[39] the fourth-order Møller−Plesset perturbation theory (MP4) was substituted by the computationally less demanding MP2 approach. The detail description of the G3MP2B3 method can be found on page S37 of Supporting Information.

We investigated substituent effects on the rates of radical cyclization using transition-state theory with Wigner tunneling corrections[29] and obtained the branching ratio of reaction products by adapting a method similar to that described in the Rice−Ramsperger−Kassel−Marcus (RRKM) theory. The Marcus theory has served to separate thermodynamic and intrinsic contributions to activation energies, as proposed by Murdoch.[27] With calculations of natural bond orbitals (NBO)[40−46] (NBO 4.0 implemented in Gaussian software), we analyzed a possible orbital interaction between the substituent and the radical center. Our calculated results listed in Table 1 show that the G3MP2B3 data agree reasonably with the experimental values, whereas at all other levels there are large deviations. For this reason, we undertook our calculation of all activation energies and thermodynamic data at this level, unless otherwise stated.

Results and Discussion

The reactants and two possible products—5-exo and 6-endo—of the cyclizations of α-sulfur-based 5-hexenyl radicals (α-S, α-SO, and α-SO_2) and their 5-substituted derivatives (CH_3, CN, NO_2, and NH_2) are depicted and numbered in Scheme 3.

Geometries Calculated at the B3LYP/6-31G(d) Level. The calculated transition-state structures of α-sulfur-based 5-(R)-5-hexenyl radicals in the cyclization show a chair conformation with an energy less than that of the boat counterpart; for this reason, we consider only the chair conformer of each transition-state structure. (For example, for R = CN of sulfenyl systems, in the transition-state structure, forming the 6-endo product, the chair conformation is about 4 kcal/mol less than that of the boat counterpart.) During the formation of cyclic products, either 5-exo or 6-endo, each transition-state structure is associated with the formation of one σ-bond and a cleavage of the nearby π-bond. The C_1-S_2 bond length in the transition-state structure of the forming 5-exo product (shown in Table S32) of the α-S system is within 1.746−1.765 Å, with an electron-withdrawing substituent at the C_5 position correlating with a shorter bond and an electron-donating group with a longer bond. In either the α-SO or α-SO_2 system, the C_1-S_2 bond with a similar substituent behaves oppositely to the α-S system, in which the C_1-S_2 bond is longer with an electron-withdrawing substituent (within 1.775−1.797 Å) but shorter with the donating counter-

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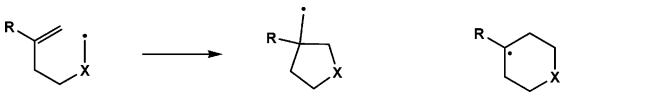
TABLE 1. Imaginary Wavenumbers/cm^{-1}, Activation Energies/kcal mol^{-1}, and Rate Coefficients/s^{-1} for the Radical Cyclizations of 5-Hexenyl- and 5-Methyl-5-hexenyl Radicals at the UB3LYP/6-31G(d), UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d), CCSD(T)/cc-pVDZ// UB3LYP/6-31G(d), and G3MP2B3 Levels

	5-exo			6-endo		
	wavenumber	$\Delta E^{\ddagger}$	rate coefficient[c]	wavenumber	$\Delta E^{\ddagger}$	rate coefficient[c]
			5-Hexenyl Radicals (1)			
UB3LYP/6-31G(d)	447.6i	6.3	1.22×10^7	414.4i	8.8	1.14×10^5
UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d)		7.2	2.68×10^6		9.6	2.95×10^4
CCSD(T)/cc-pVDZ//UB3LYP/6-31G(d)		10.4	1.11×10^4		12.8	1.24×10^2
G3MP2B3	447.9i	8.3	3.57×10^5	414.8i	10.4	7.34×10^3
exp.[a]			$2.30 \times \mathbf{10}^5$			4.10×10^3
			5-Methyl-5-hexenyl Radicals (4)			
UB3LYP/6-31G(d)	483.8i	8.8	1.15×10^5	417.8i	7.7	8.63×10^5
UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d)		9.5	3.97×10^4		8.4	2.74×10^5
CCSD(T)/cc-pVDZ//UB3LYP/6-31G(d)		12.7	1.67×10^2		12.1	5.31×10^2
G3MP2B3	483.8i	9.5	3.95×10^4	417.8i	9.4	5.48×10^4
exp.[b]			$5.30 \times \mathbf{10}^3$			9.00×10^3

[a] From ref 6b. [b] From ref 17b. [c] All rate coefficients were calculated with TST theory and a Wigner tunneling correction.

SCHEME 3



1. X = S, R = H
4. X = SO, R = H
7. X = SO_2, R = H
10. X = S , R = CN
13. X = S , R = NO_2
16. X = S , R = CH_3
19. X = S , R = NH_2
22. X = SO , R = CN
25. X = SO , R = NO_2
28. X = SO , R = CH_3
31. X = SO , R = NH_2
34. X = SO_2 , R = CN
37. X = SO_2 , R = NO_2
40. X = SO_2 , R = CH_3
43. X = SO_2 , R = NH_2

2. X = S, R = H
5. X = SO, R = H
8. X = SO_2, R = H
11. X = S , R = CN
14. X = S , R = NO_2
17. X = S , R = CH_3
20. X = S , R = NH_2
23. X = SO , R = CN
26. X = SO , R = NO_2
29. X = SO , R = CH_3
32. X = SO , R = NH_2
35. X = SO_2 , R = CN
38. X = SO_2 , R = NO_2
41. X = SO_2 , R = CH_3
44. X = SO_2 , R = NH_2

3. X = S, R = H
6. X = SO, R = H
9. X = SO_2, R = H
12. X = S , R = CN
15. X = S , R = NO_2
18. X = S , R = CH_3
21. X = S , R = NH_2
24. X = SO , R = CN
27. X = SO , R = NO_2
30. X = SO , R = CH_3
33. X = SO , R = NH_2
36. X = SO_2 , R = CN
39. X = SO_2 , R = NO_2
42. X = SO_2 , R = CH_3
45. X = SO_2 , R = NH_2

part (within 1.768−1.775 Å). This explanation also relates to the mesomeric effect of the α-S system (a more nucleophilic nature) in favor of electron-withdrawing substituents to stabilize the transition state (TS) (shorter C_1-S_2 bond), whereas the α-SO and α-SO_2 systems are more electrophilic and exhibit longer C_1-S_2 bonds with the same substituents. Other than the inductive effect, a major factor that influences the C_1-C_5 bond length of the transition-state structure in forming the 5-exo product is the steric effect of the substituents. Among the latter, the NO_2 and CH_3 groups are bulkier than other substituents, preventing the approach of the C_1 radical to the C_5 atom and thus lengthening the C_1-C_5 bond in contrast to the smaller CN and NH_2 groups.

The principal factor that influences the length of the C_1-C_6 bond in a transition-state structure for the formation of 6-endo products is the inductive effect from the substituents. The more strongly electron-withdrawing groups (CN, NO_2) extend the C_1-C_6 bond, whereas this length for the donating counterparts (CH_3, NH_2) is almost invariant in the α-S, α-SO, and α-SO_2 systems, by comparison with the nonsubstituted analogues shown in Table S33. The degree of elongation of the C_1-C_6 bond in these systems is variable. In the α-S system with CN and NO_2 substituents, the C_1-C_6 bond lengths extend by 0.12 and 0.15 Å, respectively, with NO_2 being longer. Our rationalization is that the more strongly electron-withdrawing substituent cooperates with greater displacement of the newly formed C_1-C_6 bond electrons, to extend the C_1-C_6 bond, whereas in the α-SO and α-SO_2 systems the C_1-C_6 bonds with electron-withdrawing substituents NO_2 and CN extend by 0.10−0.11 and 0.07−0.09 Å, respectively. The smaller elongation is explicable according to the increased electrophilic character of the α-SO and α-SO_2 systems, causing the displacement of the C_1-C_6 bond electrons to be less effective with the electron-withdrawing substituents.

Marcus Theory. To understand separately the intrinsic and thermodynamic contribution of substituent effects on the rate of the α-sulfur-based (5*R*)-5-hexenyl radical cyclization, we applied the Marcus theory. The Marcus equation is

$$\Delta E^{\ddagger} = \Delta E_0^{\ddagger} + {}^1/_2\Delta E_{rxn} + (\Delta E_{rxn})^2/16(\Delta E_0^{\ddagger}) \qquad (1)$$

where the activation energy, $\Delta E^{\ddagger}$, of a nondegenerate reaction is the sum of the intrinsic barrier, $\Delta E_0^{\ddagger}$, and the thermodynamic contribution, no matter whether the reaction, ΔE_{rxn}, is exothermic or endothermic. The intrinsic barrier is the hypothetical thermoneutral process, that is, a degenerate transformation. The thermodynamic contribution is an estimate of the change in activation energy caused by the substituent due to an alteration of the heat of reaction, based on an assumption that the hypersurface of potential energy behaves like two overlapping parabolas representing reactant and product energies, depicted in Figure 2.The term $(\Delta E_{rxn})^2/16(\Delta E_0^{\ddagger})$ is a correction for nonadditivity of the intrinsic and thermodynamic effects. The equation is practically equivalent to the assumption that half the reaction energy ΔE_{rxn} contributes to the activation energy $\Delta E^{\ddagger}$. An equivalent expression to solve the resulting quadratic equation for the intrinsic barrier, $\Delta E_0^{\ddagger}$, is

$$\Delta E_0^{\ddagger} = \frac{\Delta E^{\ddagger} - ({}^1/_2)\Delta E_{rxn} + \sqrt{\Delta E^{\ddagger 2} - \Delta E^{\ddagger}\Delta E_{rxn}}}{2} \qquad (2)$$

The Marcus equation permits a separation of intrinsic and thermodynamic contributions to the activation energy. We used this formula in our calculations of the intrinsic and thermodynamic contributions after obtaining the activation energy and the energy for the reaction.

Substituent Effects on Activation Energies. The calculated activation energies, reaction energies, intrinsic barriers, and thermodynamic contributions according to the formalism (2) for the radical cyclization of α-sulfur-based 5-(R)-5-hexenyl radicals are listed in Table 2. The computational results for the nonsubstituted parent radicals (R = H) exhibit a strong

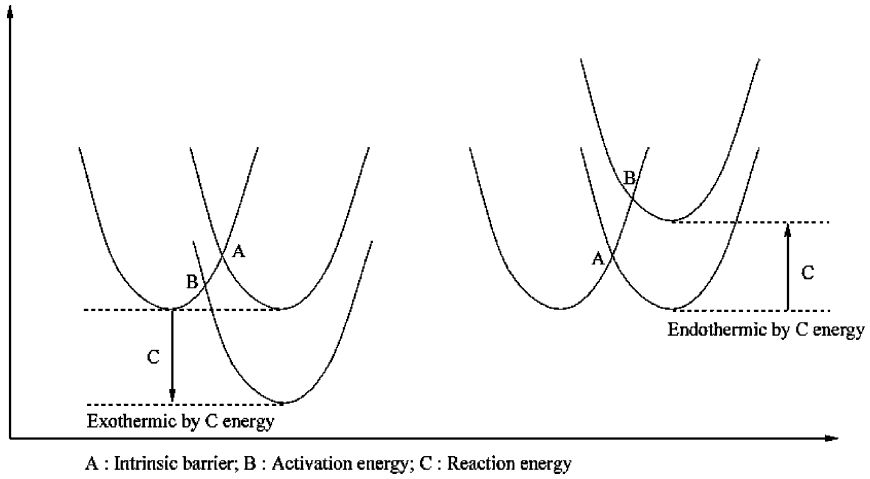


FIGURE 2. The potential energy diagrams to describe the Marcus theory model for degenerate and exothermic or endothermic reactions: (A) the intrinsic barrier of the thermoneutral reaction; (B) the activation energy of the exothermic (the left graph) or endothermic (the right one) reactions; and (C) the reaction energy.

TABLE 2. Activation Energies/kcal mol^{-1}, Reaction Energies/kcal mol^{-1}, Intrinsic Barriers/kcal mol^{-1}, and Thermodynamic Contributions/kcal mol^{-1} to the Activation Energies for the Radical Cyclization of α-Sulfenyl-, α-Sulfinyl-, and α-Sulfonyl-5-(R)-5-hexenyl Radicals[a] with the G3MP2B3 Method[b]

	5-exo				6-endo			
	$\Delta E^{\ddagger}$	ΔE_{rxn}	$\Delta E_0^{\ddagger}$	$\Delta E_{thermo}^{\ddagger}$	$\Delta E^{\ddagger}$	ΔE_{rxn}	$\Delta E_0^{\ddagger}$	$\Delta E_{thermo}^{\ddagger}$
2-S-C_5-H	11.8	−11.5	17.1		12.6	−13.7	18.8	
2-S-C_5-CN	12.5 (0.7)	−9.0 (2.5)	16.7 (−0.4)	(1.1)	8.8 (−3.7)	−21.1 (−7.4)	17.8 (−1.0)	(−2.7)
2-S-C_5-NO_2	9.9 (2.0)	−13.0 (−1.5)	15.7 (−1.4)	(−0.6)	6.3 (−6.2)	−19.0 (−5.3)	14.2 (−4.5)	(−1.7)
2-S-C_5-CH_3	13.1 (1.3)	−11.3 (0.2)	18.3 (1.2)	(0.1)	11.8 (−0.8)	−14.5 (−0.8)	18.3 (−0.5)	(−0.3)
2-S-C_5-NH_2	14.7 (2.8)	−7.9 (3.7)	18.4 (1.3)	(1.5)	11.7 (−0.8)	−16.2 (−2.5)	19.0 (0.2)	(−1.0)
2-SO-C_5-H	7.3	−19.3	15.5		8.8	−21.4	17.8	
2-SO-C_5-CN	9.5 (2.2)	−14.8 (4.6)	16.0 (0.5)	(1.7)	7.2 (−1.6)	−28.3 (−6.9)	18.6 (0.8)	(−2.4)
2-SO-C_5-NO_2	8.5 (1.1)	−18.7 (0.6)	16.5 (1.0)	(0.1)	7.2 (−1.6)	−25.4 (−4.1)	17.6 (−0.3)	(−1.3)
2-SO-C_5-CH_3	8.2 (0.9)	−18.0 (1.3)	16.0 (0.5)	(0.4)	7.7 (−1.0)	−21.9 (−0.6)	16.9 (−0.9)	(−0.1)
2-SO-C_5-NH_2	6.9 (−0.4)	−15.4 (3.9)	13.5 (−2.0)	(1.6)	6.6 (−2.2)	−22.8 (−1.4)	15.9 (−1.9)	(−0.3)
2-SO_2-C_5-H	6.4	−18.7	14.1		6.2	−23.7	15.8	
2-SO_2-C_5-CN	9.5 (3.2)	−13.9 (4.8)	15.7 (1.5)	(1.7)	5.4 (−0.7)	−29.3 (−5.6)	16.9 (1.1)	(−1.8)
2-SO_2-C_5-NO_2	6.5 (0.2)	−18.9 (−0.2)	14.4 (0.3)	(−0.1)	3.7 (−2.5)	−27.7 (−4.0)	14.2 (−1.6)	(−0.9)
2-SO_2-C_5-CH_3	7.6 (1.3)	−17.9 (0.8)	15.3 (1.1)	(0.2)	5.0 (−1.2)	−24.2 (−0.5)	14.6 (−1.2)	(0.0)
2-SO_2-C_5-NH_2	10.4 (4.1)	−13.6 (5.1)	16.5 (2.4)	(1.7)	3.7 (−2.5)	−25.2 (−1.5)	13.3 (−2.5)	(0.0)

[a] Values relative to the parent (nonsubstituted radical) are given in parentheses. [b] Thermodynamic contribution equals activation energy plus intrinsic barrier.

preference for formation of the 5-exo products, especially in α-S and α-SO systems. The stereoelectronic effect provides an explanation of the outcomes. In contrast, 6-endo products become dominant in most substituted analogues with R = CH_3, NH_2, CN, and NO_2 of α-sulfur-based systems, especially in α-SO_2. This trend is ascribed to the steric effect of the substituent at the C_5 position, which inhibits the direct formation of 5-exo products, but a detailed investigation is required for the diverse 5-exo/6-endo ratios with respect to various substituents in the α-S, α-SO, and α-SO_2 systems. We employed the Marcus theory to evaluate quantitatively the intrinsic barrier and thermodynamic contribution in these systems. As shown in Table 2, the cyclization of the nonsubstituted α-S system to form a 5-exo product has a smaller activation energy (11.8 kcal/mol) than for the formation of the 6-endo product (12.6 kcal/mol); the calculated 5-exo/6-endo product branching ratio (83.1/16.9, in Table 4) agrees satisfactorily with the experimental measurement (84/16). The Marcus analysis shows also a smaller intrinsic barrier of 5-exo products (17.1 vs 18.8 kcal/mol) and less exothermic (−11.5 vs −13.7 kcal/mol) than for formation of a 6-endo product. These two factors combine in the equation and determine the observed activation energy of the cyclization reaction. With this nonsubstituted radical as a parent compound, we assess the substituent effects based on a comparison of these calculated data. A similar treatment is applied to the α-SO and α-SO_2 systems.

For electron-withdrawing substituent CN in the α-S system, the activation energies of cyclization to form 5-exo and 6-endo are reversed with respect to the parent compound (12.5 vs 8.8 kcal/mol), and the calculated 5-exo/6-endo branching ratio is also reversed (0.2/99.8, in Table 4). The Marcus analysis shows a smaller intrinsic barrier for 5-exo formation (16.7 vs 17.8 kcal/mol) but is much less exothermic (−9.0 vs −21.1 kcal/mol) than the 6-endo product. The great exothermic reaction energy in forming the 6-endo product thus dominates the activation energy in this cyclization of the α-S−CN-substituted radical. A similar result is found for the NO_2 substituent, except for a smaller intrinsic barrier in forming the 6-endo (14.2 vs 15.7 kcal/mol) than the 5-exo product, in contrast to the CN-substituted analogue. In both cases, the electron-withdrawing substituents decrease the intrinsic barriers, in accordance with FMO theory for which the high-energy SOMO (α-S, nucleophilic) reacts rapidly with the lowered LUMO because of the strongly electron-withdrawing substituents CN and NO_2. The

degree of electron-withdrawing character is evidently greater in NO_2 so as to lower the LUMO more but is less exothermic than the CN substituent. In contrast, for electron-donating substituents CH_3 and NH_2, for which each LUMO is raised to a higher energy (NH_2 to a slightly greater extent through its more strongly donating character), the intrinsic barrier in forming either the 5-exo or 6-endo thus increases. As the thermodynamic factor is more favorable toward forming 6-endo than 5-exo product, it dominates the activation energy. The activation energies to form 6-endo-NH_2 is thus smaller than to form 5-exo-NH_2 (11.7:14.7 kcal/mol), despite the intrinsic barrier to form the 6-endo product being larger (19.0:18.4 kcal/mol). A similar result prevails in forming 6-endo-CH_3 and 5-exo-CH_3 products (11.8:13.1 kcal/mol).

In the α-SO systems, the radical center is less nucleophilic and somewhat electrophilic; some stabilization results from π-conjugation involving the lone pair on sulfur: Creary[47] suggested that the sulfinyl group stabilizes a free radical by an acceptor mechanism utilizing sulfur vacant d-orbitals. The SOMO energy level is thus expected to be lower than that of the α-S system and reacts with the raised HOMO for the electron-donating substituents (CH_3 and NH_2) or the lowered HOMO for the electron-withdrawing counterparts (CN and NO_2). The intrinsic barriers of α-SO systems in the reaction with electron-withdrawing substituents are thus expected to be greater due to a larger energy gap between the SOMO and π-bond HOMO. For example, in our calculated result, the intrinsic barrier of α-SO−CN/α-SO−NO_2 in forming 6-endo is 18.6:17.6 kcal/mol, and that of α-SO−CH_3/α-SO−NH_2 is 16.9:15.9 kcal/mol. The exothermicity of electron-withdrawing substituents CN and NO_2 is much larger in forming 6-endo products (−28.3 and −25.4 kcal/mol, respectively) than that of their electron-donating counterparts CH_3 and NH_2 (−21.9 and −22.8 kcal/mol, respectively). These two factors counterbalance each other and yield nearly equal activation energies, CN:NO_2:CH_3:NH_2 = 7.2:7.2:7.7:6.6 kcal/mol. A similar explanation is applicable to the formation of 5-exo products, except that the exothermicity is much smaller than that of forming the 6-endo counterparts. Despite the smaller intrinsic barriers for formation of 5-exo products, the calculated activation energy barriers are thus larger than those for formation of the corresponding 6-endo counterparts.

The α-sulfonyl (α-SO_2) system is remarkable for its lack of stabilizing effect on a radical center through the lack of a lone pair on the sulfur atom. Bordwell and Liu[48] suggested that increasing the positive charge on sulfur also destabilizes the electron-deficient radical, supported by high-level calculations on the SCH_2•, $SOCH_2$•, and SO_2CH_2• systems that show a significantly unstable SO_2CH_2•. α-Sulfonyl radicals are thus highly electrophilic, kinetically unstable, and reactive to undergo carbon−carbon bond formation with alkenes.[49] The SOMO energy level in this system would decrease further and approach the raised π-bond HOMO in the electron-donating substituents. The intrinsic barriers are thus expected to be further decreased relative to those of the α-SO-substituted counterparts. Our calculated result is consistent with this prediction in the formation of either 5-exo or 6-endo products for which most α-SO_2-substituted intrinsic barriers are smaller than those of their α-SO-substituted counterparts. The α-SO_2−NH_2 has the smallest intrinsic barrier (13.3 kcal/mol) due to the smallest SOMO to π-bond HOMO gap, but its 5-exo counterpart is exceptionally high (16.5 kcal/mol), likely due to the steric effect of NH_2 orientation in this congested transition structure with an α-SO_2−NH_2 five-membered ring, which raises the energy. In contrast, the unexpectedly small intrinsic barrier in forming the 6-endo product with α-SO_2−NO_2 (14.2 kcal/mol) might be related to π-conjugation of NO_2 with the radical in the transition structure, which stabilizes that state. These questions remain open for future investigation. The exothermicity factor is larger for 6-endo products than for the 5-exo counterparts, which results in smaller activation energies in the formation of 6-endo cyclization products.

TABLE 3. Calculated Rate Coefficients[a]/s^{-1} at 298 K for Radical Cyclization of α-Sulfenyl-, α-Sulfinyl-, and α-Sulfonyl-5-(R)-5-hexenyl Radicals to Form 5-exo and 6-endo Products

	5-exo		6-endo	
	k_1[b]	k_1'[c]	k_2[d]	k_2'[e]
2-S-C_5-H	1.01×10^3	3.12×10^{-5}	2.04×10^2	4.17×10^{-7}
2-SO-C_5-H	2.64×10^6	1.56×10^{-7}	1.68×10^5	9.47×10^{-10}
2-SO_2-C_5-H	1.37×10^7	9.56×10^{-7}	1.05×10^7	1.08×10^{-9}
2-S-C_5-CN	3.37×10^2	6.21×10^{-4}	2.02×10^5	7.93×10^{-10}
2-S-C_5-NO_2	2.09×10^4	4.24×10^{-5}	1.15×10^7	1.04×10^{-6}
2-S-C_5-CH_3	6.87×10^1	8.03×10^{-6}	9.02×10^2	5.36×10^{-7}
2-S-C_5-NH_2	7.59×10^0	2.46×10^{-4}	1.27×10^3	3.44×10^{-8}
2-SO-C_5-CN	3.61×10^4	1.02×10^{-5}	1.92×10^6	1.18×10^{-13}
2-SO-C_5-NO_2	1.72×10^5	5.76×10^{-8}	1.92×10^6	6.66×10^{-12}
2-SO-C_5-CH_3	3.89×10^5	4.87×10^{-7}	1.58×10^6	1.27×10^{-9}
2-SO-C_5-NH_2	1.83×10^6	2.47×10^{-4}	9.42×10^6	4.64×10^{-9}
2-SO_2-C_5-CN	3.30×10^4	2.62×10^{-5}	3.02×10^7	2.97×10^{-13}
2-SO_2-C_5-NO_2	7.23×10^6	7.27×10^{-7}	9.54×10^8	5.42×10^{-11}
2-SO_2-C_5-CH_3	9.34×10^5	1.24×10^{-6}	8.02×10^7	2.04×10^{-9}
2-SO_2-C_5-NH_2	1.09×10^4	5.24×10^{-6}	7.90×10^8	7.23×10^{-9}

[a] Based on activation energies at the G3MP2B3 level. [b] k_1: rate coefficient for the forward reaction from the reactant to form the 5-exo product. [c] k_1': rate coefficient for the reverse reaction from the 5-exo product to form the reactant. [d] k_2: rate coefficient for the forward reaction from the reactant to form the 6-endo product. [e] k_2': rate coefficient for the reverse reaction from the 6-endo product to form the reactant.

Calculation of Rate Coefficients. Employing the transition-state theory (TST), we calculated the rate coefficients at 298 K for radical cyclization of α-sulfenyl-, α-sulfinyl-, and α-sulfonyl-5-(R)-5-hexenyl radicals collected in Table 3; the branching ratios of 5-exo and 6-endo channels calculated according to the method described for the RRKM theory and some experimental data are presented in Table 4. We take the G3MP2B3 energies for these calculations. In Table 3, k_1 represents the rate coefficient for the forward reaction in forming the 5-exo product, whereas k_1' is for the reverse reaction; analogously, k_2 for 6-endo, and its reverse, k_2'. We used this equation for the calculation

$$k_d = k^W \sigma \frac{k_B T}{h} \frac{Q_{TS}}{Q_{React.}} \exp\left(-\frac{E_{TS} - E_{React.}}{RT}\right) \qquad (3)$$

in which k_d is the rate coefficient in question; the various Q values denote the partition functions of the reactants (α-sulfenyl-, α-sulfinyl-, and α-sulfonyl-5-(R)-5-hexenyl radicals), and the transition states (5-exo and 6-endo TS). E_{TS} and $E_{React.}$ represent the total energies of the transition state and the reactant, respectively; k_B is Boltzmann's constant and h Planck's constant; σ denotes the symmetry number of the reactant; k^W indicates the corresponding Wigner tunneling correction.[29]

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TABLE 4. Calculated Branching Ratios[a] of 5-exo to 6-endo Products for Radical Cyclization of α-Sulfenyl-, α-Sulfinyl-, and α-Sulfonyl-5-(R)-5-hexenyl Radicals, with Some Experimental Data

	Calculated		Experiment[b]	
	5-exo	6-endo	5-exo	6-endo
2-S-C_5-H	83.1	16.9	84	16
2-SO-C_5-H	94.0	6.0	95.5	4.5
2-SO_2-C_5-H	56.6	43.4	76	24
2-S-C_5-CN	0.2	99.8		
2-S-C_5-NO_2	0.2	99.8		
2-S-C_5-CH_3	7.1	92.9	11	89
2-S-C_5-NH_2	0.5	99.5		
2-SO-C_5-CN	1.9	98.1		
2-SO-C_5-NO_2	8.2	91.8		
2-SO-C_5-CH_3	19.8	80.2	23	77
2-SO-C_5-NH_2	16.3	83.7		
2-SO_2-C_5-CN	0.1	99.9		
2-SO_2-C_5-NO_2	0.8	99.2		
2-SO_2-C_5-CH_3	1.2	98.8	2.5	97.5
2-SO_2-C_5-NH_2	0	100		

[a] Based on activation energies and rate coefficients calculated at the G3MP2B3 level. [b] From ref 23.

$$k^{W} = 1 + \frac{1}{24}\left(\frac{h\nu^{\ddagger}}{k_B T}\right) \quad (4)$$

in which $\nu^{\ddagger}$ is the imaginary frequency at the saddle point. Our calculated values of k^{W} are around 1.1−1.3.

In Table 3, the calculated rate coefficients (k_1s) for formation of 5-exo products of the nonsubstituted reactants are larger than those (k_2s) for formation of 6-endo products. We follow the method described by Brauman et al.[50] for the calculation of branching ratio. The calculated branching ratio in Table 4 agrees satisfactorily with the experimental data except for the α-SO_2 radical, which exhibits a larger deviation. For the substituted counterparts, the rate constants of k_1 and k_2 are reversed; the products thus prefer the 6-endo structure, and the calculated branching ratio (α-S-5-(R) =CH_3) of 5-exo to 6-endo is 7.1:92.9, consistent with the experimental data 11:89. For α-S-5-(R) = NH_2, the analogous branching ratio becomes 0.5:99.5, predominantly favoring 6-endo formation, as also in both cases with α-S-5-(R) = CN and NO_2. In the sulfinyl cases, the rate coefficients for 6-endo formation decrease but still dominate such that, although for R = CH_3 (α-SO-5-CH_3-5-hexenyl radical) k_2 is less than 10 times as large as k_1, the calculated branching ratio between the 5-exo and 6-endo products is 19.8:80.2, consistent with the experimental data 23:77. A similar result holds for R = NH_2, but for R = CN and NO_2, k_2s are more than 10 times as large as k_1s, and the calculated ratios much favor 6-endo products (over 90%). Like the sulfonyl system, k_2s increase much more in the substituted radicals, disregarding the character of the substituents, than do k_1s: for R = CH_3, the calculated branching ratio of 5-exo/6-endo products is 1.2:98.8, consistent with experimental data 2.5:97.5. A similar result holds for both R = CN and NO_2 (more than 99% in favor of 6-endo). An extreme case in our calculated result occurs at R = NH_2 for which only the 6-endo product is predicted (the preference is 100%).

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Conclusion

The substituent effects on the rate of radical cyclization of α-sulfenyl-, α-sulfinyl-, and α-sulfonyl-5-(R)-5-hexenyl radicals, in which R = H, CN, NO_2, CH_3, and NH_2, are rationalized according to the calculated intrinsic barrier and thermodynamic contributions derived from Marcus theory in conjunction with frontier molecular orbital theory. Our calculations of branching ratios of 5-exo/6-endo cyclization products (R = H and CH_3) reproduce the data from experiment. The α-sulfonyl-substituted species display almost exclusive regioselectivity (formation of 6-endo products) disregarding the type of substituents, whereas for the nonsubstitute d counterparts, the predominant cyclization products are 5-exo ra1dicals; the 5-exo/6-endo ratio decreases in the following order: α-sulfinyl-(α-SO-) > α-sulfenyl-(α-S-) > α-sulfonyl-(α-SO_2-), consistent with experimental observations.

Acknowledgment. The National Science Council of the Republic of China (NSC 94-2113-M-003-005) supported this research; the National Center for High-Performance Computing provided the Gaussian package and computer time. We thank Professors M. Hayashi, J. C. Jiang, and C. F. Yao for helpful discussion of calculations of rate coefficients and interaction between molecular orbitals.

Supporting Information Available: Cartesian coordinates and energies of stationary points reported in this paper can be found on pages S2−S31; bond lengths and angles of reactants, transition structures (5-exo and 6-endo) on pages S32−S34, activation energies on page S35, reaction energies on page S36, and that of the G3MP2B3 method on page S37. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061614A