

We examined the importance of electrostatic interactions between active site residues of triosephosphate isomerase and portions of the substrate dihydroxyacetone phosphate. Our results indicate that the charge interactions examined contribute equally to binding in the wild-type and Asp 165 mutant enzymes. This is consistent with the experimental observation that substrate binding does not change substantially upon replacement of Glu 165 by Asp. Furthermore, our results suggest that less effective interactions between Lys 13 and the non-phosphate portion of DHAP in the mutant transition state for enolization may, at least partially, explain the observed drop in catalytic activity upon mutation of

Glu 165 to Asp. Other explanations for the observed drop in k_{cat} have been proposed, and more simulations and the X-ray structure of the mutant are required to differentiate between the possibilities.

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Registry No. TIM, 9023-78-3; DHAP, 57-04-5; Glu, 56-86-0; Asp, 56-84-8; Lys, 56-87-1.

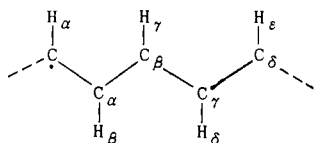
ESR Study of 2-Substituted 2-Adamantyl Radicals. Configuration and Long-Range Hyperfine Interaction¹

Mitsuo Kira,* Mieko Akiyama, Michiko Ichinose, and Hideki Sakurai*

Contribution from the Department of Chemistry, Faculty of Science, Tohoku University, Aoba-ku Sendai 980, Japan. Received March 31, 1989

Abstract: Structure and long-range hyperfine interaction in 2-adamantyl, 5,7-dimethyl-2-adamantyl, and the various 2-substituted radicals (substituent = CH₃, CH₂SiMe₃, OSiMe₃, SSiMe₃, CH₂GeMe₃, etc.) were studied by ESR. The origin of the long-range hyperfine interaction is discussed on the basis of the comparison between experimental and theoretical hfs values. The pyramidal nature of the radical center introduced by a proper substituent at the 2-position of 2-adamantyl radicals has been found to exert significant influence to the long-range interaction. The analyses of hfs values for persistent 2-bis(trimethylsilyl)methyl-2-adamantyl radical and the 5,7-dimethyl derivative were made by the assistance of the ENDOR spectrum. The very small hfs values observed for the bis(trimethylsilyl)methyl methine protons not only show almost perpendicular arrangement of the C_α-H_β bond to the singly occupied p π orbital but also suggest that the constant A in the Heller-McConnell equation would be positive on the basis of the positive temperature dependence.

The electronic and geometric structure of organic radicals has been usually discussed on the basis of the ESR hyperfine splitting (hfs) values. Among them, the hfs values due to the α and β protons are of primary importance since the mechanism of the interactions has been well established theoretically and these hfs values can be related to the empirical expressions such as the McConnell² and the Heller-McConnell³ equations. The hfs values for more remote protons (γ , δ , etc.) have also been known to depend on the radical geometry.⁴ Considerable effort has centered



on establishing the reasonable relationship between the long-range proton hfs and the radical structure.⁵ Recent experimental⁶ and theoretical⁷ studies have shown that the long-range hfs values are

actually promising as a structural probe for the geometry of the distant region from the radical center.

2-Adamantyl radicals may constitute one of the most suitable models for not only experimental but also theoretical studies of the long-range hyperfine interactions as they possess a rigid hydrocarbon framework with minimum strain. In addition, by introducing a proper substituent at the 2-position of the 2-adamantyl radical, the effect of pyramidal nature of the radical center on the long-range hfs values would be examined. In spite of a number of ESR studies on 2-adamantyl radicals in adamantane matrix⁸ as well as in solution,⁹ the hfs parameters had not been determined accurately before we accomplished the present study.¹⁰ Moreover, γ -irradiation of adamantane studied by different groups has produced conflicting results.⁴ We now report the first detailed study of the ESR spectra of 2-adamantyl and 2-substituted 2-adamantyl radicals and discuss the long-range hyperfine interaction in this system. It should be stressed that the main difficulty in assigning the hfs values of 2-adamantyl radical has been overcome by comparing the ESR parameters with those of 5,7-

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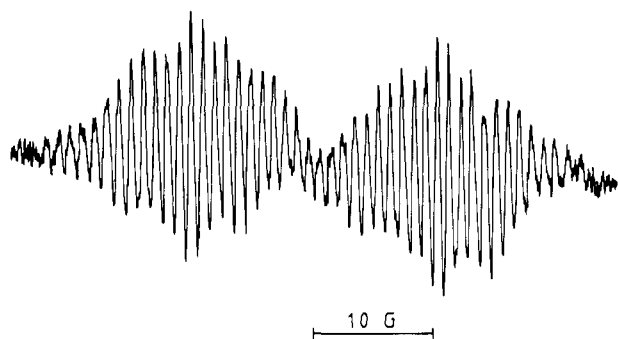


Figure 1. ESR spectrum of **1a** at -137 °C.

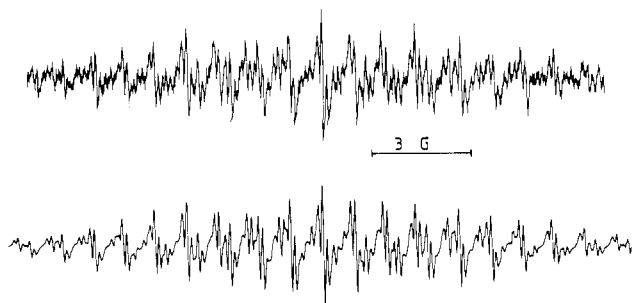


Figure 2. (a) Higher-field half of an ESR spectrum of **1a** at -137 °C recorded by using low modulation frequency. (b) Simulated spectrum by using hfs values shown in Table I.

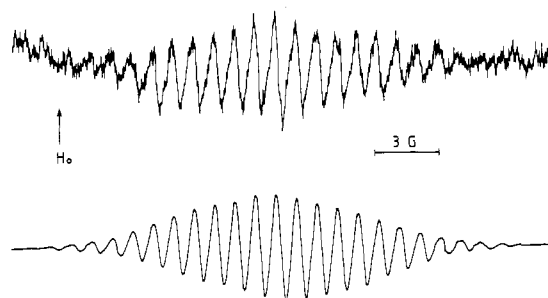
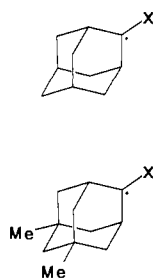


Figure 3. (a) Higher-field half of an ESR spectrum of **1b** at -133 °C. (b) Simulated spectrum by using hfs values shown in Table I.

dimethyl-2-adamantyl radicals which advantageously lack the hfs due to δ protons in the ESR spectra.

Results and Discussion

ESR Spectra. The following 2-adamantyl, 5,7-dimethyl-2-adamantyl, and 2-substituted radicals in cyclopropane solution were generated photochemically at low temperatures in an ESR cavity. The observed and simulated ESR spectra of some of these radicals are shown in Figures 1–10. Ring protons are labeled



- 1a, X = H; 2a, X = OSiMe₃;
 3a, X = SSiMe₃; 4a, X = CH₂SiMe₃;
 5a, X = CH(SiMe₃)₂; 6, X = CH₃;
 7, X = CH₂Si(1-Pr)₃; 8, X = CH₂GeMe₃;
 9, X = CH₂OBU-t.

- 1b, X = H; 2b, X = OSiMe₃;
 3b, X = SSiMe₃; 4b, X = CH₂SiMe₃;
 5b, X = CH(SiMe₃)₂.

conventionally as shown in Figure 11. All the hfs values analyzed for these radicals are listed in Table I. The assignments are based on the following discussion.

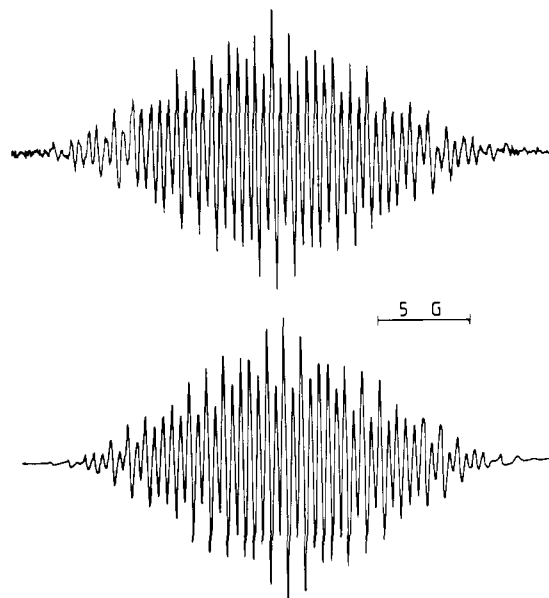


Figure 4. (a) ESR spectrum of **2a** at -12 °C. (b) Simulated spectrum by using hfs values shown in Table I.

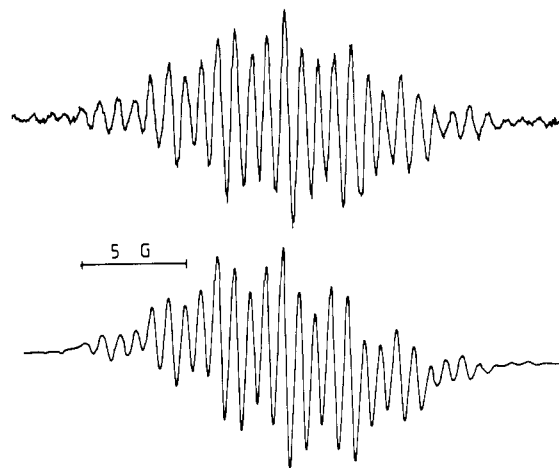


Figure 5. (a) ESR spectrum of **3a** at -10 °C. (b) Simulated spectrum by using hfs values shown in Table I.

The ESR spectrum of **1a** was analyzed expectedly into a doublet of three sets of triplets further split into two sets of quintets. The hfs values obtained for **1a** were 20.73 (1 H), 2.78 (2 H), 1.93 (2 H), 0.12 (2 H), 4.06 (4 H), and 0.98 (4 H) G at -137 °C. A doublet was assigned unambiguously to H_a . The smallest hfs value (0.12 G) can be assigned to H_a , while the hfs was often unresolved in the spectra of other 2-substituted 2-adamantyl radicals. An essential point in discussing the long-range coupling of 2-adamantyl radicals is to distinguish the two triplet hfs values due to H_β and H_δ . The assignment was ensured by comparing the hfs patterns between **1a** and **1b**: the hfs values of **1b** were found to be 20.55 (1 H), 1.93 (2 H), 3.90 (4 H), and 0.94 (4 H) G at -133 °C. The hfs values were very similar between **1a** and **1b**, except for missing a triplet hfs in the latter. If we reasonably assume that the perturbation of two methyl groups on the spin population of **1a** may be ignored, two large hfs values of the triplets in **1a** are assigned to the two δ protons. The only ambiguity may remain on the assignment of the two quintets due to two sets of γ -protons. We assigned the larger hfs to the γ -eq rather than the γ -ax protons since the former protons are in a W-plan arrangement with the half-occupied orbital and, therefore, should have relatively large positive hfs values. Another basis is that the smaller hfs of the two quintets did not change significantly through a series of 2-substituted 2-adamantyl radicals. Whereas INDO-UHF calculations¹¹ predict the small but positive hfs for γ -eq protons

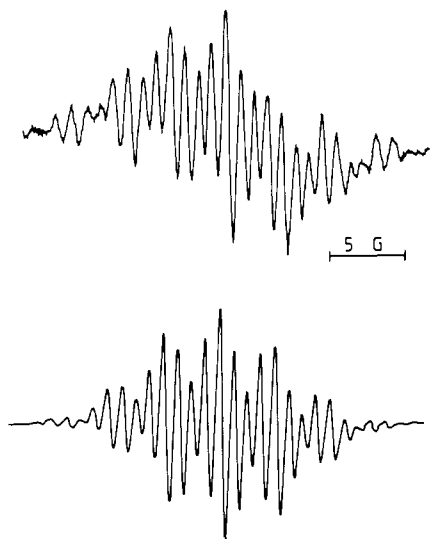


Figure 6. (a) ESR spectrum of **3b** at -19 °C. (b) Simulated spectrum by using hfs values shown in Table I.

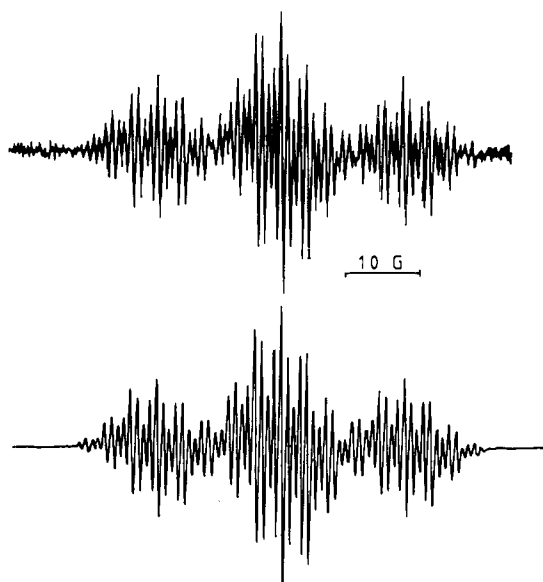
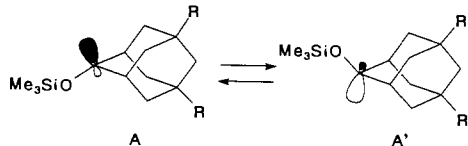


Figure 7. (a) ESR spectrum of **4a** at -11 °C. (b) Simulated spectrum by using hfs values shown in Table I.

against the present assignment, failure of the estimation of the γ -proton hfs values may be regarded as an intrinsic inclination of the INDO method (vide infra).

An ESR spectrum of **2b** was analyzed into four sets of triplets at -137 °C; the hfs values were 5.07, 4.42, 1.24, and 0.62 G. As the solution warmed to -8 °C, the splitting pattern of the spectrum changed to a triplet (4.94 G) further split into two quintets (2.23 and 0.93 G). Apparently, two pairs of triplets for γ -ax (1.24 and 0.62 G) and γ -eq (4.42 and ~ 0 G) protons at -137 °C are averaged into two quintets at -8 °C (0.93 and 2.23 G, respectively). The β -proton hfs values of **2a** and **2b** are significantly larger than those of **1a** and **1b**, indicative of partial eclipsing of the C_β -H bond with the half-occupied orbital on C_α . The ESR spectra of **2a** and **2b** showed selective line-width broadening at



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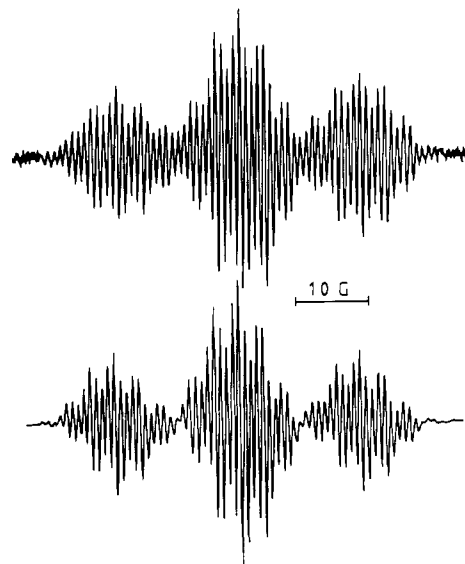


Figure 8. (a) ESR spectrum of **4b** at -10 °C. (b) Simulated spectrum by using hfs values shown in Table I.

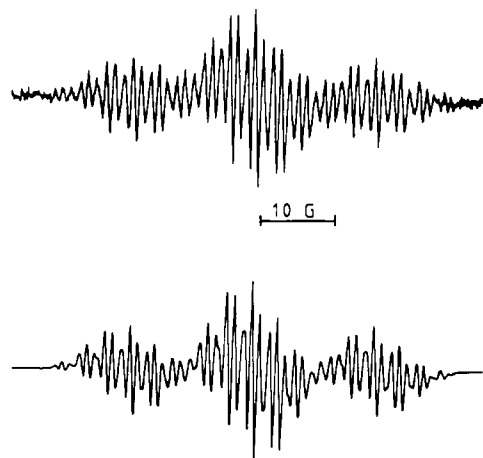


Figure 9. (a) ESR spectrum of **8** at -10 °C. (b) Simulated spectrum by using hfs values shown in Table I.

the intermediate temperatures due to the two equivalent structure A and A'. The exchange rates were determined by comparing the experimental spectra to the simulated spectra obtained by solving the modified Bloch equations for the two-jump system.¹² From a plot of $\ln(k/T)$ versus $1/T$, the following Eyring parameters for **2b** were obtained: $\Delta H^\ddagger = 4.2$ kcal/mol; $\Delta S^\ddagger = 1.2$ eu. The detailed analysis for the conversion was described in a previous communication.¹⁰

The assignment of the hfs values due to ring protons for other 2-substituted 2-adamantyl radicals was made rather readily after the procedure mentioned above for **1a** and **1b**. It should be interesting to note that the g value for **3a** (2.0031) was comparable with that of t -Bu₂CSSiMe₃ ($g = 2.0033$)¹³ but significantly smaller than those of usual α -thioalkyl radicals ($g = \sim 2.004$ – 2.005).¹⁴

INDO MO Calculation. In order to investigate the hfs values and the dependence on the configuration of **1a** and **2a**, semi-empirical INDO-UHF calculations¹¹ were carried out for **1a** and 2-hydroxy-2-adamantyl radical (**10**) as a model of **2a**. The results are shown in Tables II and III. Throughout the calculation, standard C-C and C-H bond lengths and tetrahedral H-C-H

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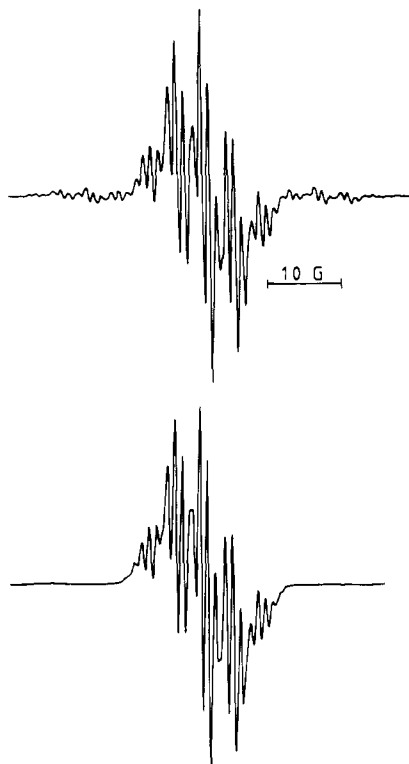


Figure 10. (a) ESR spectrum of **5b** at $-77\text{ }^{\circ}\text{C}$. (b) Simulated spectrum by using hfs values shown in Table I.

and C–C–C bond angles were used except for the parameters around the radical center, $\dot{\text{C}}$. The $\text{C}_{\alpha}\text{--}\dot{\text{C}}\text{--}\text{C}_{\alpha}$ bond angle and the bond length of C–H were assumed to be 109.5° and 1.08 \AA , respectively. The calculated hfs values did not depend seriously on the $\text{C}_{\alpha}\text{--}\dot{\text{C}}\text{--}\text{C}_{\alpha}$ angle. The C–O and O–H bond lengths and C–O–H bond angle were taken to be 1.43 \AA , 0.96 \AA , and 109.5° , respectively. For the radical **10**, the hfs values were calculated for the following four different structures: (i) planar configuration with the hydroxy hydrogen eclipsed by the singly occupied $p\pi$ orbital on $\dot{\text{C}}$, (ii) planar configuration with the O–H bond perpendicular to the $p\pi$ orbital, (iii) pyramidal configuration with the hydroxy hydrogen at the eclipsed position for the front-side lobe of the singly occupied orbital, and (iv) pyramidal configuration with the hydroxy hydrogen at the anti position for the lobe. At the pyramidal configuration, the angle that the C–O bond makes to the ring was taken as 36° from the ab initio study of 1-hydroxycyclohexyl radical. The action of the annihilation operators¹⁵ reduced the absolute values of hfs uniformly but did not change seriously the trends found by the calculation without annihilation. The INDO calculation predicts that the hfs values of the ring protons in 2-adamantyl radicals depend strongly on the pyramidal nature of the radical center. As expected, the α -proton hfs values are calculated to be smaller for the pyramidal than for the planar conformation, while the β -proton hfs values are larger for the pyramidal configuration. The long-range hfs values are also influenced by the pyramidalization. The hydroxy rotation around C–O bond does not change effectively the hfs values of the ring protons in **10**.

Planarity of the Radical Center. The angular dependence of β -proton hfs values can be represented by the following Heller–McConnell equation,³ where θ_{β} means the dihedral angle between a singly occupied $p\pi$ orbital at the radical center and a $\text{C}_{\alpha}\text{--}\text{H}_{\beta}$ bond:

$$a_{\beta} = A + B \cos^2 \theta_{\beta} \quad (1)$$

Values of 0–5 and 40–50 G have been suggested for constants A and B , respectively.¹⁶ Very small β -proton hfs values for both

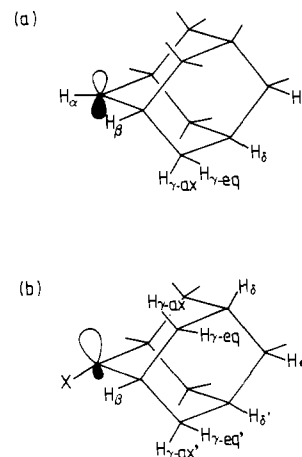


Figure 11. Labeling scheme for ring protons of 2-adamantyl radical.

1a and **1b** suggest strongly a planar geometry around the radical centers with the β -proton lying in the nodal plane of the half-occupied orbital on C_{α} . The hfs of the α -proton in **1a** and **1b** (20.73 and 20.55 G, respectively) are consistent with INDO values for the planar 2-adamantyl radical. Moreover, negative temperature gradients of the absolute values of the α -proton hfs values (-4.5×10^{-3} and $-3.6 \times 10^{-3}\text{ G/K}$ for **1a** and **1b**, respectively) are also compatible with the planar configuration. The planarity of the radical center has been recently discussed rather extensively on the basis of the Frank–Condon envelope observed in the photoelectron spectra of **1a**.¹⁷

On the other hand, 2-trimethylsiloxy-2-adamantyl radicals, **2a** and **2b**, should be pyramidal as indicated by the relatively large β -proton hfs and the line-width alternation in the ESR spectra. In addition, the observed hfs values of **2b** at $-137\text{ }^{\circ}\text{C}$ are in good agreement with INDO calculations for the pyramidal 2-hydroxy-2-adamantyl radical (**10**). It is interesting to compare the hfs values of β - and γ -eq protons of **2b** at $-137\text{ }^{\circ}\text{C}$ with those of the pyramidal 1-adamantyl radical reported by Krusic, Rettig, and Schleyer.¹⁸ The β - (6.58 G) and γ -eq (4.66 G) hfs values of 1-adamantyl radical correspond rather nicely with those of **2b**. Therefore, **2b** may be taken as pyramidal to an extent comparable with the 1-adamantyl radical; there are a wealth of ESR data supporting the nonplanarity of mono-, di-, and trialkoxyalkyl radicals.¹⁹ The origin of the effects of the electronegative substituents on the pyramidalization of the carbon-centered radicals has been understood by focusing attention on the following two electronic factors: (a) the σ inductive effect of the electronegative atom²⁰ and (b) the π conjugative effect of the electronegative atom.²¹ Dewar and Bingham have proposed that at least two conjugative substituents are required to enforce the radical pyramidalization.²¹ In contrast, ab initio analysis²² suggests that the inductive effect is primarily responsible for the pyramidalization.

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Table I. Hfs Parameters of 2-Adamantyl Radicals

R	X	compd	T/°C	¹ H hfs/G					
				a _β	a _{γ-eq}	a _{γ-ax}	a _δ	a _ε	a _χ
H	H	1a	-137	1.93	4.06	0.98	2.78	0.12	20.73 ^a
Me	H	1b	-133	1.93	3.90	0.94			20.55 ^a
H	OSiMe ₃	2a	-12	5.07	2.33	0.93	1.88	0.10	
Me	OSiMe ₃	2b	-8	4.94	2.23	0.93			
			-137	5.07	4.42	1.24			
					(0.04) ^b	0.62			
H	SSiMe ₃	3a	-10	2.32	3.02	0.84	2.32		
Me	SSiMe ₃	3b	-19	2.21	2.96	0.80			
H	CH ₂ SiMe ₃	4a	-11	2.48	3.52	0.88	2.48		16.62 ^c
Me	CH ₂ SiMe ₃ ^d	4b	-16	2.48	3.26	0.85			16.63 ^c
H	CH(SiMe ₃) ₂ ^e	5a	-6	1.09	3.51	0.93	2.55		1.48 ^f
					3.55				
			-77	1.05	3.51	0.90	2.51		1.10 ^f
					3.37				
Me	CH(SiMe ₃) ₂ ^e	5b	-16	1.09	3.51	0.93			1.42 ^f
					3.35				
			-77	1.05	3.51	0.90			1.06 ^f
					3.37				
H	CH ₃	6	-145	2.50	3.38	0.93	2.50		23.22
H	CH ₂ Si(<i>i</i> -Pr) ₃	7	-10						17.70
H	CH ₂ GeMe ₃	8	-10	2.33	3.53	0.89	2.33		16.63
H	CH ₂ OBu- <i>t</i>	9	-10	2.51	3.53	0.98	2.51		13.00

^a¹H hfs of H_α. ^bEstimated; see text. ^c¹H hfs of methylene protons. ^da_{Si}/G = 33.15. ^ea_{Si}/G = 30.67 at -77 °C. ^f¹H hfs of a methine proton. ^ga_{Si}/G = 31.55 at -77 °C.

Table II. INDO-UHF Calculated Hfs Values of 2-Adamantyl Radical^a

configuration	¹ H hfs/G					
	a _α	a _β	a _{γ-ax}	a _{γ-eq}	a _δ	a _ε
planar ^b	-20.48	1.16	-1.41	0.96	4.07	-0.15
planar ^{b,c}	-19.23	1.08	-1.32	0.93	3.62	-0.12
pyramidal ^d	-14.2	1.86	-1.19 ^e	-0.40 ^e	3.00 ^e	-0.14
			-1.43 ^f	2.54 ^f	4.64 ^f	

^aStandard C-C and C-H bond lengths and tetrahedral H-C-H and C-C-C bond angles were used. The C_α-C-C_α is assumed to be 109.5°. ^bThe angle (θ¹) which the C-H_α bond makes to the C_α-C-C_α was taken to be 0°. ^cAnnihilation operator method was applied by using CINCLO, QCPE, No. 323.¹⁵ ^dRather arbitrarily, θ¹ was taken to be 20°. ^eHfs values for the protons at the same side of the front-side lobe of the SOMO. ^fHfs values for the protons at the opposite side of the front-side lobe of the SOMO.

zation. Present experimental results indicate the pyramidal configuration may arise from introducing only one electronegative group at the radical center, being incompatible with the Dewar-Bingham model. The barrier of the pyramidal inversion increases monotonously with the number of the alkoxy substituents: observed ΔH[‡] values were 4.6 kcal/mol for **2b**, 5.7 kcal/mol for 2-methyl-1,3-dioxolane-2-yl,^{19f} and more than 10 kcal/mol for 2-methoxy-1,3-dioxolanyl.^{19j}

Since the pyramidal configuration may be reflected on the β-proton hfs values which depend on the extent of the direct spin delocalization due to hyperconjugation, the β-proton hfs values can be a good indication of the pyramidal configuration of the radical center. Sizable β-proton hfs values were observed for the radicals, **3a,b**, **4a,b**, and **6-9**, indicative of the shallow pyramidal configuration in these radicals. Pyramidal configuration deduced for **4-9** may give support for the similar configuration of *tert*-butyl radical which has long been disputed.²³ The very small β-proton hfs values for **5a,b** are suggestive of favoring the planar configuration because of the steric bulkiness of the 2-substituent.

Long-Range Hyperfine Interaction. A number of theoretical studies on the γ-proton hfs have been carried out for planar *n*-propyl radical as a simplified model by using INDO,^{5a,b} VB,^{5c} and ab initio⁷ methods. The γ-proton hfs should depend on the

Table III. INDO-UHF Calculation of the Hfs Values of 2-Hydroxy-2-adamantyl Radical

radical structure		¹ H hfs/G				
θ ¹ /deg	α/deg	a _β	a _{γ-ax}	a _{γ-eq}	a _δ	a _ε
0	0	1.26	-1.32 ^b	-1.18 ^b	3.72 ^b	-0.14
			-1.28 ^c	0.57 ^c	3.48 ^c	
0	90	1.15 ^b	-1.27	0.90 ^b	3.40	-0.13
		1.21 ^c		0.82 ^c		
36	0	3.18	-1.15 ^d	3.62 ^d	4.04 ^d	-0.10
			-0.79 ^e	-1.01 ^e	1.62 ^e	
36	180	4.06	-1.14 ^d	3.54 ^d	4.08 ^d	-0.09
			-0.72 ^e	-1.01 ^e	1.31 ^e	

^aThe adamantane ring structure was assumed to be the same as the parent 2-adamantyl radical. The angles θ¹ and α were defined to be the angle which the C-O bond makes to the C_α-C-C_α plane and the dihedral angle between the OH bond and the (front-side) lobe of the SOMO, respectively. The bond lengths of C-O and O-H, and the bond angle of C-O-H were taken to be 1.43 and 0.96 Å, and 109.5°, respectively. ^bHfs values for protons at the same side of the hydroxy hydrogen. ^cHfs values for protons at the opposite side of the hydroxy hydrogen. ^dHfs values for protons at the opposite side of the front-side lobe of the SOMO. ^eHfs values for protons at the same side of the front-side lobe of the SOMO.

θ_β, the dihedral angle between the C_α-C_β bond and the half-occupied 2pπ orbital, and θ_γ, the dihedral angle between the C_βH_γ bond and the C_αC_β plane. An empirical expression has been derived by INDO calculations as a function of the two angles, θ_β and θ_γ. The most prominent feature is the large positive contribution to the hfs in the W-plan conformation, i.e., θ_β = 0°, θ_γ = 180°, due to the direct homohyperconjugation mechanism. Whereas the spin polarization contribution to the γ-proton hfs values is conformationally dependent, its magnitude is predicted by the INDO method to be negative for all θ_γ.^{5a,b} The discrepancy of the γ-proton hfs values between observed and INDO calculated may be attributed to this insufficient estimation of the spin polarization contribution. On the other hand, Ellinger et al.⁷ have more recently reported the conformational dependence of the γ-proton hfs values of *n*-propyl radicals calculated by the ab initio method. The γ-proton hfs values depend on θ_β and θ_γ also in the ab initio analysis, but the most striking feature is the indirect contribution change in sign at θ_γ = 120°. The ab initio conclusion was supported by recent experimental results of the ESR study of the acyclic aliphatic radicals.⁶ In the planar 2-adamantyl radical, the γ_{ax} and γ_{eq} protons are in the conformations, θ_β =

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Table IV. Comparison of the γ -Proton Hfs Values of 2-Adamantyl Radicals with the ab Initio Calculated Values for *n*-Propyl Radical in the Appropriate Conformation

radical	position	θ_β /deg	θ_γ /deg	γ -proton Hfs	
				calcd ^a	obsd
planar	γ -eq	-30	180	3.21 (2.52)	4.06 ^b
	γ -ax	-30	60	-0.77 (-0.77)	0.98 ^b
pyramidal ^d	γ -eq	-120	-180	0.89 (0.28)	~ 0 ^c
	γ -ax	-120	-60	-0.49 (-0.62)	0.62 ^c
	γ -eq'	0	-180	4.37 (3.59)	4.42 ^c
	γ -ax'	0	60	-0.69 (-0.64)	1.24 ^c

^a Calculated γ -proton hfs values for *n*-propyl radical. The data are taken from Table XIV of ref 7a, where the quasi-localized MO's are used for the calculation of the indirect contribution. The value in parentheses is based on the calculation by using the canonical MO's. ^b Observed values for **1a** at -137 °C. ^c Observed values for **2b** at -133 °C. ^d The angle α formed by the C-H bond with the $C_\alpha-C-C_\alpha'$ plane is taken to be 54.5°, by assuming the tetrahedral geometry around the radical center, while the actual α for **2b** may be much smaller than the value. See text.

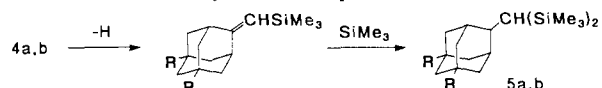
-30°, $\theta_\gamma = 60^\circ$ and $\theta_\beta = -30^\circ$, $\theta_\gamma = 180^\circ$, respectively. In this situation, ab initio calculations estimate the hfs values of -0.70 and 3.21 G, respectively, being nicely in agreement with the observed values for **1a** (0.98 and 4.06 G, respectively).

The discussion is extended to the nonplanar radical **2b**. We assume here the change of hybridization influences only the dihedral angles, θ_β and θ_γ , and therefore the above relationship for the γ -proton hfs values is applicable to the nonplanar radicals, **2a,b**. Taking the half-occupied orbital as sp^3 hybridized, γ_{eq} and γ_{ax} protons at the same side of the rear-side lobe of the orbital make the angles as follows by the definition in the literature: $\theta_\beta = -120^\circ$ and $\theta_\gamma = -180^\circ$, and $\theta_\beta = -120^\circ$ and $\theta_\gamma = -60^\circ$, respectively. The other γ_{eq} and γ_{ax} protons have the angles: $\theta_\beta = 0^\circ$ and $\theta_\gamma = -180^\circ$, and $\theta_\beta = 0^\circ$ and $\theta_\gamma = 60^\circ$, respectively. In spite of rough approximation, the estimated γ -proton hfs values are in nice accord with the observed values for **2b**, as shown in Table IV. The results suggest that the Ellinger's ab initio calculation method⁷ would be promising as a method for better prediction of the long-range coupling constants.

It should be noted that the average of $a_{\gamma_{eq}}$ and $a_{\gamma_{ax}}$ in the pyramidal configuration is found smaller than the corresponding value for the planar radical not only theoretically but also experimentally. The averaged $a_{\gamma_{eq}}$ for 2-substituted 2-adamantyl radicals studied here decreased actually with increasing a_β as the measure of the pyramidity.

Small 2-substituent effects were observed on δ -proton hfs for 2-substituted 2-adamantyl radicals. Hfs values for δ -protons have been known to depend largely on the conformation, which influences the through-space and through-three-bond interaction between the singly occupied orbital at the radical center (ϕ_0) and the $C_\alpha-H_\delta$ σ -bonding orbital (ϕ_{CH}), as revealed by Kawamura et al.²⁴ In 2-adamantyl radicals, the through-bond interaction would determine the hfs value, while the through-space interaction may be unimportant. Since the interaction of the ϕ_{CH} with the $C_\alpha-C_\beta$ σ -bonding orbital (ϕ_{CC}) is regarded to be constant among the substituted 2-adamantyl radicals, the substituent effect may be determined by the change of the interaction between ϕ_{CC} and ϕ_0 which depends on the configuration of radical. Observed small decreases of the δ -proton hfs values in the pyramidal radicals may thus be understood on the similar basis of the discussion for the γ -proton hfs values.

Observation of the Invisible β -Proton Hfs Values in 5a and 5b. Prolonged irradiation of a mixture of 2-methyleneadamantane, a large excess of trimethylsilane, and di-*tert*-butyl peroxide (DTBP) gave a persistent 2-bis(trimethylsilyl)methyl-2-adamantyl radical (**5a**). Similarly, the ESR spectrum of the 5,7-dimethyl



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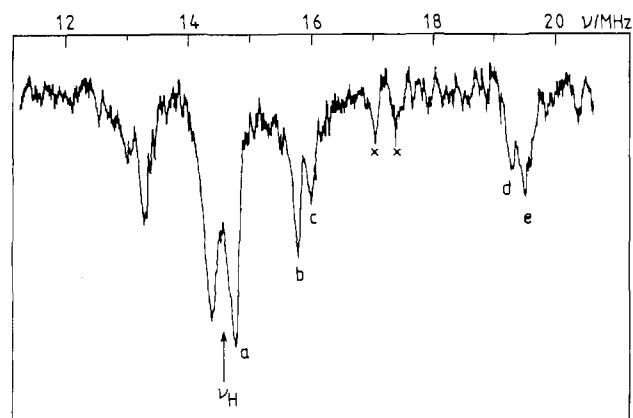


Figure 12. ENDOR spectrum of **5b** at -70 °C. ENDOR signals are denoted by a-e, while apparent signals denoted by x were not reproducible.

derivative (**5b**) is obtained as shown in Figure 10. These radicals would be formed by similar reaction pathways to the generation of a persistent radical, *t*-Bu₂CCH(SiMe₃)₂, reported by Ingold et al.²⁵

While the ESR spectra at low modulation revealed the existence of the hfs of ca. 0.15 G due to methyl protons of two trimethylsilyl groups, the spectral patterns were rather simplified by overlapping hfs lines and depended on temperatures. Although the analyses of the hfs values were very difficult, they were made with the assistance of the ENDOR spectrum of **5b** (Figure 12), which showed the existence of five proton hfs values: 3.52, 3.39, 1.03, 0.88, and 0.12 G, at -70 °C. With reference to these hfs values, the final hfs values for **5a** and **5b** were determined by ESR spectral simulation, as shown in Table I.

The hfs value due to a unique methine proton of bis(trimethylsilyl)methyl group is unambiguously determined to be ca. 1 G. The hfs value increased with increasing temperatures. Ingold et al. have reported several persistent radicals with the type of R₂CCH(SiMe₃)₂ whose β -proton hfs values are too small to be determined and therefore are specified as "invisible" β -hydrogens.^{25,26} The very small β -proton hfs values observed by our hands not only show almost perpendicular arrangement of the $C_\alpha-H_\beta$ bond to the singly occupied $p\pi$ orbital but also suggest that the constant *A* in eq 1 would be positive on the basis of the positive temperature dependence.

Experimental Section

General. ¹H and ¹³C NMR spectra were recorded on a Varian EM-390 and on a JEOL FX-90Q instruments, respectively. Infrared spectra were recorded on a Hitachi EPI-G₂ spectrometer. Mass spectra were measured on a JMS-D 300 spectrometer.

ESR Spectroscopy. ESR spectra were recorded on a Varian E-12 instrument (9.5-GHz frequency, 3300-G magnetic field, and field modulation of 100 kHz). Temperature was controlled by the use of a Varian variable-temperature accessory and was calibrated with a copper-constantan thermocouple. The field sweep of the spectrometer was calibrated with an anthracene cation radical solution in H₂SO₄. ENDOR spectra were recorded on a Varian E-112 spectrometer with an ENDOR accessory.

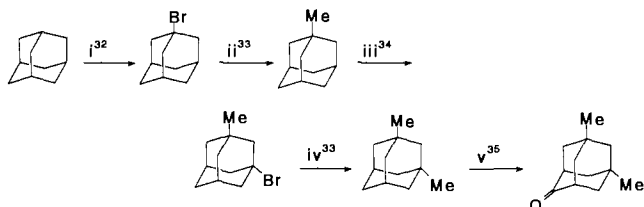
The following solutions were prepared for the generation of the pertinent radicals: for **1a,b** and **6**, the corresponding 2-bromoadamantane, trimethylsilane, and DTBP in cyclopropane (ca. 1:1:1.2 v/v); for **2a,b** and **3a,b**, the corresponding adamantanone (or adamantanethione), trimethylsilane, and DTBP in cyclopropane (ca. 1:1:1.2 v/v); for **4a,b**, the corresponding methyleneadamantane, trimethylsilane, DTBP in cyclopropane (ca. 1:0.5:1.2 v/v); for **7** and **8**, methyleneadamantane, the corresponding metal hydride, DTBP in cyclopropane (1:0.5:1.2 v/v); for **9**, methyleneadamantane and DTBP in cyclopropane (1:1:1 v/v). Photolysis was carried out in a cavity of the ESR spectrometer with a 500-W Ushio super-high pressure mercury arc lamp. The ESR spectra of **4a** and

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4b changed gradually to those of **5b** and **5b** during the irradiation, respectively, while the rates depended on the relative concentration of trimethylsilane and the methyleneadamantane. The spectra of pure **5a** and **5b** were obtained by prolonged irradiation of a solution in a large excess of trimethylsilane. **5a** and **5b** were so persistent that the ESR spectra from -119 to 0 °C and the ENDOR spectra at around -70 °C were observed even after turning off the light.

Materials. Adamantanone,²⁷ 2-bromoadamantane,²⁸ 2-bromo-2-methyladamantane,²⁹ methyleneadamantane,³⁰ and adamantanethione³¹ were prepared by similar methods reported in the literature. 5,7-Dimethyladamantanone was prepared by the following route. The syn-



thetic procedure of each step is known in the literature, but modification was required especially for steps ii and iv. Thus, the methylation of the corresponding 1-bromoadamantane was achieved with methylmagnesium bromide in *n*-butyl ether, instead of the use of methyl Grignard reagent in diethyl ether in a pressure bottle at 100 °C.

1-Methyladamantane. To a methyl Grignard reagent prepared from magnesium (27 g, 1.1 mol) and excess methyl bromide in *n*-butyl ether, 1-bromoadamantane (60 g, 0.28 mol) was added and the mixture was heated gradually and maintained at around 70 °C to control the gas evolution and salt precipitation. Stirring at 90 – 100 °C was continued for a further 0.5 h; the usual workup gave the title compound (39 g, 93% yield), bp 112 °C (75 mmHg) (lit. 195 °C).³⁶

Similarly, **1,3-dimethyladamantane** was prepared in 78% yield, bp 126 °C (100 mmHg) (lit. 201.5 °C).³⁷

5,7-Dimethyl-2-adamantanone. According to the literature, a mixture of 1,3-dimethyladamantane (10 g, 61 mmol) and concentrated H_2SO_4 (150 mL) was stirred vigorously for 5 h. After the usual workup, the residual organic materials was treated with a silica gel column with first hexane, and then a mixture of hexane and ether (4:1, then 3:1). Pure 5,7-dimethyl-2-adamantanone was obtained in a yield of 0.61 g (5.6%):³⁸ 1H NMR (CCl_4) δ 0.92 (s, 6 H), 1.53 (m, 2 H), 1.73 (m, 8 H), 2.48 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 2.87 (q), 30.7 (s), 44.8 (t), 46.1 (d), 50.4 (t),

218.3 (s). Selective decoupling showed the coupling of 4.9 Hz (triplet) for the signal of the carbonyl carbon: IR (CCl_4 solution) 1728 cm^{-1} (ν_{CO}); MS m/z (rel intensity) 178 (M^+ , 100), 107 (96.4); HRMS m/z 178.1349 (calcd for $C_{12}H_{18}O$, m/z 178.1356).

2-Bromo-5,7-dimethyladamantane. To an ether (10 mL) solution of 5,7-dimethyl-2-adamantanone (0.48 g, 2.7 mmol) was added an ether (10 mL) suspension of lithium aluminum hydride (0.17 g, 4.5 mmol). After stirring for 2 h at room temperature, hydrolysis, and then extraction with ether, the organic layer was dried over $MgSO_4$. The residual after evaporating solvents was analyzed by GLC and GC-MS and found to be mostly the expected 2-hydroxyadamantane. Without further purification, a mixture of the residual and an HBr aqueous solution (47%) was refluxed for 11 h at 80 °C. After extracting with dichloromethane, the usual workup afforded 2-bromo-5,7-dimethyladamantane (0.62 g, 94%): 1H NMR ($CDCl_3$) δ 0.83 (s, 3 H), 0.88 (s, 3 H), 1.29 (m, 4 H), 1.59 (m, 4 H), 2.00 (m, 1 H), 2.18 (m, 3 H), 4.52 (m, 1 H); IR (CCl_4) 2913, 2844, 1448, 1193, 956, 784, 765, 720 cm^{-1} ; MS m/z (rel intensity) 244 (1.9), 242 (2.9), 163 (100); HRMS m/z 242.0671 (calcd for $C_{12}H_{19}^{79}Br$, m/z 242.0671).

5,7-Dimethyl-2-adamantanethione. To a mixture of 5,7-dimethyl-2-adamantanone (0.446 g, 2.5 mmol) and pyridine (3 mL), was added P_4S_{10} (0.14 g, 0.31 mmol) at 90 °C portionwise. After refluxing for further 11 h, the reaction mixture was poured into pentane (40 mL). Usual workup and then purification with preparative TLC afforded 5,7-dimethyl-2-adamantanethione (0.26 g, 54%): 1H NMR (CCl_4) δ 0.96 (s, 3 H), 1.56 (m, 8 H), 1.78 (m, 2 H), 3.38 (m, 2 H); MS m/z (rel intensity) 194 (100), 138 (32.1), 107 (39.4), 104 (50.3); HRMS m/z 194.1145 (calcd for $C_{12}H_{18}^{32}S$, m/z 194.1129).

5,7-Dimethyl-2-methyleneadamantane. To a THF (10 mL) solution of 5,7-dimethyl-2-adamantanone was added trimethylsilylmethyl Grignard reagent prepared from chloromethyltrimethylsilane (0.83 g, 6.7 mmol) and magnesium (0.16 g, 6.7 mmol) in THF. The mixture was refluxed for 2 h. Hydrolysis, ether extraction, drying over $MgSO_4$, and then evaporation of the solvent gave 0.5 g of residual. To the residual, which was dissolved in THF (3 mL), was added *n*-butyllithium in hexane (1.35 M, 6.2 mL) at -30 °C. After stirring for 10 min, addition of methanesulfonyl chloride (0.24 g, 2.1 mmol) and then stirring for 12 h at room temperature, the usual workup gave the title compound in 25% yield (0.15 g): 1H NMR (CCl_4) δ 0.92 (s, 6 H), 1.37 (m, 2 H), 1.55 (m, 8 H), 2.58 (m, 2 H), 4.53 (m, 2 H); MS m/z (rel intensity) 176 (44.8), 161 (37.4), 105 (100), 91 (20.8); HRMS m/z 176.1571 (calcd for $C_{13}H_{20}$, m/z 176.1565).

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Registry No. **1a**, 21517-94-2; **1b**, 81814-95-1; **2a**, 75890-76-5; **2b**, 81814-96-2; **3a**, 122521-81-7; **3b**, 122521-82-8; **4a**, 122521-83-9; **4b**, 122521-84-0; **5a**, 122521-85-1; **5b**, 122539-60-0; **6**, 122521-86-2; **7**, 122521-87-3; **8**, 122521-88-4; **9**, 122521-89-5; **10**, 81814-97-3; adamantane, 281-23-2; 1-bromoadamantane, 768-90-1; 1-methyladamantane, 768-91-2; 1-bromo-3-methyladamantane, 702-77-2; 1,3-dimethyladamantane, 702-79-4; 5,7-dimethyl-2-adamantane, 33670-21-2; 2-hydroxy-5,7-dimethyladamantane, 122521-90-8; 2-bromo-5,7-dimethyladamantane, 122521-91-9; 5,7-dimethyl-2-adamantanethione, 122521-92-0; 5,7-dimethyl-2-methyleneadamantane, 122521-93-1; chloromethyltrimethylsilane, 2344-80-1.

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