Conformational Analysis by EPR Spectroscopy. 3. Radicals Derived from Cyclohexanone

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Abstract: EPR spectra have been obtained for 16 different free radicals produced by X-irradiation of cyclohexanone and other alkyl-substituted cyclohexanones trapped in an adamantane matrix. From the magnitude of the observed proton hyperfine splittings of the parent radical, 2-cyclohexanonyl, it is concluded that the preferred conformation at low temperatures is a half-chair form similar to cyclohexene. Temperature-dependent selective line broadening and shifting effects have been interpreted in terms of a ring inversion process between half-chair conformations. The parent radical has an activation enthalpy of 3.70 ± 0.07 kcal mol^{-1} and an activation entropy of −2.3 ± 0.3 eu. Substituent effects on $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, and on the enthalpy and entropy differences between the two nondegenerate conformations of unsymmetrically substituted radicals, suggest that the ring inversion process occurs via a boat transition state. Matrix effects on the derived parameters are small except in the case of radicals with large substituents.

I. Introduction

Since 1950, when Barton[1] first explored the relationship between structure and reactivity for cyclohexane, the conformational properties of both cyclic and acyclic molecules have been extensively investigated. Among the many systems studied, six-membered rings derived from cyclohexane, by virtue of their relative abundance and importance as structural units in natural products, have received a great deal of attention and are consequently the best understood. Dynamic magnetic resonance techniques[2] have played an important role in the accumulation of this information.

Most applications of these techniques have involved diamagnetic systems. However, a few studies of the conformational properties of free radicals by EPR spectroscopy have appeared. Notable among these is the determination of the activation energy for ring inversion in the cyclohexyl radical from the behavior of its EPR spectrum as a function of temperature.[3] Selective line broadening has also been observed in the spectra of radicals derived from piperidine[4] and dioxane,[4,5] semidione[6] and cyclohexenone[7] radical anions, and some alicyclic free radicals.[8] The effect of substituents on both the conformational preferences and ring inversion mechanisms of five- and six-membered ring radicals has, however, not been extensively investigated, partly because the experimental conditions required for the generation of high concentrations of free radicals are not normally conducive to studies of their spectra over a wide temperature range.

A valuable approach to this problem was provided by the discovery of the adamantane matrix technique.[9] Radicals produced by high-energy irradiation of suitable precursors in this host are "indefinitely" stable because of the slowing down of translational diffusion and yet exhibit "isotropic" EPR spectra because of their high degree of rotational mobility. The temperature range over which the radicals may be studied is limited, in first approximation, only by the difference in the melting point and the temperature(s) of the phase transition(s) to an orientationally ordered structure. This "plastic-crystal" range extends over 300 K in the case of adamantane.[10] For this reason, a wide variety of radicals have proven amenable to study with this technique.[11] The focus in the present contribution is on the 2-cyclohexanonyl radical and some of its alkyl derivatives, a system first examined by us in 1972.[12] Succeeding papers in this series will examine the conformational properties of radicals derived from cyclohexene,[13] cyclopentanone,[14] and cyclopentene.[15] In all cases, we have been able to draw interesting conclusions regarding the geometries of these radicals, the nature of the processes responsible for the interconversion of their conformational isomers, and the effects of substituents on their structural and dynamic properties.

II. Experimental Section

II.1. Equipment. EPR spectra were obtained with an X-band Varian E-4 spectrometer system equipped with an E-204 low-frequency modulation unit and an E-257 variable-temperature accessory. First and second derivative signal presentations were employed. The temperature controller was calibrated by a thermocouple immersed in *n*-pentane for

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the lower temperature range and in glycerol for the higher temperature range; temperatures reported over the range 100 to 330 K are believed to be accurate to ±2 K. Care was taken to avoid both modulation broadening and power saturation of the spectra. Typically, EPR spectra of cyclohexanonyl radicals in adamantane could be recorded at power levels up to 10 mW without noticeable saturation effects. Magnetic field sweep calibration was checked with an aqueous solution of Fremy's salt, and g values were determined by comparison with an internal standard of the free radical N,N'-diphenylpicrylhydrazyl (DPPH). The microwave frequency was measured with a Hewlett-Packard Model 5246L electronic counter and a Model 5257A transfer oscillator plug-in unit. X-Irradiation was done on an XRD-1 X-ray generator with a Cu-target tube.

II.2. Chemicals. Adamantane (Aldrich, puriss grade) was purified by dissolving in n-heptane (about 10 mL per g of adamantane) on a hot plate, adding activated charcoal (NuChar-C190-N, 2 g per 100 g of adamantane), and boiling for 30 min, filtering the hot solution through paper, concentrating the filtrate until crystallization just started, adding 25 mL of n-heptane to redissolve the crystals, and then letting the solution cool slowly over a a period of hours. The supernatant liquid was decanted and the crystals dried on a vacuum line until the vapor pressure dropped to that of adamantane (~0.2 torr at room temperature). A second batch of crystals was recovered from the supernatant liquid by immersion in ice water for an hour. The remaining spent liquor was discarded. The first batch of crystals showed no sharp signals discernible above the noise level. The second batch tended to contain detectable amounts of an impurity at the highest gain settings of the spectrometer.

Adamantane-d_{16} (97.7 atom % D) was the gift of Merck, Sharp, and Dohme of Canada, Ltd., and was used as received.

Cyclohexanone and the 2-methyl, 3-methyl, 4-*tert*-butyl, 2,6-dimethyl, and 3,3,5,5-tetramethyl derivatives were purchased from Aldrich Chemical as was the 3,3-dimethylcyclohexanol used to make the 3,3-dimethylcyclohexanone by acid–dichromate oxidation. The 2-ethyl and 4-ethyl compounds were purchased from Chemical Samples Co. Pfaltz & Bauer also supplied 4-ethylcyclohexanone. Chemical Procurement Laboratories, Inc., supplied the 4-isopropylcyclohexanone, and Eastman Kodak provided 4-methylcyclohexanone. Each was first used as received. If the spectra indicated the presence of impurities, the ketone was distilled. For 2-ethylcyclohexanone, the material as received distilled over the temperature range 141–178 °C (lit.[16] value 174–178 °C); only the top fraction from 174–178 °C was used in the samples reported in this account.

II.3. Deuterated Ketones. Deuteration was accomplished by basic exchange between D_2O and the parent perhydro ketones. A small amount of ketone, typically about 2 mL, was placed in a shaker tube with five times excess (mole basis) D_2O and about 20 kernels of K_2CO_3. These were shaken together overnight, and then the water layer was carefully siphoned off and replaced with fresh D_2O and K_2CO_3. Three or four exchanges were sufficient for essentially complete deuteration in positions vicinal to the carbonyl function for cyclohexanones which contained no alkyl groups similarly placed. Alkyl substitution at the 2 position made deuteration difficult and incomplete, as has been noted by Malhotra and Johnson.[17] The appearance of the EPR spectrum was used as a measure of the completeness of deuteration.

II.4. Sample Preparation. For liquids which presented no problems of toxicity, flammability, or air sensitivity, the substance was placed in a test tube (20 mm × 135 mm), about 0.25 g of adamantane was added, and the adamantane was dissolved in the substance by heating with a heat gun. The resulting solution was then quenched by immersion in cold water. The damp crystals were suction dried on a Büchner funnel, washed briefly with a cold solution of n-heptane saturated with adamantane, and allowed to air dry. Cylindrical pellets about 3 mm in diameter and 5 mm long were pressed on a Parr pellet press.

A vacuum line preparation was used for other substances and for samples made in perdeuterioadamantane. Adamantane was placed in a glass tube and degassed with several freeze–thaw cycles. The material to be studied was likewise degassed and then condensed into the adamantane tube. The tube was sealed off under vacuum and then the materials mixed by means of repeated sublimation from one end of the tube to the other. The tube was then opened and the pellet pressed in the usual manner. Four cycles usually produced satisfactory pellets.

Irradiation was carried out with use of a special brass fixture which fit into the opening of the X-ray tube. The pellet was slipped into a slot on the inside of the fixture and held in place by two plugs of plastic. The fixture was then screwed into a mount on the X-ray tube. The low-temperature fixture had an attached dewar into which refrigerant could be placed. After irradiation (usually 5 min), the sample was removed and placed in a quartz sample tube. In the case of low-temperature irradiation, the sample was capped and placed in liquid nitrogen until it could be put into the spectrometer.

Table I. g Values and Proton Hyperfine Splitting Constants of 2-Cyclohexanonyl Radicals in Adamantane[a]

radical	temp range studied,[b] K	g value	a_1, G	a_6,[c] G	$a_{6'}$,[c] G
2-cyclohexanonyl (cyho)	159–321	2.0048	18.0	23.5	43.7
2-cyho-1-d_1	159–321	2.0048	2.75[d]	23.4	43.7
2-cyho-$1,3,3$-d_3	159–313	2.0047	2.75[d]	23.4	43.7
1-Me-2-cyho[e]	211–330	2.0044		19.3[f]	38.7[f]
4,4'-Me_2-2-cyho	211–313	2.0046	18.0	26.4	40.8
3-Et-2-cyho	211–313	2.0048	17.7	22.7	41.7
3-Me-2-cyho	201–328	2.0047	18.0	26.5	40.3
4-Me-2-cyho	152–353	2.0047	18.1	25.3	41.5
5-Me-2-cyho	182–310	2.0047	18.0	20.4	44.1
1,3-Me_2-2-cyho[e]	201–374	2.0043		19.3	38.7
5-Et-2-cyho	182–310	2.0047	18.5	20.0	44.4
5-i-Pr-2-cyho	100-313	2.0079	18.0	23.4	43.7
1-Et-2-cyho[g]	220–340	2.0050		28.5	28.5
5-t-Bu-2-cyho[h]	100-313	2.0044	18.9	35.0	35.0
6,6'-Me_2-2-cyho[i]	211–313	2.0049	17.5		
4,4',6,6'-Me_4-2-cyho[j]	211–313	2.0048	17.7		

[a] g values accurate to ±0.003 and hfs to ±0.1 G except where indicated. [b] Useful temperature range below which the spectrum becomes noticeably anisotropic. [c] Observed value at lowest temperature studied. There is a small decrease in the sum of the two β-proton hfs with increasing temperature. [d] Deuterium hfs. [e] a_β = 18.7 G, three protons. [f] ±1.0 G. [g] a_β = 9.5 G, two protons. [h] a_3 = 1.75 G, two protons. [i] $a_\gamma(CH_3)$ = 1.44 G, six protons. [j] $a_\gamma(CH_3)$ = 1.32 G, six protons.

II.5. Computations. Spectra were simulated with ISOEPR on an XDS Sigma-7. EXALL, BDATA, EYRING, and other editing and plotting programs were run on the University of Pittsburgh PDP-10 time-sharing system in either batch or interactive mode. Both computer systems were equipped with Calcomp plotting facilities. A complete description of the programs used in this work is given elsewhere.[18] Quoted errors in the activation parameters are 95% confidence limits on the average values.

III. Results

III.1. General. EPR spectra of 2-cyclohexanonyl radicals produced and trapped in adamantane are "isotropic" and exhibit line shapes which are largely symmetric over a wide temperature range. Adamantane is a well-known example of a "plastic" crystal in which there is long-range orientational disorder above the solid–solid phase transition at 208 K.[10] Guest molecules (and free radicals) which occupy lattice sites normally occupied by host molecules have, if they are no larger than adamantane, at least as much mobility as the molecules they replace. Consequently, at higher temperatures motional averaging serves to remove all of the magnetic anisotropies which are present. At lower temperatures, and particularly below 208 K, the EPR spectra of radicals trapped in adamantane become increasingly "anisotropic". In the case of 2-cyclohexanonyl radicals, the important anisotropic term in the spin Hamiltonian is the **g** tensor.[19,20] Incomplete averaging of the components of **g** results in a spectrum in which the high-field lines are more intense than the low-field ones. Anisotropies in the hyperfine terms are less important, especially for the β protons which are involved in exchange. Hence, we use simple isotropic coupling schemes to analyze the spectra and correct for differences in intensity where they exist. In some cases, $C_{10}D_{16}$ was used as a host to further reduce contributions to the line widths from matrix hyperfine interactions.

Table I lists the g values and hyperfine splitting (hfs) parameters of the 16 radicals studied in this work. These were determined by comparing the experimental spectra at the lowest temperature studied with computer-simulated spectra in each case. Above this temperature, the first six radicals listed in Table I exhibited spectra which showed selective line broadening as a function of temperature, the next six radicals listed exhibited spectra which showed

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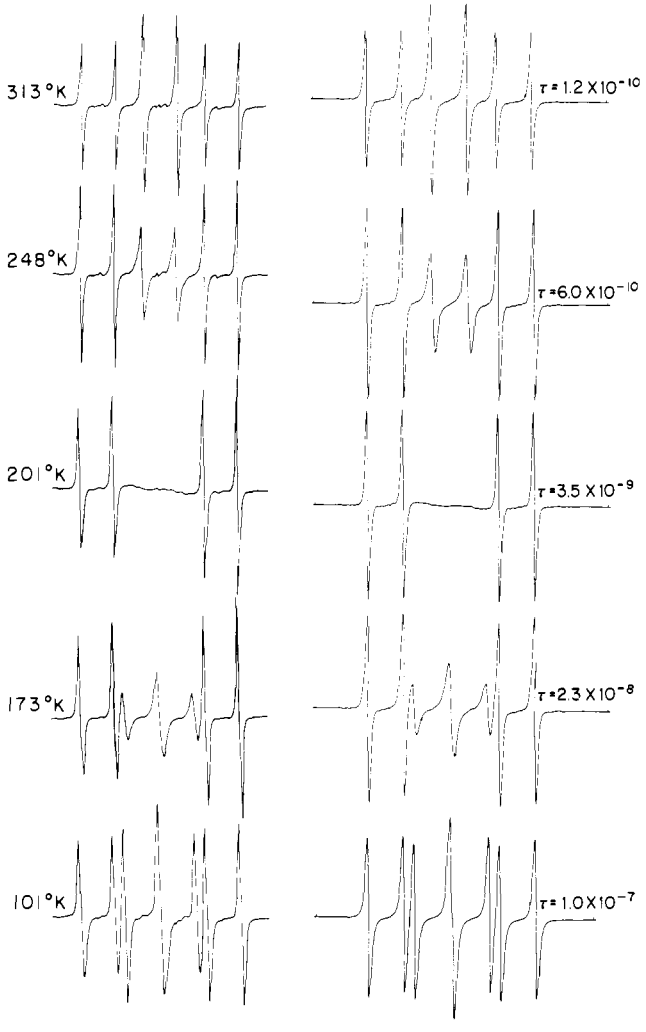

Figure 1. Observed (left) and synthesized (right) EPR spectra of the 2-cyclohexanonyl radical in $C_{10}D_{16}$ at selected temperatures.

both selective broadening *and* a shift of line positions as a function of temperature, and the last four radicals exhibited spectra which showed neither line broadening nor shifting line positions over the temperature range of this study. In what follows, a representative radical of each type will be discussed in detail, and then the data for all other radicals will be summarized.

III.2. Radicals Exhibiting Selective Line Broadening. This group includes the parent radical, 2-cyclohexanonyl, the partially deuterated 2-cyclohexanonyl-*1*-d_1 and 2-cyclohexanonyl-*1,3,3*-d_3 radicals, and the 1-methyl, 4,4′-dimethyl, and 3-ethyl derivatives. Figure 1 shows the spectra observed for the parent radical at selected temperatures over the range for which it was studied. At low temperatures, the 2-cyclohexanonyl radical has an eight-line spectrum which may be attributed to a single unpaired electron spin interacting with three inequivalent protons, with $a_1 \simeq 18$, $a_6 \simeq 23$, and $a_{6'} \simeq 43$ G. Two lines in the center of the low-temperature spectra shown in Figure 1 are not resolved. As the temperature is raised, the center four lines broaden and eventually disappear, all the while maintaining their positions relative to the outer lines. Further increases in temperature lead to the appearance of a new pair of lines centered on the average of the low-temperature lines. This new pair of lines eventually reaches a relative intensity that is twice that of the outside lines, which have remained invariant in height and position during the temperature scan. The high-temperature spectra may be assigned to two equivalent protons, with $a_{6,6'} \simeq 33$ G, and a single proton with $a_1 \simeq 18$ G. All of these effects were found to be completely reversible.

The experimental spectra shown in Figure 1 were obtained with $C_{10}D_{16}$. In this host, weak lines attributable to the 2-cyclohexanonyl-*1*-d_1 radical are also observed. The relative intensity

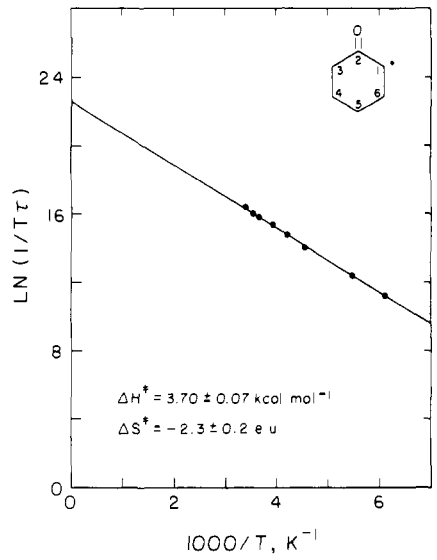

Figure 2. Eyring plot for the 2-cyclohexanonyl radical.

of these lines increases with increasing time and/or temperature, suggesting that (irreversible) chemical exchange between the guest and host occurs. This interpretation was confirmed by separate labeling experiments.[21]

It is apparent from the above that the 2-cyclohexanonyl radical provides yet another example of the alternating line width effect,[22] in which EPR lines arising from transitions in which the spin components of geminal β protons are different broaden selectively. This behavior may be attributed to a conformational change which averages the magnetic environments of the interacting β protons, i.e., ring inversion. Computer simulations of the observed spectra based on this model, which assumes that the two β protons exchange positions at a temperature-dependent rate, are also shown in Figure 1. From each fit, we extract a value for the conformational lifetime τ at a particular temperature T. A plot of ln $(1/T\tau)$ against $1/T$ is shown in Figure 2. From the slope, the enthalpy of activation was determined to be $\Delta H^{\ddagger} = 3.70 \pm 0.07$ kcal mol^{-1}. The entropy of activation, $\Delta S^{\ddagger}$, is -2.3 ± 0.3 eu and the free energy of activation, $\Delta G^{\ddagger}_{298}$, is 4.38 ± 0.12 kcal mol^{-1}.

Two additional features were included in our analysis which should be mentioned here. First, it was found that the sum of the β-proton hyperfine couplings is not constant over the entire temperature range, decreasing from 67.2 G at 93 K to 66.0 at 294 K. This small change may be attributed to a change in the thermally averaged values of the dihedral angles between the β-proton C–H bonds and the p orbital of the α carbon with increasing torsional motion about the C_α–C_β bond. As the values of τ are a sensitive function of the difference in β-proton hfs, we adjusted the values of the low-temperature limiting hfs in order to obtain satisfactory fits at intermediate temperatures. This was done with use of the well-known relation between the β-proton coupling and dihedral angle (vide infra). Second, it was also found that the line shape of an individual hyperfine component changes with temperature, becoming less Gaussian at higher temperatures. This is not unreasonable, as purely Gaussian lines are expected only in the rigid lattice limit whereas Lorentzian lines are expected in the limit of short rotational correlation times. Knowledge of the correct line shape function is important in the simulation of the experimental spectra. Hence, we developed a procedure[18] which could be used to estimate the percent Gaussian character of an invariant line at a particular temperature and used this result to define the line shape used in fitting the entire spectrum at that temperature. A similar procedure was followed for all radicals studied in this work. The activation parameters for the radicals that exhibit selective line broadening only are summarized in Table II.

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Table II. Activation Parameters for 2-Cyclohexanonyl Radicals Which Exhibit Selective Line Broadening Only

radical	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
2-cyclohexanonyl (cyho)	3.70 ± 0.07	−2.3 ± 0.3
2-cyho-*1,3,3-d*$_3$	3.90 ± 0.23	−1.5 ± 1.3
1-Me-2-cyho	2.76 ± 0.89	−4.5 ± 3.6
4,4′-Me$_2$-2-cyho	8.80 ± 0.32	14.5 ± 1.3
3-Et-2-cyho	6.28 ± 0.45	3.7 ± 1.6

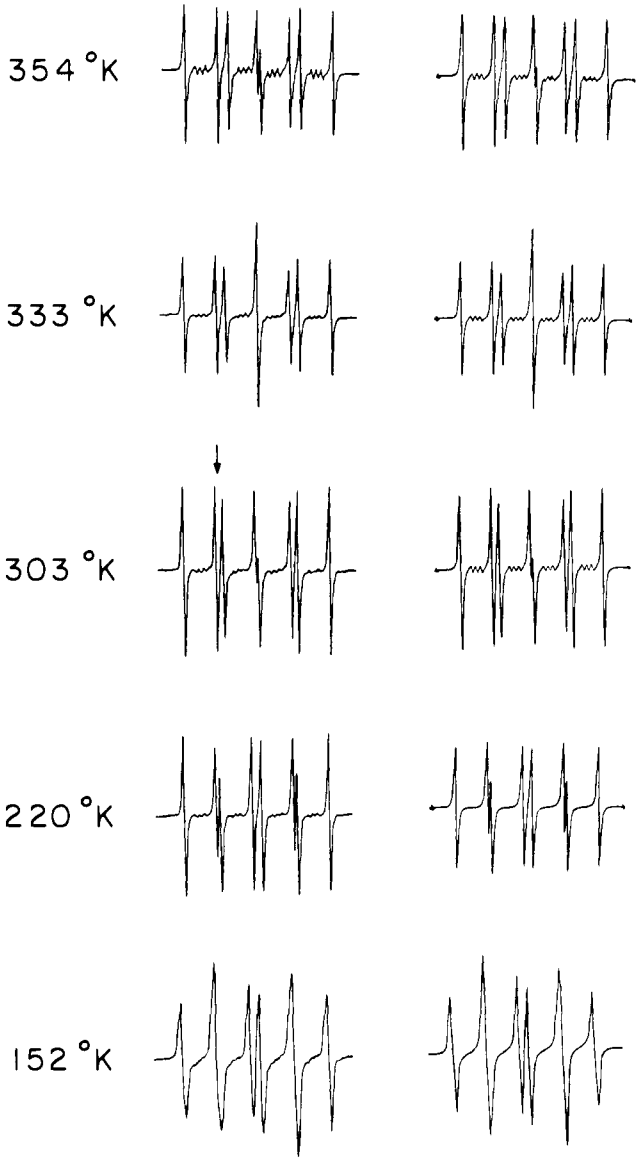


Figure 3. Observed (left) and synthesized (right) EPR spectra of the 5-methyl-2-cyclohexanonyl radical in $C_{10}D_{16}$ at selected temperatures. The arrow denotes two of the lines which should have equal peak heights in the absence of exchange.

III.3. Radicals Exhibiting Selective Line Broadening and a Shift of Line Positions. This group includes the 3-, 4-, and 5-methyl-2-cyclohexanonyl radicals, the 1,3-dimethyl-2-cyclohexanonyl radical, and the 5-ethyl- and 5-isopropyl-2-cyclohexanonyl radicals. To illustrate their behavior, we show in Figure 3 a series of experimental and computed spectra of the 5-methyl derivative at selected temperatures. Like the parent radical, 5-methyl-2-cyclohexanonyl exhibits an eight-line spectrum at the lowest temperature studied. It also has an α-proton hfs of ~18 G and overall width which remain essentially constant over the entire temperature range. However, unlike the parent, there is no obvious coalescence point at which certain lines broaden and disappear. Instead, the four inner lines show a change of position relative to the outer lines with a change in temperature. The two

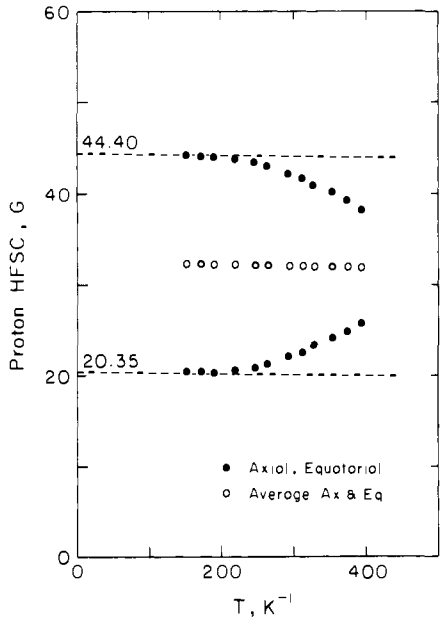


Figure 4. Temperature dependence of the β-proton hyperfine splitting constants of the 5-methyl-2-cyclohexanonyl radical.

protons responsible for these variable splittings are the β protons; their hfs sum to about 64 G at all temperatures. In addition, selective line broadening is observed at some temperatures for the radicals in this group. Note, for example, that the second and third lines in the spectrum of 5-methyl-2-cyclohexanonyl at 303 K do not have equal peak heights, as would be expected for two lines of equal width. This effect is more pronounced in a second-derivative spectrum.

The spectral changes shown in Figure 3 may be explained by assuming that the 5-methyl-2-cyclohexanonyl radical has two conformations of different energy, with temperature-dependent relative populations and lifetimes. The β-proton hfs used to simulate the spectra of this radical over the temperature range 152–354 K are plotted in Figure 4. At low temperatures, where the conformational energy difference is large compared to kT, the EPR spectrum is that of the more stable conformation, with a_6 = 20.4 and $a_{6'}$ = 44.1 G. As the temperature is increased, the less stable conformation is populated and the β-proton hfs become more nearly equal since the *pseudo*axial (equatorial) proton spends more time in a *pseudo*equatorial (axial) position. Thus, the *observed* β-proton hfs are the low-temperature limiting values weighted by the appropriate populations. Ultimately, the two conformations would have equal populations. In this limit, not yet reached in Figures 3 and 4, the two β protons would become equivalent, and the spectrum would be similar to that of the parent radical at high temperatures. Selective line broadening will be observed at intermediate temperatures only if the conformational lifetimes are short compared to the inverse difference of their β-proton hfs.

Of all the radicals that show population changes with temperature, only the 5-methyl derivative provides data which clearly indicate the limiting values of the β-proton hfs. For all radicals in this group, an iterative technique was used to determine the difference in the low-temperature limiting values. The data from the 5-methyl radical were used as a test of the method. In this analysis, it was assumed that the radicals exist in only two conformations and that a plot of ln (K_T) vs. $1/T$ should be linear. The equilibrium constant K_T depends on the difference in the observed hfs, $\delta_T = a_T - e_T$, and the difference in the low-temperature limiting values, $\Delta = A - E$, through the relation

$$K_T = \frac{\Delta - \delta_T}{\Delta + \delta_T} \quad (1)$$

Clearly, Δ must be larger than the largest δ_T; a value 0.01 G larger than this maximum δ_T was used as a starting point. Seven values

Table III. Activation Parameters and Differences in Enthalpy and Entropy for 2-Cyclohexanonyl Radicals Which Exhibit Both Selective Line Broadening and Shifting Line Positions

radical	$\Delta H^{\ddagger}_1$,[a] kcal mol^{-1}	$\Delta S^{\ddagger}_1$,[a] eu	$\Delta H^{\ddagger}_2$,[a] kcal mol^{-1}	$\Delta S^{\ddagger}_2$,[a] eu	ΔH,[b] kcal mol^{-1}	ΔS,[b] eu
3-Me-2-cyho	3.00 ± 0.56	−3.9 ± 2.1	5.15 ± 0.17	1.9 ± 0.6	1.42 ± 0.02	3.5 ± 0.1
4-Me-2-cyho	0.55 ± 0.10	−11.8 ± 0.4	2.20 ± 0.11	−9.4 ± 0.4	1.66 ± 0.04	2.4 ± 0.2
5-Me-2-cyho	2.02 ± 1.05	−6.7 ± 3.8	5.46 ± 1.42	0.2 ± 5.1	3.04 ± 0.03	5.4 ± 0.1
1,3-Me_2-2-cyho	0.14 ± 0.23	−14.1 ± 0.8	1.58 ± 0.25	−10.8 ± 0.9	1.67 ± 0.03	3.1 ± 0.1
5-Et-2-cyho	3.30 ± 1.59	−10.9 ± 5.7	6.72 ± 1.59	−7.5 ± 5.7	3.40 ± 0.36	3.3 ± 1.4
5-*i*-Pr-2-cyho	3.68 ± 1.57	0.0 ± 6.4	4.47 ± 1.61	0.4 ± 6.5	0.76 ± 0.03	0.3 ± 0.2

[a] Determined from plots of ln $(1/T\tau)$ vs. $1/T$. [b] Determined from plots of ln (K_T) vs. $1/T$.

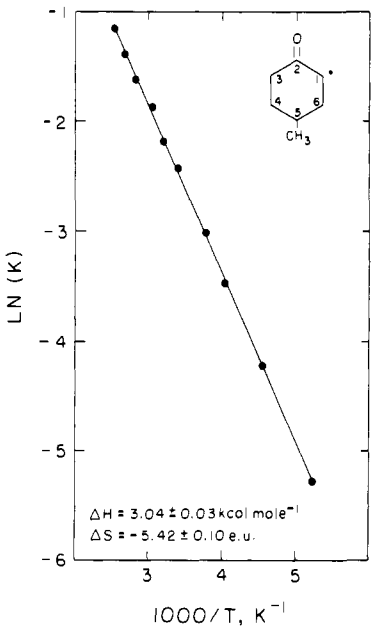


Figure 5. Plot of ln K vs. $1/T$ for the 5-methyl-2-cyclohexanonyl radical.

of Δ, spread over a reasonable range, were then used in eq 1 to compute K_T at each temperature, and the linear correlations of the ln (K_T) vs. $1/T$ plots were noted. The value Δ* for which the correlation is a maximum was then used as the center point for a new series of calculations with a smaller increment. This procedure was continued until the increment in Δ was less than 0.01 G. In the case of the 5-methyl radical, the value of Δ computed in this way was 24.05 G, in good agreement with that measured from the low-temperature spectrum (23.7 G). With use of Δ = 24.05, the fractional population of the more stable conformer, $f_T = (a_T - E)/\Delta$, and the equilibrium constant K_T were then calculated at each temperature. A plot of ln (K_T) vs. $1/T$ for the 5-methyl-2-cyclohexanonyl radical is shown in Figure 5. This yields a conformational enthalpy difference, ΔH, of 3.04 ± 0.03 kcal mol^{-1} and an entropy difference, ΔS, of 5.42 ± 0.10 eu.

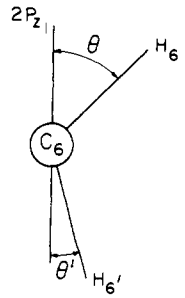
The spectra were then fit for line position with the relative populations determined above. If the fits were satisfactory, selective line broadening was introduced by allowing the lifetime of the separate conformations to vary. This was done through the adjusted rate constant matrix, whose elements r_{ij} are related to the lifetimes by $r_{ij} = 1/\tau_{ij}$. Symmetrically placed elements are related by the ratios of the populations (e.g, for two conformations, there are two off-diagonal elements, r_{12} and $r_{21} = r_{12}(p_1/p_2)$). Fitting was done by selecting several plausible values of r_{12} and generating spectra, yielding a set of lifetimes for each conformation. These were plotted in the usual way to determine the activation parameters for the forward and reverse reactions involved in the conformational change. In the case of the 5-methyl-2-cyclohexanonyl radical, these are $\Delta H^{\ddagger}_1$ = 2.02 ± 1.05 kcal mol^{-1}, $\Delta S^{\ddagger}_1$ = −6.7 ± 3.8 eu, $\Delta H^{\ddagger}_2$ = 5.46 ± 1.42 kcal mol^{-1}, and $\Delta S^{\ddagger}_2$ = 0.2 ± 5.1 eu, where the subscripts 1 and 2 refer to the conformations of higher and lower energy, respectively. The enthalpy and entropy differences calculated from these data are consistent with those determined from the plot in Figure 5, although they are less accurate because of the smaller temperature range over which broadening occurs. This may be taken as evidence for the correctness of our assumption of a two-site model for the exchange process. The thermodynamic parameters for the radicals in this group are summarized in Table III.

III.4. Radicals Exhibiting No Temperature Dependence. This group includes the 1-ethyl-, 5-*tert*-butyl-, 6,6′-dimethyl-, and 4,4′,6,6′-tetramethyl-2-cyclohexanonyl radicals. Their EPR parameters are listed in Table I.

IV. Discussion

IV.1. Radical Stability. The radical which is detected following irradiation of a doped adamantane sample is not necessarily the one which is most stable in this host. Both 2-methylcyclohexanone and 2-ethylcyclohexanone damage on both sides of the carbonyl function to yield two radicals. In each case, the radical damaged opposite the alkyl group is produced in greater yield. Similarly, irradiation of 3-methyl- and 3,3′-dimethylcyclohexanone gives primarily the 4-methyl- and 4,4′-dimethyl-2-cyclohexanonyl radicals. However, when two radicals are formed, invariably the one having the alkyl group(s) closer to the radical site is the more stable. For example, annealing a sample containing both the 1-methyl and 3-methyl radicals at 300 K leads to a complete decay of the latter after about 10 min. In contrast, the spectrum of the 1-methyl radical was observable even after the sample had been kept at room temperature for up to 2 days after irradiation. Possible channels for free radical decay in adamantane have been discussed elsewhere.[21]

IV.2. Radical Structures. It is known[19] that 2-alkanonyl radicals are largely alkyl in character and that a structure with the unpaired electron on C_1 makes the principal contribution to the ground-state wave function of radicals of this type. A second structure, having the unpaired electron on oxygen, contributes about 15%. Consequently, we expect (and observe) large hfs from the protons attached to C_6 (β in the EPR sense) and small hfs from the γ protons attached to C_3. As the β protons in the 2-cyclohexanonyl radical are magnetically inequivalent at low temperatures, it is clear that the preferred conformation is one in which the two C_6–H bonds make different angles with respect to the axis of the p orbital on C_1. These angles are defined in the sketch below.



The dependence of the β-proton hfs on dihedral angle is given by

$$a_\beta^{H} = B_0 + B_2 \cos^2 \theta \qquad (2)$$

where B_0 and B_2 are empirical constants reflecting contributions to the hfs from spin polarization and hyperconjugative mechanisms. These have the values 0.8 and 44.3 G, respectively, for

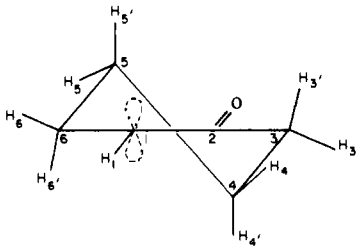
Table IV. Dihedral Angles Derived from the β-Proton Hyperfine Splittings of 2-Cyclohexanonyl Radicals

radical	a_6,[a] G	$a_{6'}$,[a] G	θ'
5-Me-2-cyho	20.4	44.4	11.6
5-Et-2-cyho	20.8	45.3	11.6
1-Me-2-cyho	19.3	38.7	13.4
1,3-Me_2-2-cyho	19.6	39.2	13.5
3-Me-2-cyho	23.4	44.4	14.6
2-cyho	23.4	43.7	15.0
5-*i*-Pr-2-cyho	23.7	44.0	15.1
3-Et-2-cyho	22.7	41.7	15.4
4-Me-2-cyho	25.2	41.9	17.7
4,4'-Me_2-2-cyho	26.4	40.8	19.4

[a] Low-temperature limiting values. [b] Calculated from eq 2 by assuming $B_0 = 0$ and $\theta + \theta' = 60°$.

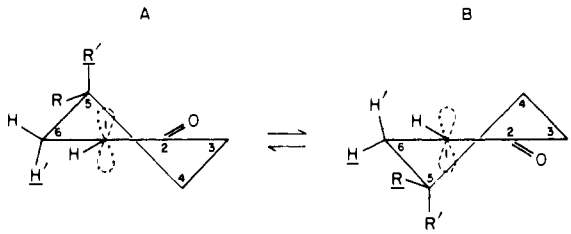
open-chain secondary 2-alkanonyl radicals.[19] To determine the dihedral angles in 2-cyclohexanonyl, we assume that C_6 is sp^3 hybridized (yielding $\theta + \theta' = 60°$) and that $B_0 = 0$. Taking $a_6 = 23.4$ and $a_6' = 43.7$ G as the low-temperature limiting hfs for the β protons, we then calculate angles of $\theta = 45°$ and $\theta' = 15°$ for the 2-cyclohexanonyl radical. These angles are not strong functions of the assumed values of B_0 and B_2, at least within reasonable limits.

Force-field calculations for some unsaturated cyclic hydrocarbons suggest two possible structures for a six-membered ring containing two adjacent sp^2 centers, the half-chair and the boat.[23] The half-chair structure has dihedral angles of about 14° and 46°, whereas the boat structure has dihedral angles of about (−) 40° and 80°. Thus, we can safely conclude that the stable conformation of the 2-cyclohexanonyl radical is the half-chair structure



as it is in cyclohexene.[24] In this structure, four of the ring carbon atoms (C_1, C_2, C_3, and C_6) lie in a plane, the two remaining ring carbons are displaced above and below this plane, and all methylene C–H bonds are staggered with respect to each other. The protons on C_4 and C_5 are nearly axial and equatorial, while those on C_3 and C_6 are *pseudo*axial and *pseudo*equatorial. The important types of destabilizing interactions for this structure are the 1,3-axial/*pseudo*axial (involving the C_5/C_3 and C_4/C_6 protons), the 1,2-equatorial/*pseudo*equatorial (involving the C_4/C_3 and C_5/C_6 protons), and the 1,2-diequatorial (involving the C_4/C_5 protons).[25] These same interactions should also be important for 2-cyclohexanonyl derivatives providing that their structure is also of the half-chair form. A similar treatment for those radicals exhibiting inequivalent β protons at low temperatures, summarized in Table IV, shows that this is the case. The largest deviations from the half-chair conformation upon single methyl substitution are for the 5-methyl derivative, which has $\theta' \simeq 12°$, and for the 4-methyl derivative, which has $\theta' \simeq 19°$.

The half-chair form of the six-membered ring exists as a mixture of two mirror-image conformations, A and B, which should be degenerate in the parent radical and in all symmetrically substituted derivatives. However, single substitution at positions 3, 4, 5, or 6 would be expected to introduce an energy difference between A and B, as it does in the analogous positions of cyclohexene (and, indeed, in any position of cyclohexane). The effect of temperature on the EPR spectra of these unsymmetrically substituted derivatives depends on this energy difference as well as the hfs of the two conformations and the height of the barrier along the reaction coordinate. Three distinct behavior patterns are possible.[19] If the rates of interconversion are slow, the EPR spectrum will consist of a mixture of lines due to the two possible conformations of the radical, and a change in temperature will result in a change of the relative intensities of the two subspectra. This type of behavior has been observed in the case of some open-chain 2-alkanonyl radicals in which the barrier to interconversion is relatively high.[19] On the other hand, if the barrier is low and the rates of interconversion are fast, only the "time-averaged" spectrum will be observed. A change in temperature will result in a shift of the position of equilibrium and a change in the observed hfs. In addition, selective line broadening may be observed if the rates of interconversion are comparable to the difference in hfs in the two conformations. This type of behavior is exhibited by several unsymmetrically substituted 2-cyclohexanonyl radicals. Here, we focus our attention on the values of ΔH derived from an analysis of their spectra (cf., Table III).



The 3-, 4-, and 5-methyl-2-cyclohexanonyl radicals have conformational enthalpy differences of 1.4, 1.7, and 3.0 kcal mol^{-1}, respectively. For comparison, the corresponding differences between the axial and equatorial forms of methylcyclohexane,[26] 2-methylcyclohexanone,[27] 4-methylcyclohexene,[28] and 3-methylcyclohexene[29] are 1.7, 1.6, 1.0, and 0.6 kcal mol^{-1}, with the equatorial conformer being the more stable in each case. The decrease in ΔH on going from methylcyclohexane to the methylcyclohexenes has been attributed to a reduction in the number of 1,3-diaxial interactions between the axial methyl group and *syn*-axial hydrogens from two to one. Since the number of such interactions in the (unsymmetrical) methyl-2-cyclohexanonyl radicals is also one, we should expect conformational energy differences of 1 kcal mol^{-1} or less. This is not the case. There are two possible explanations for this result. One is that there is a special stability associated with *axial* methyl groups in substituted 2-cyclohexanonyl radicals which is not present in their diamagnetic analogues. Such a stability might result from hyperconjugation involving the methyl group and spin density in the 2p orbital on C_1. It is known that open-chain 2-alkanonyl radicals with ethyl or propyl groups attached to the radical site have their β-methyl or -ethyl groups eclipsed with the p orbital containing the unpaired electron. The conformation stability associated with this arrangement could be as large as 5 kcal mol^{-1}.[19] If a similar figure applied to 2-cyclohexanonyl radicals with methyl groups in the 3, 4, or 5 positions, it would reverse the relative stability normally associated with equatorial and axial substituents in six-membered rings. It would also explain the somewhat larger value of ΔH in the 5-methyl derivative, since an axial substituent in this position is closer to the radical site than in the 3 and 4 positions. In addition, the (small) changes in dihedral angle with methyl substitution are consistent with this interpretation.

A second possibility is that the preferred conformation of the methyl groups in the 3-, 4-, and 5-methyl-2-cyclohexanonyl radicals is equatorial, as it is in other six-membered rings with

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0–2 sp^2 centers, including the 3- and 4-methylcyclohexanesemidiones.[6] In that event, we cannot explain the somewhat larger values of ΔH in the former. Nonetheless, we can more easily rationalize the changes in ΔH which occur with other substituents (cf. Table III) by considering the influence of the matrix. The 1,3-dimethyl and 5-ethyl derivatives have conformational enthalpy differences (1.7 and 3.4 kcal mol^{-1}) which are only slightly larger than the 3-methyl and 5-methyl derivatives. This is consistent with published results on similarly substituted cyclohexanes.[25] However, the 3-ethyl and 5-isopropyl derivatives have much smaller values of ΔH, $\sim$0 and 0.8 kcal mol^{-1}, respectively. (Here we assume that the absence of a temperature effect on the line positions of the 3-ethyl-2-cyclohexanonyl radical signals a near-zero conformational enthalpy difference.) Part of the decrease in ΔH for the 3-ethyl derivative may be attributed to the 2-alkyl ketone effect, known to be important for substituents larger than methyl.[25] But this will account for only $\sim$0.5 kcal mol^{-1}, and it does not explain the decrease observed for the 5-isopropyl derivative. The only other effect that will explain the observed differences, if the equatorial conformer is inherently more stable, is that this form is destabilized in the solid-state environment of the adamantane host. This is reasonable as space filling models clearly show that the axial conformer occupies less spherical volume than the equatorial one, particularly for bulky substituents. That guest–host interactions might be important is also demonstrated by the finding that the 1-ethyl- and 5-*tert*-butyl-2-cyclohexanonyl radicals exhibit equivalent β-proton hfs at all temperatures examined in adamantane. In contrast, the 5-*tert*-butyl derivative shows *in*equivalent β-proton hfs in solution experiments at 305 K.[30] Thus, it appears that the solid matrix distorts the cyclohexanonyl ring of these derivatives into a conformation with C_1, C_2, C_3, C_5, and C_6 nearly coplanar, yielding equal dihedral angles for the two C_6 β protons. We may also conclude, from the magnitude of the side chain β-proton hfs in the 1-ethyl-2-cyclohexanonyl radical, that the γ-methyl group is locked into a conformation which eclipses the p orbital at the radical site.

IV.3. Activation Parameters. The activation enthalpy for ring inversion in the 2-cyclohexanonyl radical is 3.7 kcal mol^{-1}. This value is somewhat less than that for its closest structural analogue, cyclohexene, which has $\Delta H^{\ddagger}$ = 5.3 kcal mol^{-1}.[23,31] The mechanism of cyclohexene ring inversion has been the subject of considerable study, both experimental and theoretical.[24] It is now believed that the most probable path for half-chair interconversion in cyclohexene is via a true boat transition state. This view is consistent with the results of several dynamic NMR experiments. For example, Jensen and Bushweller[32] showed that derivatives containing one or two substituents on C_4 and C_5 had free energy barriers 1–2 kcal mol^{-1} higher than that of the parent and suggested that these differences were due to increases in the torsional energy associated with eclipsing about the C_4–C_5 bond. In a later study, Bernard and St. Jacques[33] found a very high $\Delta G^{\ddagger}$ of 8.4 kcal mol^{-1} for 3,3,6,6-tetramethylcyclohexene which was considered to be a reflection of strong nonbonded interactions between methyl groups at the "prow" positions of the boat form. The calculated strain-energy barrier in cyclohexene itself is 6.6 kcal mol^{-1},[23] in reasonable agreement with the observed free energy barrier of 5.3 kcal mol^{-1}. The force-field calculations also suggest that a large ($\sim$80%) fraction of the barrier to ring inversion is due to torsional strain in the transition state, with smaller contributions from bond angle bending and nonbonded interactions.

Given the structural similarity of most of the radicals studied in this work and cyclohexene, it is reasonable to assume that the boat structure is also the maximum energy configuration on the energy profiles of the potential energy surfaces governing their interconversions, as shown in Figure 6. If so, then it should be possible to rationalize the differences observed in Tables II and III in terms of substituent effects on the ground-state and/or

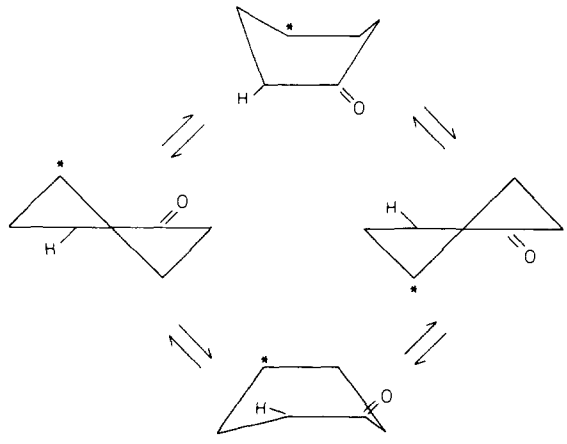

Figure 6. Reaction pathway for the conformational interconversion of the 2-cyclohexanonyl radical assuming a boat transition state.

transition-state energies. Consider, first, the parent radical whose $\Delta H^{\ddagger}$ is 1.6 kcal mol^{-1} less than that of cyclohexene. Although not large, we believe that this difference is significant and probably reflects the reduced double bond character in the 2-cyclohexanonyl radical.[19] Ring interconversion in cyclohexene can be realized without serious deformations of the ethylenic system; however, some decrease in the torsional contributions to the barrier might be expected if the ring were made more flexible. Further, increasing the C_1–C_2 bond length might also decrease the magnitude of the prow–prow interactions in the transition state. This interpretation is supported by the finding that cyclohexanesemidione, which also possesses two adjacent sp^2 centers and has a C_1–C_2 bond order of $\sim$1.6, has an enthalpy of activation of 4.0 kcal mol^{-1}.[6] In this connection, it is interesting to note that the value of $\Delta H^{\ddagger}$ in the 2-cyclohexanonyl radical is not much larger than the value of the internal rotation barrier in propane (3.3 kcal mol^{-1}).[25,34]

Only one deuterated species was examined thoroughly in this study, the 2-cyclohexanonyl-*1,3,3-d*$_3$ radical. Although small differences were found between its activation parameters and those of the corresponding protonated species, they are not statistically significant at the 95% confidence level. Ogawa and Fessenden also found no difference in the temperature dependence of the EPR spectra of the C_6H_{11} and C_6D_{11} (cyclohexyl) radicals.[3] In contrast, the introduction of a methyl group at the radical site markedly lowers the activation enthalpy to 2.8 kcal mol^{-1}. Since this value is less than the internal rotation barrier in propane, it would appear that the decrease in $\Delta H^{\ddagger}$ reflects a destabilization of the ground state, possibly because of steric repulsion between the eclipsed carbonyl oxygen and the methyl group. This effect is now considered to be small in 2-methylcyclohexanone, but it may be larger in the 1-methyl radical owing to the smaller dihedral angle ($\sim$0°) and shorter C_1–C_2 bond distance. Hyperconjugative effects may also contribute to a reduction of the barrier in 1-methyl-2-cyclohexanonyl. 4,4′-Dimethyl substitution, on the other hand, results in a barrier to ring interconversion which is substantially greater than that in 2-cyclohexanonyl itself. In the parent radical, the hydrogens on C_4 and those on C_3 and C_5 must pass each other at some stage along the reaction coordinate. These four eclipsings are replaced by four CH_3–H eclipsings in the 4,4′-dimethyl derivative. Thus, some enhancement of the barrier is expected. However, the increase observed, 8.8 − 3.7 = 4.1 kcal mol^{-1} or $\sim$1 kcal mol^{-1} per CH_3–H interaction, seems large in comparison with the torsional barriers of structurally related alkanes.[34]

The reaction pathway for conformational interconversion of cyclohexene, assuming a boat transition state, is twofold degenerate. The same would be expected to be approximately true for the 2-cyclohexanonyl radical and its symmetrically substituted derivatives (cf. Figure 6). However, in certain unsymmetrically

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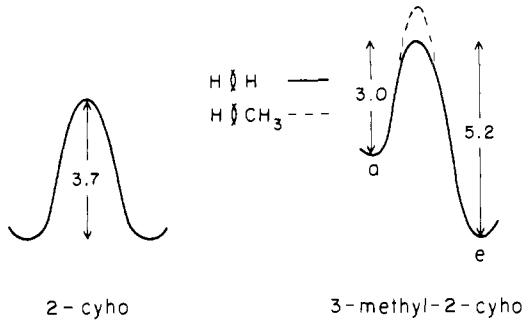
substituted derivatives, the two transition states are not equivalent and the reaction path degeneracy is lifted. An example is the 3-methyl-2-cyclohexanonyl radical. Here, one boat form has hydrogens at both prow positions [H⦶H] and the second has one hydrogen replaced by a methyl group [CH_3⦶H]. As comparable distances separate the prow positions of the boat form of cyclohexene and the 1,3-diaxial positions of chair cyclohexane,[23] we can expect that the two transitions states will differ in energy by ~ 1 kcal mol^{-1}. To a first approximation, then, we can neglect the higher energy pathway and assume that the activation parameters for the 3-methyl-2-cyclohexanonyl radical describe the lower energy pathway involving the H⦶H transition state, as shown in the sketch below.



An examination of the features of this pathway, together with molecular models, suggests that the $5.2 - 3.7 \sim 1.5$ kcal mol^{-1} enhancement of the barrier in the 3-methyl derivative is again primarily torsional in nature. This is because there is one CH_3–H interaction which is not present in the parent radical. Similar considerations would also apply to the 6-methyl-2-cyclohexanonyl radical, not observed on irradiation of 3-methylcyclohexanone in adamantane.

In other unsymmetrically substituted radicals, the two reaction pathways should remain essentially degenerate. The 4-methyl- and 5-methyl-2-cyclohexanonyl radicals are two examples; here, both transition states have hydrogens at the two prow positions. Nonetheless, the substituent effects on the activation parameters can be analyzed in much the same way. The 5-methyl derivative has forward and reverse activation enthalpies of 2.0 and 5.5 kcal mol^{-1}. The $5.5 - 3.7 \sim 1.8$ kcal mol^{-1} increase in the barrier is somewhat larger than that in the 3-methyl derivative, but this is reasonable as there are now two CH_3–H eclipsings which occur at or near the transition state. The data for the 4-methyl radical are more difficult to rationalize since both activation enthalpies (0.6 and 2.2 kcal mol^{-1}) are less than that for the parent. On the other hand, the $\Delta H^{\ddagger}_1$ and $\Delta H^{\ddagger}_2$ values for the 3- and 5-ethyl-2-cyclohexanonyl radicals appear to be consistent with the proposed mechanism.

Activation entropies for the ring inversion of nonpolar molecules are usually assumed to be dictated by symmetry considerations. Thus, Anet and Yavari[23] have suggested that $\Delta S^{\ddagger} = 0$ in cyclohexene because the entropy of mixing term, $-R \ln 2$, is exactly cancelled by the path multiplicity effect. Only the latter remains in the 2-cyclohexanonyl radical as both the half-chair and boat forms are achiral. Hence, if a similar assumption can be made in this case, we expect $\Delta S^{\ddagger} \sim R \ln 2$ for the parent and those derivatives having equivalent transition states and $\Delta S^{\ddagger} \sim 0$ for the remainder. These expectations are largely fulfilled by the data reported in Tables II and III. Although difficult to measure, most $\Delta S^{\ddagger}$ values are near zero, at least within the 95% confidence limits set by our analysis. The only outstanding exceptions are the 4,4′-dimethyl derivative, which has a large positive entropy of activation, and the 4-methyl and 1,3-dimethyl derivatives, which have large negative entropies of activation.

V. Summary and Conclusions

Electron paramagnetic resonance spectra have been obtained for 16 different free radicals produced by irradiation of cyclohexanone and several of its derivatives trapped in an adamantane matrix. The magnitudes of the observed β-proton hyperfine splittings suggest that most of the radicals have the half-chair structure in which four of the ring carbon atoms lie in a plane. Both selective line broadening and changes in line positions occur with changes in temperature; these effects are interpreted in terms of a two-site model for ring inversion with total line shape analysis. In symmetrically substituted radicals, the two sites are degenerate half-chairs whereas in unsymmetrically substituted ones the two sites are energetically different. The parent radical, 2-cyclohexanonyl, has an activation enthalpy of 3.70 ± 0.07 kcal mol^{-1} and an activation entropy of -2.3 ± 0.3 eu. Substituent effects on $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, and the enthalpy and entropy differences between the two conformations of unsymmetrically substituted radicals, suggest that interconversion occurs via a boat transition state. This is the accepted inversion mechanism for the closest structural analogue, cyclohexene. Matrix effects on the derived parameters are small except in the case of radicals with large substituents.

It is difficult to assess the reliability of the thermodynamic and kinetic properties determined in this work. For example, the 4-methyl-2-cyclohexanonyl radical appears to have both activation enthalpies and entropies which are inconsistent with expectations based on the proposed inversion mechanism. An important question is whether this signals the involvement of another reaction pathway or, alternatively, whether there are systematic errors in the treatment of the data for this species. A useful test is provided by the calculated free energies of activation, listed in Table V for 12 different radicals. The $\Delta G^{\ddagger}_{298}$ values for the unsymmetrically substituted ones are for the more stable conformer. It is observed that the 4-methyl radical has a free energy of activation which lies between that of the 3- and 5-methyl derivatives, as expected for a mechanism involving a boat transition state. Similarly, the $\Delta G^{\ddagger}_{298}$ values for the 1,3- and 4,4′-dimethyl derivatives, which have "anomalous" $\Delta S^{\ddagger}$ values, are reasonable. We therefore conclude that the free energies of activation are somewhat more reliable measures of the substituent effects on the barriers to ring inversion in 2-cyclohexanonyl radicals, a process which almost certainly occurs by the proposed mechanism for all derivatives studied in this work. That difficulties might be encountered in the determination of both forward and reverse $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values is not too surprising given the small degree of broadening observed in the spectra of unsymmetrically substituted radicals (cf. Figure 3). The possible contributions to the observed line shapes from a variety of other magnetic interactions in the solid state also complicate the situation. Clearly, careful studies of these radicals in solution will be required in order to remove some of these ambiguities.

Table V. Free Energies of Activation for Selected 2-Alkanonyl Radicals

radical	$\Delta G^{\ddagger}_{298}$, kcal mol^{-1}
1-methyl-2-cyclohexanonyl	4.11 ± 1.34
2-cyclohexanonyl (-*1,3,3-d*$_3$)	4.38 ± 0.13 (4.35 ± 0.43)
3-methyl-2-cyclohexanonyl	4.58 ± 0.25
4-methyl-2-cyclohexanonyl	5.00 ± 0.12
5-methyl-2-cyclohexanonyl	5.40 ± 2.10
1,3-dimethyl-2-cyclohexanonyl	4.80 ± 0.37
4,4′-dimethyl-2-cyclohexanonyl	4.51 ± 0.49
3-ethyl-2-cyclohexanonyl	5.18 ± 0.65
5-ethyl-2-cyclohexanonyl	8.96 ± 2.30
5-isopropyl-2-cyclohexanonyl	4.35 ± 2.50

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Registry No. 2-cyho, 40528-46-9; 2-cyho-*1*-d_1, 94519-46-7; 2-cyho-*1,3,3*-d_3, 94519-47-8; 1-Me-2-cyho, 94519-48-9; 4,4′-Me_2-2-cyho, 94519-49-0; 3-Et-2-cyho, 94519-50-3; 3-Me-2-cyho, 68347-98-8; 4-Me-2-cyho, 94519-51-4; 5-Me-2-cyho, 40471-53-2; 1,3-Me_2-2-cyho, 94519-52-5; 5-Et-2-cyho, 94519-53-6; 5-*i*-Pr-2-cyho, 94519-54-7; 1-Et-2-cyho, 94519-55-8; 5-*t*-Bu-2-cyho, 57643-24-0; 6,6′-Me_2-2-cyho, 94519-56-9; 4,4′,6,6′-Me_2-2-cyho, 94519-57-0.