

Application of Electron Spin Resonance Spectroscopy to Problems of Structure and Conformation. XXVII. Cyclohexanone Iminoxy Radicals¹

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Abstract: A number of cyclohexanone iminoxy radicals have been synthesized for which the esr hyperfine splitting constants at C-2 (axial and equatorial), C-3 (equatorial), and C-6 (axial and equatorial) can be assigned. The 2- and 4-alkyl or the *cis*-3,5-dimethylcyclohexanone iminoxy radicals display a strong conformational preference in which the alkyl groups occupy the equatorial position. However, for *cis*-2,6-dimethylcyclohexanone iminoxy radical the preferred conformation involves the alkyl groups in the axial position to avoid a *cis* methyl-oxygen interaction. Rapid time averaging of chair conformations occurs for 2,2-dimethyl, 4,4-dimethyl, or the unsubstituted cyclohexanone iminoxy radical at 25°. However, below -80° (coalescence temperature) 2,2,6,6-tetramethylcyclohexanone iminoxy radical has a conformational lifetime >10⁻⁶ sec ($\Delta G^{\ddagger}_{193^\circ} \sim 3.5$ kcal/mol). Examples of long-range hyperfine splitting (2.5 V) are provided by the iminoxy radicals derived from the oximes of bicyclo[3.1.0]hexan-3-one, bicyclo[3.3.1]nonan-3-one, and adamantanone.

Gilbert and Norman^{3,4} have reported the esr spectra for cyclohexanone iminoxy radical (rapidly time averaged) and a few rigid derivatives including 4-*tert*-butylcyclohexanone iminoxy, bicyclo[3.2.1]octan-3-one iminoxy, and tropinone iminoxy radicals. We have extended this work to a number of other flexible and rigid cyclohexanone oxime derivatives. By use of carbon disulfide as solvent a better resolution has been obtained than previously reported in methylene chloride, benzene, or dimethyl sulfoxide solution. However, the line widths were still 0.5 G or larger and additional use was made of specifically deuterated compounds where necessary. Low concentrations of the cyclohexanone iminoxy radical, and much higher concentrations of more stable iminoxy radicals, are produced by the reaction of solid lead tetraacetate with the oximes in carbon disulfide solution. Higher steady-state concentrations of iminoxy radicals could be produced by the slow decomposition of *tert*-butyl peroxyoxalate in carbon disulfide in the presence of the oximes at room temperature. Our studies have led to a modification of the reported hfsc for cyclohexanone iminoxy radicals²⁻⁷ and to the assignment of conformation to a number of alkylated cyclohexanone iminoxy radicals which display conformational preference.

Results and Discussions

Flexible Iminoxy Radicals Which Undergo Ring Inversion. Iminoxy radicals are recognized to be σ radicals maintaining syn and anti configuration about the carbon-nitrogen double bond. We will refer to the syn α -methylene group (C-2 in **1a**) as *cis* to the spin label and anti α -methylene group (C-6 in **1a**) as *trans*.

(1) Work supported by a grant from the National Science Foundation.

(2) North Atlantic Treaty Organization Fellow, 1968.

(3) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 86 (1966).

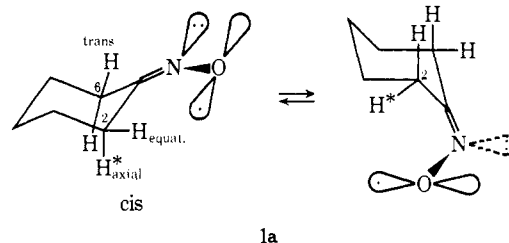
(4) R. O. C. Norman and B. C. Gilbert, *J. Phys. Chem.*, **71**, 14 (1967).

(5) A. Caragheorghopol, M. Hartmann, R. Kühmstedt, and V. E. Sahini, *Tetrahedron Lett.*, 4161 (1967).

(6) A. Caragheorghopol, U. Gräfe, M. Hartmann, V. E. Sahini, and K. Wermann, *ibid.*, 3035 (1970).

(7) (a) H. Căldăraru, N. Bărbulescu, L. Ivan, and V. E. Sahini, *ibid.*, 3039 (1970); (b) H. Căldăraru and M. Moraru, *ibid.*, 3183 (1971).

Inversion of the cyclohexane ring will cause axial and equatorial hydrogens to be exchanged but will not interconvert the *cis* and *trans* arrangement of methylene groups. Examination of the iminoxy radicals **1a-k'**



at 25° clearly demands the assignment of hyperfine splitting constants given in Table I.

Table I. Assignment of Hyperfine Splitting Constants (gauss) in Cyclohexanone Iminoxy Radicals, 25°, Carbon Disulfide Solution

Structure	a^N	a_2^H (cis)	a_3^H (cis)	a_6^H (trans)
a	30.5	~1.4	~1.4	~1.4
b	30.5		1.4	
c	30.5	1.4		1.4
d	30.4	1.25		1.25
e	30.4			
f	30.4	1.65	1.25	1.25
g	30.5	~1.65	~1.45	
h	30.4		1.45	
i	29.3	1.15 ^a	1.15	0.30 ^a
j	29.3		1.15	
k	29.3		1.15	
k'	29.3	1.15 ^a	1.15	

^a $a^H_{CH_3}$.

Oxidation of the oxime from 2,2-dimethylcyclohexanone gave only a single radical whose hfsc's require the methyl groups to be *trans* to iminoxy oxygen atom. From 2,2-dimethyl-6,6-di(trideuteriomethyl)cyclohexanone oxime a mixture of about equal parts of two isomers (**k** and **k'**) was obtained.

Assignment of Axial and Equatorial Hfsc at C-2,3,6. The spectra observed for 4-methyl-, 4-isopropyl-, or

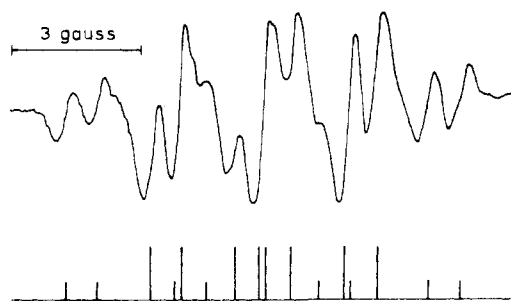
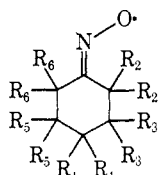
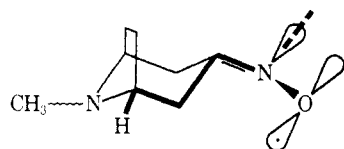


Figure 1. First derivative esr spectrum of the low-field multiplet of the nitrogen triplet observed for tropinone iminoxy radical at -25° in methylene chloride. The stick diagram utilizes $a^H = 2.5$ (1 H), 2.0 (3 H), and 0.75 G (1 H).



- 1a**, $R_2-R_6 = H$
b, $R_2 = R_6 = D$; $R_3-R_5 = H$
c, $R_3 = R_5 = D$; $R_2, R_4, R_6 = H$
d, $R_3 = R_5 = CH_3$; $R_2, R_4, R_6 = H$
e, $R_3 = R_5 = CH_3$; $R_2 = R_6 = D$; $R_4 = H$
f, $R_4 = CH_3$; $R_2, R_3, R_5, R_6 = H$
g, $R_6 = CH_3$; $R_2-R_5 = H$
h, $R_6 = CH_3$; $R_2 = D$; $R_3-R_5 = H$
i, $R_2 = R_6 = CH_3$; $R_3-R_5 = H$
j, $R_2 = R_6 = CD_3$; $R_3-R_5 = H$
k, $R_2 = CD_3$; $R_6 = CH_3$; $R_3-R_5 = H$
k', $R_2 = CH_3$; $R_6 = CD_3$; $R_3-R_5 = H$

4-*tert*-butylcyclohexanone iminoxy radical were not completely resolved. However, the spectra were all quite similar to tropinone iminoxy radical (**2**) for which



$$a^H = 2.5 \text{ (1 H), } 2.0 \text{ (3 H), } 0.75 \text{ (1 H) G}$$

we could obtain a resolved spectrum (Figure 1) in which a large doublet, medium quartet, and a small doublet splitting is observed. This result permits the assignment of axial and equatorial hfsc of Table II to be

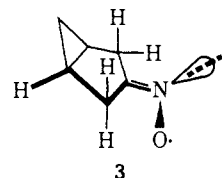
Table II. Assignment of Axial and Equatorial Hyperfine Splitting Constants for Cyclohexanone Iminoxy Radicals

a^H	Substituent				
	None	4- <i>tert</i> -Butyl ^a	4- <i>iso</i> -propyl	Methyl	6-Methyl ^b
C-2-axial		1.7	1.7	$\sim 2.0^c$	$\sim 1.8^c$
C-2-equatorial		1.7	1.7	$\sim 2.0^c$	$\sim 1.8^c$
C-2 av (cis)	$\sim 1.4^d$	(1.7)	(1.7)	(~ 2.0) ^c	(1.8) ^c
C-3-axial		< 0.5	< 0.5	< 0.5	< 0.5
C-3-equatorial		2.4	2.25	$\sim 2.0^c$	$\sim 1.8^c$
C-3 av	$\sim 1.4^d$	(~ 1.3)	(~ 1.2)		
C-6-axial		1.7	1.70	$\sim 2.0^c$	$\sim 1.8^c$
C-6-equatorial		0.6	0.55	~ 0.7	
C-6 av (trans)	$\sim 1.4^d$	(1.15)	(1.12)	(~ 1.3)	

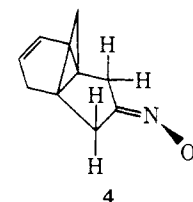
^a Deuteration to give 2,2,6,6-tetradeuterio-4-*tert*-butylcyclohexanone oxime yields an iminoxy radical with $a^N = 30.5$, $a^H = 2.4$ G. ^b Deuteration to give the 2,6,6-trideuterio-2-methylcyclohexanone oxime yields iminoxy radical with $a^N = 30.4$, $a^H = 2.3$ G. ^c Average value of H-2a, H-2e, H-3e, and H-6a. ^d Average value of H-2, H-3, and H-6.

made. This assignment is completely confirmed by a study of a variety of other substituted cyclohexanone iminoxy radicals showing conformational preferences, e.g., the iminoxy radical formed from α -methylcyclohexanone oxime in which the methyl occupies a trans-equatorial position (at C-6 according to structure 1).

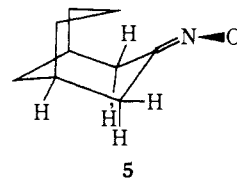
Rigid Bicyclic Iminoxy Radicals. In addition to 2 mentioned previously, iminoxy radicals 3-6 were examined.



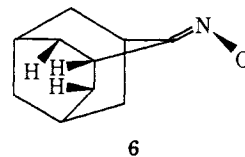
$$a^N = 29.6; a^H = 2.3 \text{ (2 H), } 2.15 \text{ (2 H), } 1.25 \text{ (1 H) G}$$



$$a^N = 29.5; a^H = 2.6 \text{ (1 H), } 2.05 \text{ (2H), } 1.2 \text{ (1 H) G}$$



$$a^N = 30.4; a^H = 2.55 \text{ (2 H), } 1.95 \text{ (2 H), } 0.75 \text{ (1 H) G}$$



$$a^N = 30.4; a^H = 1.9 \text{ (3 H) G}$$

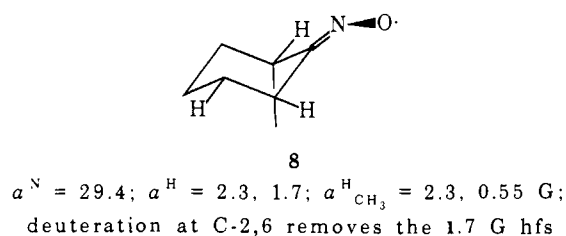
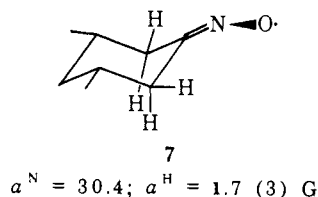
The bicyclic nitroxides 2-5 present a consistent hfs pattern. Using the numbering system of 1a it would appear that $a^{H_3} = 2.55$ in 5, 2.3 in 3, and either 2.5 or 2.0 G in 2; $a^{H_{6e}}$ (or 6-endo) = 0.75 in 5, 1.2 in 4, 1.25 in 3, and 0.75 G in 2; $a^{H_{2a}}$ (or 2-endo) = 2.55 in 5, 2.6 in 4, 2.3 in 3, and 2.5 or 2.0 G in 2; $a^{H_{2a}}$ (or 2-axial) = $a^{H_{6a}}$ (or 6-exo) = 1.95 in 5, 2.05 in 4, 2.15 in 3, and 2.0 G in 2. The near equivalence of the hfsc for H-2e and H-3e is also shown by 6 where only three nearly equivalent hydrogen atoms are found. The absence of hfs by the trans α hydrogen atom in 6 indicates that the hfs at the trans α position comes mainly from π -spin density at the unsaturated carbon atom. In 6 the trans α atom would be in the node of the carbon p_z orbital ($\theta = 0^\circ$) and hyperconjugation could not occur since $a^H = f \cos^2 \theta$. The carbon spin density undoubtedly arises by spin polarization without electron transfer in the σ radical. In the parent cyclohexanone iminoxy radical the grossly different values of a^H for trans (C-6) hydrogen atoms ($a^H = 1.7$ and 0.6) reflect the relative dihedral angles involved which for cyclohexanone itself are reported to be 113° (axial) and 4.5° (equatorial).⁸ Conversely, the appreciable hfsc for the cis α hydrogen in 6, even though it is in the plane of the spin label,

(8) G. Lamaty and J. P. Roque, *Tetrahedron Lett.*, 3293 (1967).

indicates that carbon π spin density is not involved in this interaction. This hydrogen atom does not form a satisfactory zig-zag arrangement with the nitrogen sp^2 orbital with unpaired spin density and it appears that a through space interaction involving the oxygen spin density is involved.⁴

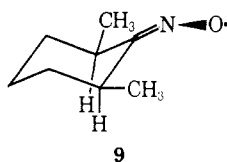
The rigid iminoxy radicals **3**, **5**, and **7** provide further examples of the highly stereospecific 2.5-V long range interaction⁹ between a β -hydrogen atom and an orbital with unpaired electron spin density (*i.e.*, the nitrogen sp^2 orbital). This geometry is indicated with heavy lines in structures **2** and **3**.

cis-2,6- and -3,5-dimethylcyclohexanone Iminoxy Radicals. The two dimethylcyclohexanone iminoxy radicals (**7** and **8**) appear to have a high conformational



preference. The diequatorial conformation assigned to **7** is based on the absence of a 2.3-G coupling by an equatorial hydrogen at C-3. In **8** the diaxial conformation is assigned on the basis of the absence of a 1.7-G coupling by the axial hydrogen at C-6 and by the presence of a fairly good zig-zag arrangement (2.5 V) of bonds and nitrogen sp^2 orbital for the axial methyl group at C-2 ($a^{H_{CH_3}} = 2.3 \text{ G}$).

Methyl groups at the equatorial positions must have $a^H \sim 0$ since for 2,2,6,6-tetramethylcyclohexanone iminoxy radical the time-averaged spectrum at 25° gives $a^{H_{CH_3}}(2) = 1.15 = (2.3 + 0)/2 \text{ G}$. Furthermore, in camphor or fenchone iminoxy radicals the 1-methyl groups which are close to the plane of the spin label do not give rise to hfs which is also the case for the equatorial methyl group in 2-methylcyclohexanone iminoxy radical. The preference of conformation **8** over **9** indicates that the steric requirement of a 2,5-diaxial



methyl-methyl interaction is smaller than for a *cis* methyl-oxygen interaction,¹⁰ a phenomenon also observed in the oxime, where the spectrum clearly shows absorptions, characteristic of H-2e and H-6e.¹¹ The lowered value of a^N of 29.3–29.4 G in **1i-k'**, **8**, or the

(9) G. A. Russell, P. R. Whittle, and J. J. McDonnell, *J. Amer. Chem. Soc.*, **89**, 5515 (1967).

(10) F. Johnson and S. K. Malhotra, *ibid.*, **87**, 5492 (1965).

(11) W. F. Trager and A. C. Huitric, *Tetrahedron Lett.*, 825 (1966).

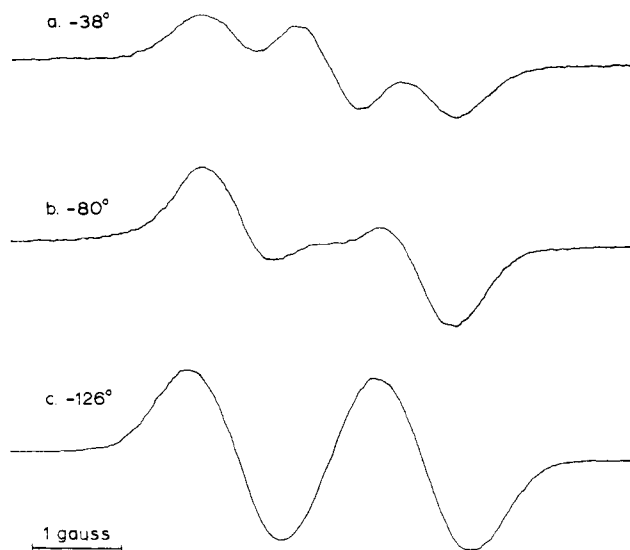


Figure 2. First derivative esr spectrum of the low-field multiplet of the nitrogen triplet observed for 2,2,6,6-tetra(trideuteriomethyl)cyclohexanone iminoxy radical at -38° (top), -80° (middle), and -126° (bottom).

iminoxy radical of 2,2,6-trimethylcyclohexanone oxime apparently reflects steric hindrance from the *cis*-methyl groups at C-2.

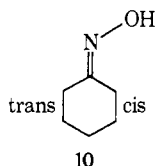
Frozen Conformation of 2,2,6,6-Trimethylcyclohexanone Iminoxy Radical at Low Temperatures. The spectrum of radical **1i** is completely time averaged at 25°. Upon lowering the temperature the lines due to a^H broaden and at temperatures below -80° become sharp again. The spectrum is quite complicated and we have been unable to synthesize it exactly. The value of $a^{H_{3e,cis}}$ can be obtained from the spectrum of **1j** (Figure 2) and varies from 2.0 G at -85° to 2.3 G at -150° (pentane solution). The overall width of each nitrogen line for **1i** remained constant at 11.0 G over the temperature range studied. This line width is consistent with $a^{H_{CH_3}} = 2.3$ (axial at C-2), $a^{H_{3e}} = 2.3$, and $a^{H_{CH_3}} = 0.6 \text{ G}$ (axial at C-6).

From 2,2-dimethyl-6,6-di(trideuteriomethyl)cyclohexanone oxime there was obtained a mixture of **1k** and **1k'** which at -100° gave a broad doublet for **1k**, $a^H = 2.5 \text{ G}$. For **1k'** a complex multiplet is observed wherein each nitrogen line had a width of 9.1 G which by comparison with **1i** means that *trans* methyl groups in the high temperature spectrum of **1k'** have a hfs of $11.0 - 9.1 = 1.9 \text{ G}$, *i.e.*, $a^H = 1.9/6 = 0.3 \text{ G}$ (time averaged). Figure 2 presents some typical data observed for 2,2,6,6-tetra(trideuteriomethyl)cyclohexanone iminoxy radical (**1j**). At $+40^\circ$ each nitrogen line can be simulated by $a^H = 1.05 (2 \text{ H})$, line width = 0.85 G. At -120° the conformation is frozen, $a^H = 2.0 (1 \text{ H})$, line width = 1.0 G. The coalescence temperature is observed to be $-80 \pm 2^\circ$. We have not yet succeeded in stimulating the spectrum for **1j** at intermediate temperatures (perhaps because of unresolved deuterium coupling) or of **1i** at low temperatures (perhaps because of restricted rotation of methyl groups). From the coalescence temperature of **1j** a conformational lifetime of $\sim 5 \times 10^{-6} \text{ sec}$ at -80° is indicated and a ΔG^\ddagger for ring inversion of $\sim 3.5 \text{ kcal/mol}$. By analogy with cyclohexane semidione and 3,3,5,5-tetramethylcyclohexane semidiones ($\Delta H^\ddagger = 4.0$ and 2.6 kcal/mol ,

respectively)¹² it seems likely that the unsubstituted cyclohexanone iminoxy radical might have a higher E_a than the 2,2,6,6-tetramethyl analog. For cyclohexanone it has been estimated by pmr¹³ that ΔG^\ddagger for ring inversion is <5.1 kcal/mol at -170° whereas it has been observed that cyclohexanone oxime *O*-methyl ether has $\Delta G^\ddagger = 5.6 \pm 0.5$ kcal/mol at -152° and cyclohexyl radical has been found by esr to have $E_a = 4.9$ kcal/mol for ring inversion.¹⁴

The stability of cyclohexanone iminoxy radicals increases with alkyl substitution, particularly at the α position. Thus the esr signal of **1i** was detectable for several days and is similar to di-*tert*-butyl iminoxy radical.¹⁵

Proton Magnetic Resonance of Cyclohexanone Oximes. Syn and anti equatorial and axial hydrogen atoms at the α position of **10** are readily distinguished by chemical shift.^{11,16} There has been some discussion as to whether deshielding at the cis position (from oxy-



gen lone pairs) or at the trans position (from the nitrogen lone pair) is more important.¹¹ From Table III

Table III. Pmr Chemical Shifts (δ) of α -Hydrogen Atoms in Substituted Cyclohexanone Oximes

Substituent	Cis α			Trans α		
	Axial	Equat.	Av	Axial	Equat.	Av
4- <i>tert</i> -Butyl ^{a,b}	1.71	3.39	2.55	2.05	2.48	2.26
None ^{a,b}			2.52			2.23
2,2-Dimethyl ^c			2.48			
<i>cis</i> -2,6-Dimethyl ^d		3.39			2.63	
<i>trans</i> -2,6-Dimethyl ^d		3.64		2.36		
2,6,6-Trimethyl ^c		3.45				
2,2,6,6-Tetramethyl ^c			1.29 ^e			1.13 ^e

^a Reference 11. ^b CDCl₃. ^c CS₂. ^d CCl₄. ^e Methyl singlet.

(12) G. A. Russell, G. R. Underwood, and D. C. Lini, *J. Amer. Chem. Soc.*, **89**, 6636 (1967).

(13) F. R. Jensen and B. H. Beck, *ibid.*, **90**, 1066 (1968).

(14) S. Ogawa and R. W. Fessenden, *J. Chem. Phys.*, **41**, 994 (1964).

(15) J. L. Brokenshire, G. D. Mendenhall, and K. U. Ingold *J. Amer. Chem. Soc.*, **93**, 5278 (1971).

(16) H. Saitô, K. Nukada, and M. Ohno, *Tetrahedron Lett.*, 2124 (1964).

it is apparent that deshielding at the cis position is more important, particularly when the pmr of the oxime of 2,2-dimethylcyclohexanone is considered. These conclusions are strongly supported by paramagnetic shifts obtained by addition of the shift reagent Eu(dpm)₃.¹⁷

Experimental Section

The esr spectra were recorded with a Varian Associates V-4500 spectrometer equipped with a variable-temperature accessory. Hyperfine splitting constants for hydrogen atoms were measured on the low-field nitrogen multiplet which in all cases was the best resolved. Computer simulations were performed with a Japan Electron Optics Laboratory JNM-RA-1 spectrum accumulator.

Reagents. The undeuterated ketones were purchased or prepared according to literature descriptions. Deuteration at the α position was carried out by refluxing the ketone for 24 hr with a 100-fold excess of deuterium oxide in the presence of a trace of potassium carbonate. The pmr spectra of the oximes prepared from these ketones showed them to contain $<10\%$ of α -hydrogen atoms. 3,3,5,5-Tetradeuteriocyclohexanone was prepared by Dr. R. Smakman, University of Amsterdam. The oxime was free of α -hydrogen atoms by pmr and gave a parent peak at *m/e* 117. *cis*- and *trans*-2,6-dimethylcyclohexanone oximes (mp 79 and 118°, respectively) were prepared¹⁸ and their structures confirmed by pmr. 2,6,6-Trimethylcyclohexanone was present in the methylation product of 2-methylcyclohexanone. It was separated from 2,2,6,6-tetramethylcyclohexanone by conversion to the semicarbazone (the tetramethyl compound does not give a semicarbazone) followed by acidic hydrolysis.^{18,19} 2,2-Dimethyl-6,6-di-(trideuteriomethyl)cyclohexanone and 2,2,6,6-tetra(trideuteriomethyl)cyclohexanone were prepared from the ketones by alkylation with trideuteriomethyl iodide (Merck, Sharp, and Dohme of Canada, Ltd.) and sodium amide in ether.¹⁸ The pmr spectrum indicated a deuterium content of at least 99% of theory. The bicyclo-[3.1.0]hexan-3-one and tricyclo[4.3.1.0]dec-3-en-8-one employed have been previously described.²⁰

Acknowledgment. The 2,2,6,6-tetra(trideuteriomethyl)cyclohexanone was prepared by Dr. G. Hamprecht. Additional computer simulations for the low-temperature spectrum of its iminoxy radical were performed by Dr. H. Angad Gaur (Technical University, Delft). D. S. Leniart and J. S. Hyde obtained the endor spectra of 2,2,6,6-tetramethylcyclohexanone iminoxy radical in ethylbenzene solution which confirms our high temperature assignment. Pmr spectra were recorded at 100 MHz at the Institute for Organic Chemistry, T.N.O., Utrecht.

(17) A. Mackor, unpublished results.

(18) A. Haller and R. Cornubert, *ibid.*, **41**, 367 (1927).

(19) R. Cornubert, P. Anziani, A. Aubry, P. Hartman, and M. Lemoine, *Bull. Soc. Chim. Fr.*, 636 (1950).

(20) G. A. Russell, J. J. McDonnell, P. R. Whittle, R. S. Givens, and R. G. Keske, *J. Amer. Chem. Soc.*, **93**, 1452 (1971).