An Electron Spin Resonance Study of Conformational Inversion in 4-Alkylpiperidine Nitroxides

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The advantages of e.s.r. spectroscopy for the investigation of conformational changes involving low energy barriers have been exploited in a detailed study of a series of substituted piperidine nitroxides. The nitroxides were generated in methylene chloride solution and their e.s.r. spectra were recorded from −100 to +35°. Detailed analysis of the spectra confirms that rapid chair–chair inversion takes place and computer simulation of the spectra obtained at different temperatures leads to accurate values for the associated activation parameters, $\Delta G^\ddagger$, $\Delta H^\ddagger$, and $\Delta S^\ddagger$. The observed variation with temperature of the coupling constants of the C(2) and C(6) axial hydrogens is rationalised in terms of rapid inversion at the nitrogen atom.

N.M.R. spectroscopy has been much used for the determination of activation parameters in conformational changes in organic molecules. In particular, barriers ($\Delta G^\ddagger$) in cyclic systems < *ca.* 22·6 kJ mol^{-1} can be measured using n.m.r. techniques[1] only by the attainment of very low temperatures (<−150°) with the attendant experimental difficulties concerning solvent system, solubility, viscosity, and temperature control. E.s.r. spectroscopy on the other hand offers the possibility of study of such rapid interconversions within a

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[1] (*a*) G. Binsch, 'Topics in Stereochemistry,' eds. E. L. Eliel and N. L. Allinger, Interscience, New York, vol. 3, 1968; (*b*) F. R. Jensen and C. H. Bushweller, *J. Amer. Chem. Soc.*, 1969, **91**, 5774.

more accessible temperature range provided that the molecule contains a radical centre.[2] A convenient series of cyclic organic radicals is the piperidine nitroxides in which chair–chair inversion can cause the hyperfine splitting constant of the C(2) and C(6) hydrogens to change by as much as 1·7 mT. It follows that a barrier of *ca.* 18·8 kJ mol^{-1} should be measurable relatively non-paramagnetic molecules such as cyclohexanones, which are difficult to study using n.m.r. methods.[7]

RESULTS

The series of substituted hydroxylamines (1) has been prepared and, in methylene chloride solution, converted by u.v. irradiation into the corresponding nitroxide radicals.

TABLE 1

Parameters used for computer matching of experimental e.s.r. spectra[f]

R	H[a]				Me[b]				Pr^i[c]				Bu^t[d]		Me$_2$[e]		
T (°C)	$a^{ax}_{2,6}$/mT	$a^{eq}_{2,6}$/mT	Δ/mT	$10^8\tau_A$ = $10^8\tau_B$/s	$a^{ax}_{2,6}$/mT	Δ/mT	$10^8\tau_A$/s	$10^8\tau_B$/s	$a^{ax}_{2,6}$/mT	Δ/mT	$10^8\tau_A$/s	$10^8\tau_B$/s	$a^{ax}_{2,6}$/mT	Δ/mT	$a^{ax}_{2,6}$/mT	Δ/mT	$10^8\tau_A$ = $10^8\tau_B$/s
+35	1·957														2·03	0·065	0·105 ± 0·005
+30	1·957	0·365	0·050	0·085 ± 0·005	1·960	0·070	0·58 ± 0·05	0·035 ± 0·003	1·975	0·060	1·02 ± 0·15	0·03 ± 0·002	1·980	0·055			
+23									1·990	0·055	1·48 ± 0·15	0·04 ± 0·003					
+20	1·975	0·355	0·050	0·110 ± 0·005	1·970	0·065	0·70 ± 0·04	0·038 ± 0·002					1·990	0·050	2·03	0·065	0·16 ± 0·01
+12	1·980	0·355	0·050	0·145 ± 0·005													
0	2·015	0·345	0·050	0·18 ± 0·05	2·000	0·058	2·38 ± 0·16	0·095 ± 0·005	2·035	0·045	5·4 ± 1	0·1 ± 0·02	2·030	0·045	2·08	0·065	0·48 ± 0·03
−20	2·027	0·380	0·050	0·8 ± 0·5	2·020	0·050	10·5 ± 3·5	0·30 ± 0·10	2·060	0·037	32 ± 7	0·4 ± 0·1	2·065	0·037	2·13	0·065	0·9 ± 0·3
−40	2·072	0·380	0·050	3·2 ± 0·5	2·065	0·048	36 ± 6	0·65 ± 0·10	2·105	0·033	108 ± 18	0·9 ± 0·1	2·105	0·030	2·17	0·065	5·0 ± 0·2
−60	2·110	0·380	0·050	8·0 ± 0·5	2·105	0·034	153 ± 37	1·8 ± 0·3	2·140	0·033	570 ± 340	3·0 ± 1·5	2·165	0·030	2·22	0·060	12 ± 1
−70															2·25	0·060	23 ± 1
−80	2·155	0·380	0·050	22·0 ± 5	2·150	0·030	1050 ± 490	7·5 ± 2·5					2·185	0·030	2·30	0·045	40 ± 5
−84									2·195	0·033	*ca.* 14,800	*ca.* 40					
−90															2·33	0·045	100 ± 50
−100	2·217	0·380	0·040	200 ± 50	2·210	0·030	*ca.* 19,800	*ca.* 60	2·230	0·033			2·245	0·030	2·35	0·042	400 ± 20

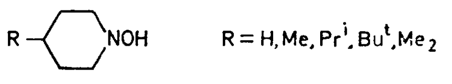
[a] For all temperatures a_N = 1·690 mT; $a^{ax}_{3,5} = a^{eq}_4$ = 0·065 mT; $a^{ax}_{3,5} = a^{ax}_4$ = 0. [b] For all temperatures a_N = 1·680 mT; $a^{eq}_{2,6}$ = 0·380 mT; $a^{ax}_{3,5}$ = 0·065 mT; $a^{eq}_{3,5} = a^{ax}_4$ = 0. [c] As for *b* except $a^{eq}_{2,6}$ = 0·400 mT. [d] For all temperatures a_N = 1·680 mT; $a^{eq}_{2,6}$ = 0·400 mT; $a^{ax}_{3,5}$ = 0·065 mT. [e] For all temperatures a_N = 1·670 mT; $a^{eq}_{2,6}$ = 0·460 (+35 to −80°), 0·465 (−90°), 0·470 mT (−100°); $a^{ax}_{3,5}$ = 0·065 mT; $a^{eq}_{3,5}$ = 0. [f] Errors in coupling constants are judged to be ±0·005 mT, those in Δ values ±0·001 mT. The ranges of error quoted for τ values represent the limits beyond which there was a visual difference between simulated and experimental spectra. The subscripts A and B refer to the more and less stable conformations respectively.

easily. In addition the greater sensitivity of e.s.r. spectroscopy alleviates the solubility problem.

Although the piperidine nitroxides have received much attention, and the temperature dependence of their spectra established, the potential of the method does not appear to have been fully exploited. For instance activation energies for the chair–chair inversion in piperidine nitroxide have been estimated using the variation of relative peak heights with temperature[3,4] (E_A *ca.* 25 kJ mol^{-1}); these studies were limited by the use of chemical oxidants for radical production. Somewhat better precision was obtained using photochemical production of the radicals and a modification of the coalescence temperature method[5] ($\Delta G^\ddagger = 20{\cdot}9 \pm 0{\cdot}4$ kJ mol^{-1}).

Considerably more information can be obtained by accurate measurements of $\Delta G^\ddagger$ at a series of temperatures; computer simulation, using a two jump model, of the experimental spectra of a series of nitroxides has proved to be a convenient means to this end.[6] A detailed knowledge of the energetics of conformational changes in piperidine nitroxides might also be expected to be applicable to geometrically similar

The e.s.r. spectra, measured at temperatures within the range −100 to +35°, were simulated by computer. Typical experimental and simulated spectra are displayed in



(I)

Figure 1 which illustrates the considerable changes with temperature and the faithful reproduction of these changes in the simulated spectra. The asymmetry noticeable in the experimental spectra is probably due to the anisotropies in the *g* tensor and the nitrogen hyperfine coupling tensor.[8]

The parameters required to match the experimental spectra by computer are summarised in Table 1 in which the subscript A refers to the more stable conformation and B to the less stable.

DISCUSSION

Activation Parameters.—The first-order rate coefficients for a simple conformational change $A \rightleftarrows B$ are inversely proportional to the lifetimes of the conformational isomers (τ_A and τ_B). Expansion of the Eyring equation[9] [$k = (\kappa kT/h)\exp(-\Delta G^\ddagger/RT)$] with subsequent

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[2] *E.g.*, G. A. Russell, G. R. Underwood, and D. S. Lini, *J. Amer. Chem. Soc.*, 1967, **89**, 6636; E. G. Janzen, 'Topics in Stereochemistry,' eds. E. L. Eliel and N. L. Allinger, Interscience, New York, vol. 6, 1972.

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[7] F. R. Jensen and B. H. Beck, *J. Amer. Chem. Soc.*, 1968, **90**, 1066.

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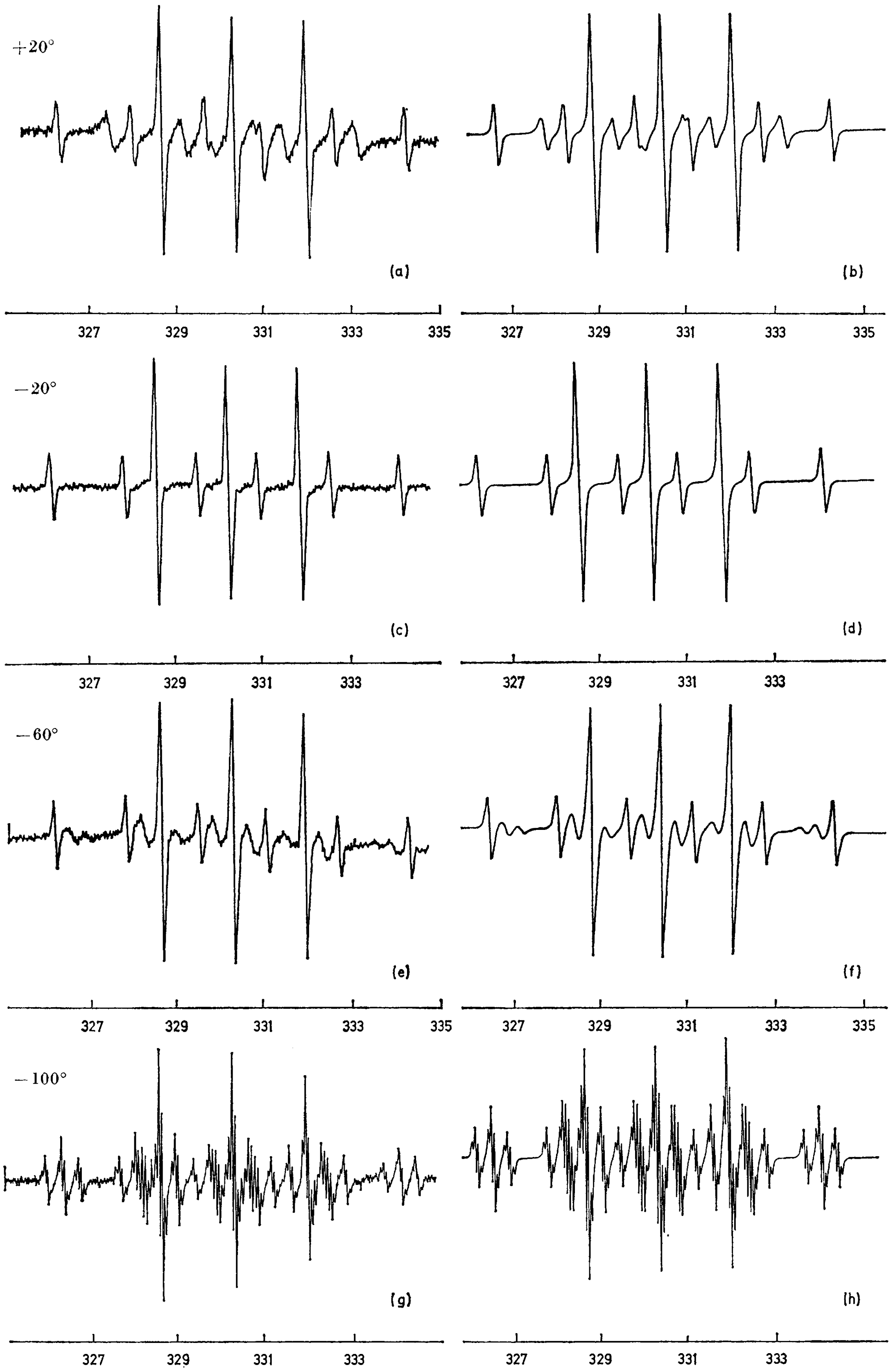

FIGURE 1 E.s.r. spectra of piperidine nitroxide: the experimental spectra are in the left-hand columns; the magnetic field is given in mT

plotting of log $(1/T\tau)$ against $1/T$ led, assuming $\kappa = 1$, to the values of $\Delta G^\ddagger$, $\Delta H^\ddagger$, and $\Delta S^\ddagger$ presented in Table 2.

Figure 2 is a typical Eyring plot; the line is drawn according to the least-squares criterion. The Figure illustrates the variation in sensitivity of the computer simulations at different temperatures to the value of τ and demonstrates clearly, from the intercepts, that $\Delta S^\ddagger_A$ is greater than $\Delta S^\ddagger_B$ and hence ΔS^0 is positive, a point to which further reference will be made.

TABLE 2

Activation parameters *

R	$\Delta H^\ddagger_A$/ kJ mol^{-1}	$\Delta S^\ddagger_A$/ J K^{-1} mol^{-1}	$(\Delta G^\ddagger_{298})_A$/ kJ mol^{-1}	$\Delta H^\ddagger_B$/ kJ mol^{-1}	$\Delta S^\ddagger_B$/ J K^{-1} mol^{-1}	$(\Delta G^\ddagger_{298})_B$/ kJ mol^{-1}	ΔG^0_{298}/ kJ mol^{-1}
H	24·3 ± 0·7	9·2 ± 2·9	21·8 ± 1·7				0
Me	31·7 ± 0·6	17·6 ± 2·5	26·4 ± 1·3	22·1 ± 0·3	9·6 ± 1·3	19·2 ± 0·8	7·1
Pr^i	36·0 ± 1·0	26·4 ± 3·8	28·0 ± 2·1	25·8 ± 0·8	22·2 ± 3·3	19·2 ± 1·7	8·8
Me$_2$	24·4 ± 0·5	5·4 ± 2·1	22·6 ± 1·3				0

* Quoted errors are obtained from the least-squares fit as the probable error defined in H. Margenau and G. M. Murphy, 'The Mathematics of Physics and Chemistry,' Van Nostrand, New Jersey, 1596, p. 519.

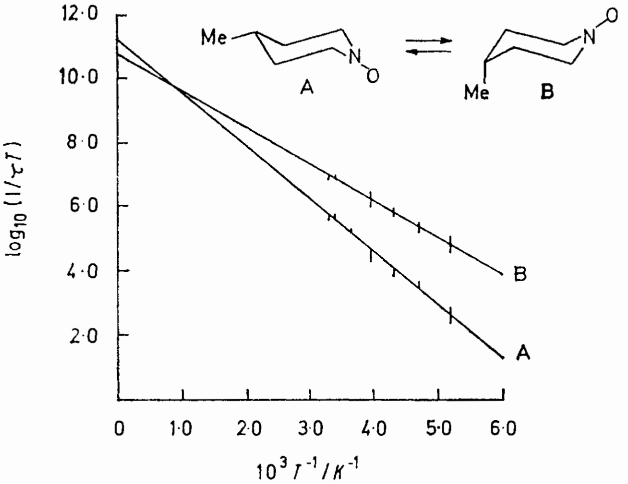

FIGURE 2 Eyring plot for 4-methylpiperidine nitroxide radical

A proper understanding of the ΔS values must take account of the various contributions to the entropies of the two states involved. The absolute entropy of an ideal gaseous system has contributions from translational, rotational, and vibrational motions and for cyclohexane Pitzer *et al.* have calculated [10] that of a total entropy of 298·2 J K^{-1} mol^{-1} the translational and rotational contributions are 259·3 J K^{-1} mol^{-1} with a relatively small contribution (38·9 J K^{-1} mol^{-1}) attributable to vibrational motion. Included in the rotational contribution is a term $-R \ln \sigma$ where σ is the symmetry number.[11] As the total mass of the molecule is the same for both conformations and the moments of inertia are expected to change but little, the translational and rotational contributions to ΔS might be expected to be insignificant. The values presented in Table 2 should therefore be capable of interpretation in terms of changes in the vibrational contribution and in the symmetry number. It is worth noting that in this context restricted rotation is treated as a vibration. It appears that the contribution of stretching and bending vibrational modes to ΔS values will be rather small. For instance for axially and equatorially chloro-substituted cyclohexanes,[12] where $\gamma_{C-Cl(eq)} = 742$ and $\gamma_{C-Cl(ax)} = 688$ cm^{-1}, $\Delta S_{max.}$ is [13] 0·25 J K^{-1} mol^{-1}. The above considerations neglect solvation effects and even though such effects are probably small in our systems, *viz.* neutral radicals in a relatively non-polar solvent, solvation of the polar nitroxide group might be important.

Thus the $\Delta S^\ddagger$ values for the symmetrically substituted nitroxides (R = H or Me$_2$) approximate to Rln2 which is consistent with the view that in inversions starting from a chair or boat form the transition state loses the plane of symmetry. On the other hand the $\Delta S^\ddagger$ values for the 4-methyl- and 4-isopropyl-piperidine nitroxides are not easily rationalised. Subtracting the expected Rln2 contribution leaves for $\Delta S^\ddagger_A$ increments of 11·8 (R = Me) and 20·6 J K^{-1} mol^{-1} (R = Pr^i) to be explained. The geometry of conformation A will be discussed further but assuming at this point a chair form with the substituent equatorial it is likely that in the transition state rotation of the substituent about the C(4)–C axis will, because it is moving towards an axial position, become more hindered. Therefore the contribution [14] towards the entropy of the transition state should be less than for conformation A leading to a negative value for $\Delta S^\ddagger$. This conclusion is reinforced by a consideration of the positive ΔS^0 values, 8·0 (R = Me) and 4·2 J K^{-1} mol^{-1} (R = Pr^i), where there can be little doubt that rotations of the 4-substituents are more hindered in conformation B (R axial) than in conformation A (R equatorial). We cannot therefore rationalise the entropy changes in simple terms.

The values of $\Delta G^\ddagger_A$ may be compared with values obtained by n.m.r. methods for other geometrically similar ring systems. For instance the barrier to inversion in cyclohexanone [7] has been estimated as <21·3 kJ mol^{-1} and in cyclohexanone *O*-methyloxime [7] as 23·4 kJ mol^{-1}; values which are comparable with that for piperidine nitroxide (21·8 kJ mol^{-1}) and 4,4-

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[10] C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488.

[11] N. Davidson, 'Statistical Mechanics,' McGraw-Hill, New York, 1962, p. 173.

[12] M. Larnaudie, *Compt. rend.*, 1952, **235**, 154; 1953, **236**, 909.

[14] K. S. Pitzer, 'Quantum Chemistry,' Prentice-Hall, New York, 1953, pp. 457 and 492.

[13] J. A. Hirsch, 'Topics in Stereochemistry,' Interscience, New York, 1967, vol. 2, p. 119.

dimethylpiperidine nitroxide (22·6 kJ mol^{-1}). The conformational preferences (ΔG^0) of the methyl and isopropyl groups are essentially the same as in the analogous cyclohexane systems.[13] The axial methyl group present in both conformations of 4,4-dimethylpiperidine nitroxide should, therefore, raise the initial state energy by *ca.* 7 kJ mol^{-1} which implies that there is a corresponding increase for the transition state as $\Delta G^{\ddagger}_{A}$ is the same as for piperidine nitroxide. These ideas are consistent with the likely pathway for the inversion of cyclohexane[15] which involves chair–chair inversion *via* a half-chair transition state. We would expect for the 4,4-dimethylpiperidine nitroxide case the disappearance of one of the 1,3-diaxial interactions upon attainment of the transition state but at the expense of the appearance of eclipsing interactions between both methyl groups and the hydrogens of the adjacent methylene group.

The Size and Temperature Dependence of the Coupling Constants.—The nitroxide formed by chemical oxidation of aza-17α-D-homoandrostane, in which the heterocycle is locked in the chair form, shows a coupling to the axial hydrogen on the carbon adjacent to the nitroxide group of the order of 2·0 mT.[4] Inspection of Table 1 reveals $a^{ax}_{2,6}$ values of a similar magnitude confirming that we are indeed dealing with chair conformations. The geometry in solution is therefore similar to that for an analogous cyclic nitroxide in the solid state.[16]

Our results support the observations[5] of Windle *et al.* that the small couplings of 0·065 mT may be assigned to the axial hydrogens at the 3- and 5-positions and the equatorial hydrogen at the 4-position (Table 1, footnote *a*). Although this assignment may appear at first sight surprising, the values are predicted by valence bond theory[17] using angles relevant to a chair conformation. Thus, using Barfield's nomenclature and graphs (ref. 17, Figures 3 and 5), θ and ϕ for the 3- and 5-hydrogens are for the axial position 60 and 30° respectively and for the equatorial position 180 and 30° leading to couplings of 0·095 and 0·020 mT for unit unpaired spin density. Similarly for the 4-position values of 0·03 and 0·18 mT are derived for the axial and equatorial hydrogens respectively.

The temperature dependence of $a^{ax}_{2,6}$ is shown in Figure 3, results which parallel those of previous workers.[4,5] A possible explanation employs a treatment[18] of analogous coupling constants in hydrocarbon free radicals which were obtained by irradiation of single crystals. An empirical relationship was found of the form $a_\beta^H = (B_0 + B_2 \cos^2\theta)\rho_C^\pi$, where ρ_C^π is the unpaired spin density in the p_z orbital of the α-carbon atom and θ is the dihedral angle between the C–H_β bond and the p_z orbital. Typically B_0 is 0·4 and B_2 5·0 mT, leading often to the neglect of the first term in comparison with the second. The simplest interpretation of this equation is that B_0 corresponds to a_β^H for $\theta = 90°$, *i.e.* is a spin polarisation term, whereas B_2 corresponds to a hyperconjugation term; the theoretical justification[19] of this equation uses valence bond theory which does not distinguish between these concepts. Alternatively, B_0 has been interpreted as being due to residual motion of the β protons in the crystal lattice,[20] when B_0 is predicted to vary with temperature. A theoretical treatment[21] has shown that a similar equation applies to simple nitroxides. This treatment implies that (i) if the C_2N–O group is planar then $a_\beta^H = B_2 \cos^2\theta \rho_N^\pi$ and (ii) if the C_2N–O group is pyramidal and is inverting rapidly, then $a_\beta^H = (B_0 + B_2 \cos^2\theta)\rho_N^\pi$, and the values of B_0 and B_2 depend upon the sign of θ (Figure 4),

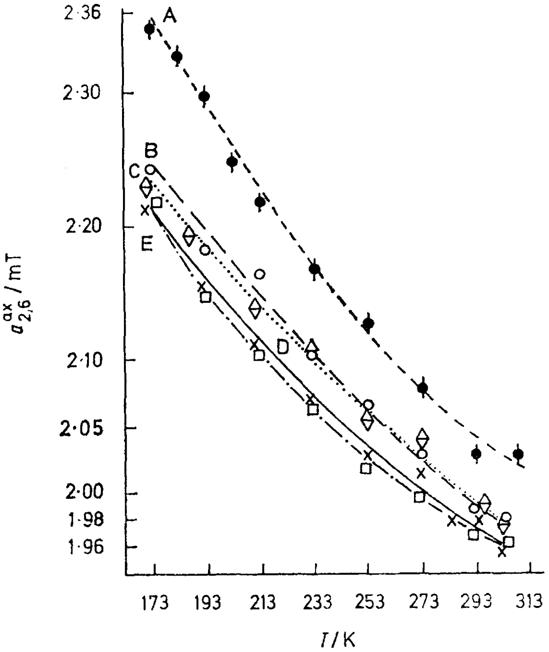

FIGURE 3 Variation of the β axial coupling constants with temperature: A, 4,4-dimethylpiperidine nitroxide; B, 4-t-butylpiperidine nitroxide; C, 4-isopropylpiperidine nitroxide; D, piperidine nitroxide; E, 4-methylpiperidine nitroxide

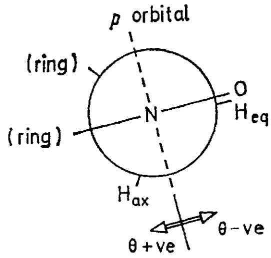

FIGURE 4 Newman projection defining the sign of θ

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[15] F. A. Bovey, E. W. Anderson, F. P. Hood, and R. L. Kornegay, *J. Chem. Phys.*, 1964, **40**, 3099.

[16] J. Lajzerowicz-Bonneteau, *Acta Cryst.*, 1968, **B24**, 196.

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presumably because of the unpaired spin density on the oxygen atom.

The last mentioned equation, in conjunction with the idea of Stone and Maki[20] can form the basis of an explanation of the temperature variation of $a^{ax}_{2,6}$. Using, for nitroalkane radical anions, a simple classical model which envisaged torsional vibration about the C–N bond axis Stone and Maki[20] deduced that $B_0 = -\frac{1}{2}\phi^2(\cos 2\theta_0)B_2$, where θ_0 is the equilibrium value of θ, and ϕ is the amplitude of the vibration. Figure 5 relates these concepts to the piperidine nitroxide case, *viz.* inversion at the nitrogen atom leads to a periodic change in the θ values for the 2- and 6-hydrogens. Assuming a chair conformation with a planar C_2N–O group at the equilibrium position gives $\theta_0^{ax} = 30°$, $\theta = \theta_0 \pm \alpha$, $\phi = 2\alpha$, and leads to the equation $a^{ax}_{2,6} = (3 - \phi^2)B_2\rho_N^{\pi}/4$. For an increase in temperature we would expect ϕ to increase, thus explaining the observed decrease of $a_{2,6}^{ax}$. A similar argument for $a^{eq}_{2,6}$ leads to the equation $a^{eq}_{2,6} = (2\phi^2)B_2'\rho_N^{\pi}/4$, where $B_2 \neq B_2'$ because of the different signs of θ_0 for the axial and equatorial hydrogens (Figure 4). A small increase in $a^{eq}_{2,6}$ with increase of temperature was indeed observed by Windle *et al.*[5] for temperatures higher than those used by us. These qualitative conclusions are not dependent either upon the equilibrium position having a planar C_2N–O group (in the solid state it is non-planar)[16] or upon the hybridisation of the nitrogen atomic orbitals. However if the orbital containing the unpaired spin had a high degree of *s* character we might expect a_N to vary with temperature, which it does not.

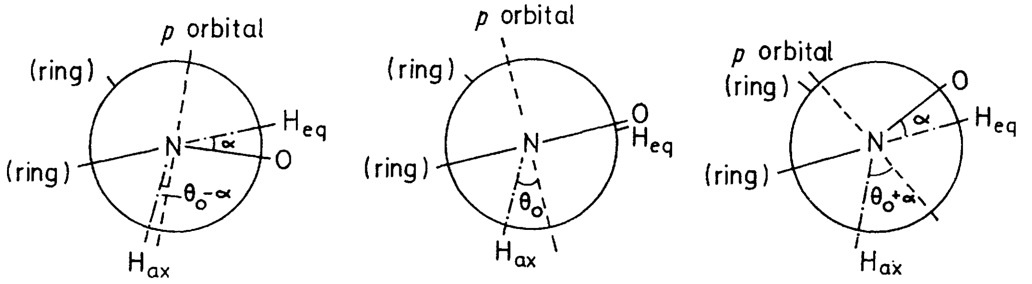
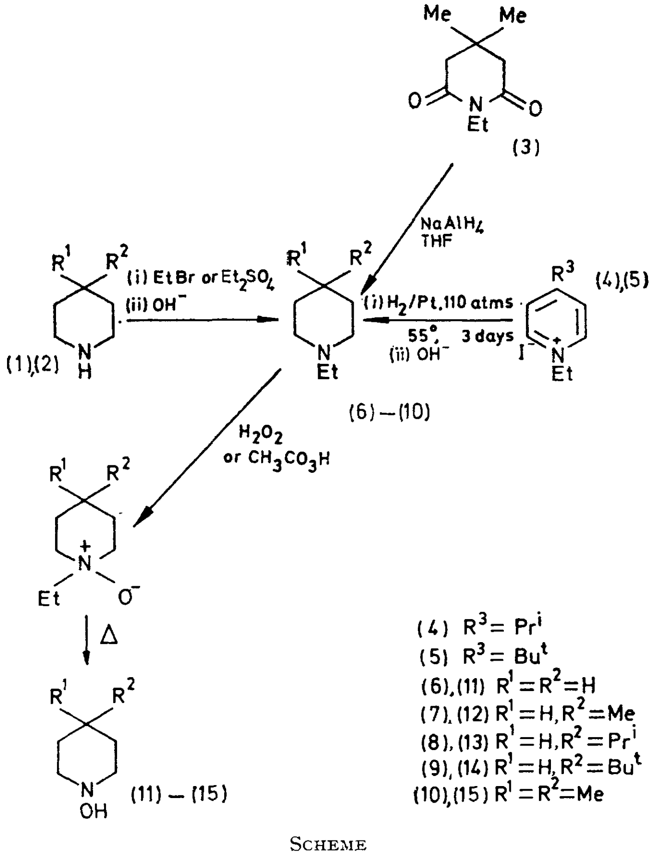


FIGURE 5 Effect of inversion at the nitrogen atom

EXPERIMENTAL

Materials.—The hydroxylamines used as precursors for the formation of nitroxides were prepared according to the Scheme, individual steps being accomplished by adaptations of methods previously described in the literature.[22] For all the intermediates ^1H n.m.r. and i.r. spectroscopic data were consistent with the expected structure and new compounds were further characterised by elemental analyses or from the mass spectrum by accurate mass measurements on the molecular ion. This information, together with other physical data, is summarised in Table 3.

E.s.r. Measurements.—The e.s.r. spectra were obtained using a Decca X3 spectrometer. A steady state concentration of nitroxide was generated *in situ* by irradiation of a sealed Spectrosil tube containing the corresponding hydroxylamine in deoxygenated methylene chloride solution with a Hanovia u.v. lamp (100 W; medium pressure) focused into the cavity.



SCHEME

The spectra were simulated using a two-jump model and the Bloch equations modified for conformational exchange.[23] The input required for the program was the hyperfine coupling constants for each conformation, the

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[22] C. T. Kyte, G. H. Jeffrey, and A. I. Vogel, *J. Chem. Soc.*, 1960, 4454; *Adv. Catalysis*, 1963, **14**, 203; W. D. Emmons, *J. Amer. Chem. Soc.*, 1957, **79**, 5528; L. M. Rice, E. E. Reid, and C. H. Grogan, *J. Org. Chem.*, 1954, **19**, 884; W. Sabel, *Chem. and Ind.*, 1966, 1216.

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TABLE 3

Characterisation of intermediates prepared according to the Scheme

Compound (Scheme number)	B.p. (mmHg) [m.p. (°C)]	Elemental analysis or mass of molecular ion Found (%) C	H	N	Calc. (%) C	H	N
1-Ethyl-4-isopropylpiperidine (8)	193—194 (760)	77·8	13·3	8·9	77·5	13·6	9·03
1-Ethyl-4-t-butylpiperidine (9)	206—208 (760)	78·0	13·9	8·5	78·1	13·6	8·3
1-Ethyl-4,4-dimethylpiperidine (10)	165—167 (760) [173·5—175, picrate]	*m/e*, 141·152159 (Calc. for $C_9H_{19}N$: *M*, 141·151748)					
1-Hydroxy-4-methylpiperidine (12)	120 (15) [a]	*m/e*, 115·099712 (Calc. for $C_6H_{13}NO$: *M*, 115·099725)					
1-Hydroxy-4-isopropylpiperidine (13)	123 (11) [38—40]	*m/e*, 143·130531 (Calc. for $C_8H_{17}NO$: *M*, 143·131012)					
1-Hydroxy-4-t-butylpiperidine (14)	135 (16) [90—90·5]	*m/e*, 157·146173 (Calc. for $C_9H_{19}NO$: *M*, 157·146662)					
1-Hydroxy-4,4-dimethylpiperidine (15)	[82—86]	*m/e*, 129·114914 (Calc. for $C_7H_{15}NO$: *M*, 129·115362)					

[a] Hot-box temperature for short path distillation.

lifetimes of the two conformations, and the linewidth in the absence of exchange.

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