Electron Spin Resonance Studies. Part XLI.[1] Investigations of Structure and Conformation. Part III.[2,3] Conformational Interconversion in some Heterocyclic Radicals

By **Bruce C. Gilbert,* Richard O. C. Norman,** and **Michael Trenwith,** Department of Chemistry, The University of York, Heslington, York YO1 5DD

Radicals have been generated in aqueous solution from pyrrolidine, morpholine, 1,4-dioxan, piperidine, and some alkyl-substituted derivatives, by reaction with ·OH at low pH. Analysis of e.s.r. hyperfine splittings and line-widths recorded over the attainable temperature range (*ca.* 5—45°) yields kinetic and thermodynamic information about conformational interconversion in these species. The five-membered-ring radicals undergo rapid interconversion between half-chair geometries; the conformational preference for a methyl group in this system is 1·4 kJ mol^{-1} at 23°. In contrast, the radical from piperidine undergoes chair–chair ring-flipping with rate constants in the range intermediate between fast and slow exchange [*e.g.* (2·5 ± 0·2) × 10^9 s^{-1} at 39°]; activation parameters for this interconversion are E_a = 30·4 ± 3·0 kJ mol^{-1} and $\log_{10} A$ = 14·5 ± 0·2.

We have previously described [2] e.s.r. results for a series of nitroxide radicals with chiral γ-substituents, placing emphasis on the diagnosis of preferred conformations, and we have also employed [3] INDO molecular orbital calculations to support e.s.r. evidence for twisting and bending in some nitro-anion-radicals. Our study of dynamic processes and conformational preferences has now been extended to radicals derived from heteroalicyclic compounds containing five- and six-membered rings. A rapid-mixing flow system and the Ti^{III}–H$_2$O$_2$ couple [1] have been employed to generate radicals by the

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[1] Part XL, B. C. Gilbert, R. O. C. Norman, and R. C. Sealy, *J.C.S. Perkin II*, 1974, 824.

[2] Part I, B. C. Gilbert and M. Trenwith, *J.C.S. Perkin II*, 1973, 1834.

[3] Part II, B. C. Gilbert and M. Trenwith, *J.C.S. Perkin II*, 1973, 2010.

reaction of the hydroxyl radical with pyrrolidine, morpholine, 1,4-dioxan, piperidine, and, in particular, some substituted derivatives.

E.s.r. spectra of radicals derived from pyrrolidine,[4] morpholine,[5] 1,4-dioxan,[6,7] and piperidine [6] have been described previously and in some cases [6] line-broadening has provided evidence for rapid conformational interconversion. The corresponding homocyclic radicals, cyclopentyl and cyclohexyl, have been prepared by electron bombardment of the parent hydrocarbons; the temperature dependences of their e.s.r. spectra have enabled more detailed conclusions about ring shape and rates of interconversion to be reached.[8,9] More recently, detailed studies of some cyclic nitroxides have also been reported; [10-14] from the line-broadening observed for piperidine nitroxide and some derivatives, activation parameters for ring-flipping and conformational preferences for a variety of alkyl substituents have been evaluated. The detailed conclusions available from this approach are illustrated by the most complete account.[14]

We have extended earlier work on the short-lived heterocyclic radicals, employing two techniques which both afford extra kinetic and thermodynamic information. One involves the investigation of line-broadening as a function of temperature (to obtain kinetic parameters). The other employs appropriate substituents to provide favourable weighting for certain conformations. Both methods have required computer simulation of observed spectra.

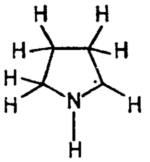
EXPERIMENTAL

The e.s.r. spectrometer, the flow system, and the procedure for measuring hyperfine splittings have been described previously.[1-3] Spectrum simulation was effected with a program kindly supplied by Dr. M. F. Chiu; the exchange routine utilises the solutions of modified Bloch equations [15] by Gutowsky and Holm.[16] Simulation was also employed to verify the measured splittings (±0·01 mT, unless stated otherwise). All materials were commercial samples except for the *N*-t-butyl derivatives of pyrrolidine and piperidine which were prepared by the method of Bottini and Roberts.[17]

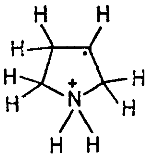
Radicals were generated in a three-way, single-stage mixing flow system with gravity feed and a total flow rate of *ca.* 250 ml min^{-1}; all solutions were deoxygenated with a nitrogen purge. Temperature variation was achieved with iced or hot water, and the mean values quoted (±2°) were measured with thermometers placed in each stream just before entry of the solutions into the cavity. Reactants were typically as follows. The first solution contained 12·5% (w/v) titanium(III) chloride solution (10—15 ml l^{-1}) and concentrated sulphuric acid (5—10 ml l^{-1}), the second hydrogen peroxide solution (100 vol.; *ca.* 5 ml l^{-1}) and concentrated sulphuric acid (5—10 ml l^{-1}), and the third the heterocyclic substrate (*ca.* 30 ml l^{-1}) and enough concentrated sulphuric acid to give an effluent pH of about 1·5.

RESULTS AND DISCUSSION

(a) *Radicals from Compounds with Five-membered Rings.*—(i) *Pyrrolidine.* The assignment [4] to the radical (1) of an e.s.r. signal having *a*(1H) 2·18 and *a*(2H) 3·51 mT, obtained with the Ti^{III}–H_2O_2 couple, is surprising for two reasons. First, the radical (1) would certainly be expected to show a nitrogen splitting [*cf.* $\cdot CHMe\overset{+}{N}H_2Et$, *a*(N) 0·335 mT (ref. 18)] and, secondly, at the pH employed, abstraction by the electrophilic hydroxyl radical should occur at positions furthest away from the positively-charged nitrogen to give the radical (2).



(1)



(2)

We have re-examined this reaction and find that the e.s.r. evidence supports assignment of the spectrum to the radical (2); the β-hydrogen splitting pattern is actually a 1 : 4 : 6 : 4 : 1 quintet [previously the outermost lines must have been obscured by noise (see Figure 1 of ref. 4)]. For a spectrum recorded at 22° the complete analysis is *a*(1H) 2·17, *a*(4H) 3·55 mT (the α- and four β-hydrogens, respectively; see Table 1), and *g* 2·0026.* The equivalence of the β-hydrogen couplings indicates either that the five-membered ring in (2) is planar or that it is undergoing some rapid interconversion process which renders these four atoms apparently equivalent. The spectrum was invariant with temperature in the region 9—39°, which is also consistent with planarity or very rapid interconversion. These findings are to be contrasted with those for the radical derived from piperidine (see later).

(ii) N-*Alkylpyrrolidines.* The radical observed during the reaction of *N*-methylpyrrolidine with Ti^{III}–H_2O_2

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* For this and other amines, traces of unassigned signals were also observed, including a singlet at *g* 2·0161 and two broad absorptions at high and low field.

[4] H. Taniguchi, *J. Phys. Chem.*, 1970, **74**, 3143.

[5] B. C. Gilbert, J. P. Larkin, and R. O. C. Norman, *J.C.S. Perkin II*, 1972, 794.

[6] W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.*, 1964, 4850.

[7] A. J. Dobbs, B. C. Gilbert, and R. O. C. Norman, *J. Chem. Soc.* (*A*), 1971, 124.

[8] R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, 1963, **39**, 2147.

[9] S. Ogawa and R. W. Fessenden, *J. Chem. Phys.*, 1964, **41**, 994.

[10] A. Hudson and H. A. Hussain, *J. Chem. Soc.* (*B*), 1968, 251.

[11] A. Hudson and H. A. Hussain, *J. Chem. Soc.* (*B*), 1968, 953.

[12] J. J. Windle, J. A. Kuhnle, and B. H. Beck, *J. Chem. Phys.*, 1969, **50**, 2630.

[13] R. E. Rolfe, K. D. Sales, and J. H. P. Utley, *Chem. Comm.*, 1970, 540.

[14] R. E. Rolfe, K. D. Sales, and J. H. P. Utley, *J.C.S. Perkin II*, 1973, 1171.

[15] A. Carrington and A. D. McLachlan, ' Introduction to Magnetic Resonance,' Harper and Row, New York, 1967.

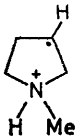
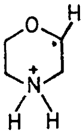
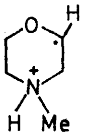
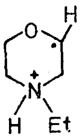
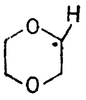
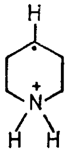
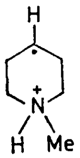
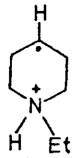
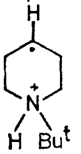
[16] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.

[17] A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, 1958, **80**, 5203.

[18] N. H. Anderson and R. O. C. Norman, *J. Chem. Soc.* (*B*), 1971, 993.

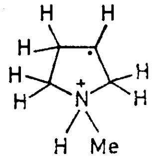
TABLE 1

Hyperfine splittings (mT [a]) for radicals derived from some heteroalicyclic compounds at pH *ca.* 1·5

Radical	T/°C [b]	a(α-H)	a(β-H) [c]	a(other) [d]
	22	2·17	3·55 (4)	
	23	2·22	3·94 (2) 3·23 (1) 3·08 (1)	
	22	2·22	4·24 (2) 2·88 (2)	
	20	1·87	4·44 (2) [e]	0·41 (N) 0·12 (2, γ-H)
	21	1·90	4·30 (1)	0·44 (N) 0·17 (1, γ-H)
	22	1·90	4·31 (1)	0·44 (N) 0·18 (1, γ-H)
	19	1·738 [f]	4·538 (2) [e,f]	0·095 (2, γ-H) [f]
	22	2·18	4·88 (4)	
	8	2·16 [h]	4·02 (2) [g,h] 1·00 (2)	
	25	2·17 [h]	3·93 (2) [g,h] 1·07 (2)	
	37	2·17 [h]	3·89 (2) [g,h] 1·10 (2)	
	8	2·19	4·01 (2) [g] 1·07 (2)	
	27	2·17	3·95 (2) [g] 1·13 (2)	
	39	2·17	3·90 (2) [g] 1·17 (2)	
	21	2·10	4·08 (2) 0·98 (2)	

[a] ±0·01 mT, unless stated otherwise. [b] ±2°. [c] Number of nuclei indicated. [d] Assignment in parentheses. [e] Sum of two β-couplings. [f] ±0·005 mT. [g] Apparent β-splittings (see text). [h] ±0·02 mT.

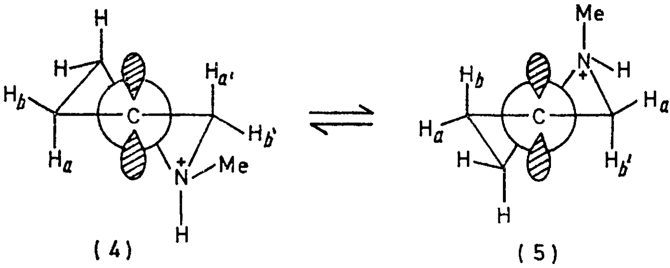
has the following splitting constants (at 23°): a(1H each) 2·22, 3·08, and 3·23 mT and a(2H) 3·94 mT (Table 1). Its g-value is 2·0028. We ascribe this signal to the radical (3) and assign the 2·22 mT splitting to the



(3)

α-hydrogen atom. These findings imply that the ring in this radical is not planar, and, furthermore, that there is some distortion which causes one pair of β C–H bonds, otherwise equivalently disposed, to subtend dissimilar angles with the orbital of the unpaired electron.* The possible flexible motion which renders the β-couplings equivalent for the radical (2) may be akin to that responsible (but not characterised) for producing line-width effects in the e.s.r. spectrum of the cyclopentyl radical in solution;[8] we note that in a recent e.s.r. study of cyclopentyl trapped in a solid matrix at 77 K non-equivalent β-hydrogen splittings were detected.[19]

The observed spectrum of the radical (3) will not correspond, in all probability, to a fixed conformation; it is thus not possible to derive torsion (dihedral) angles from the β-splittings directly. Rather, the experimental coupling constants will reflect a suitably weighted average of various possible conformations. We believe, however, that these results can be interpreted in terms of an exchange between just two 'half-chair' conformations,[20] (4) and (5), in which the pseudoaxial hydrogens have a larger splitting than the pseudoequatorial hydrogens, and also that our results support the similar, tentative suggestion advanced[21] for the cyclopentyl radical. For the conformation which is expected to be favoured [(4), with methyl pseudoequatorial], two β-hydrogens (H$_a$ and H$_{a'}$) will have a larger splitting than the others (H$_b$ and H$_{b'}$), and, although ring-flipping interchanges



(4) (5)

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* Inequivalence of the pair of hydrogens having the larger splitting could not be detected; the line-width for (3) was *ca.* 0·2 mT.

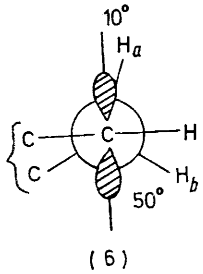
[19] A. L. Blyumenfel'd and V. I. Trofima, *Zhur. strukt. Khim.*, 1973, **14**, 230.

[20] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962.

[21] J. K. Kochi, P. Bakuzis, and P. J. Krusic, *J. Amer. Chem. Soc.*, 1973, **95**, 1516.

these pairs as indicated, the observed spectrum will resemble that of (4) to an extent which depends on the weighting of this conformer. When there is no conformational preference (as in the unsubstituted radical) *all four* hydrogens become equivalent through rapid averaging [the mean values of 3·94 and 3·08 mT and of 3·94 and 3·23 mT yield, in each case, a(2H) *ca.* 3·5 mT for (3)—this is the value of a(4H) for the radical (2); the further slight difference between two β-splittings for (3) presumably reflects the additional asymmetry introduced at nitrogen].

The following approximate analysis provides only an estimate of the torsion angles in conformations (4) and (5) and of the conformational weightings; nonetheless, it does illustrate the appropriateness of the model. Assuming that a $B\cos^2\theta$ relationship obtains,[22] with $B \cong 5{\cdot}0$ mT, we must choose a pair of torsion angles, θ and θ', [for $C{-}H_a$ and $C{-}H_b$, respectively, with $H_a\hat{C}H_b$ 120°, as in (6)] such that the value of $(B\cos^2\theta + B\cos^2\theta')$ is approximately 7·0 mT (in this instance).



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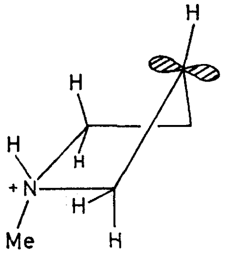

(7)

We find $\theta = 10$ and $\theta' = 50°$ [*cf.* structure (6)] and corresponding hyperfine splittings of 4·9 and 2·1 mT. The angles calculated on this basis are in good agreement with those expected for (4) and also concur with those (14 and 40°) estimated[19] for cyclopentyl in the solid state; this suggests that the preferred conformation of the radical (3) is indeed a half-chair. We note from inspection of a model of the alternative 'envelope' conformation (7) that this has torsion angles of *ca.* 10 and 70°; the sum of the appropriate calculated coupling constants, 5·5 mT, is well below the experimental value. Further, the lack of an observable nitrogen splitting from the radicals (2) and (3) is consistent with the half-chair, rather than the envelope, structure. Thus the torsion angles made by the (β) C–N bonds in the two cases are 70 and 50°, respectively, and, since a β-nitrogen splitting appears[5] to depend on $\cos^2\theta_N$, a much smaller splitting would be expected for the former. {For the morpholine radicals (see later) where θ_N is *ca.* 30°, the nitrogen splitting is 0·44 mT; using this value we predict nitrogen splittings of 0·07 and 0·24 mT, respectively, for the half-chair and envelope structures. A splitting of the magnitude of the former, but not the latter, would not be resolved [*e.g.* ΔH *ca.* 0·2 mT for (3)].}

Finally, if the expected splittings from (4) are approximately 4·9 and 2·1 mT, for H_a and $H_{a'}$ and for H_b and $H_{b'}$, respectively [and the reverse for (5)], we can calculate the weightings of each conformation necessary to reproduce the observed couplings of about 3·9 (2H) and 3·2 mT (2H). The result is 64% for (4) [and 36% for (5)], which is reasonable for a methyl group in a pseudoequatorial position; the associated free-energy change for the conversion of (4) into (5) is $+1{\cdot}4$ kJ mol^{-1}.

A lower limit of *ca.* 10^8 s^{-1} can be estimated for the rate constants for interconversion between (4) and (5) (*i.e.* the exchange rates are greater than the difference between the β-splitting constants expressed in frequency units); this reflects the lack of line-broadening effects in the spectrum of (3) at 23°. Our attempts to probe the anticipated temperature dependence of β-splittings from the radical (3) were unsuccessful; spectra recorded at 8 and 39° had unacceptably low signal-to-noise ratios.

The e.s.r. signal of the radical formed from *N*-t-butylpyrrolidine under similar experimental conditions at 22° exhibits hyperfine splittings from a single (α-) hydrogen, of 2·22 mT, and from two different pairs of hydrogens of 2·88 and 4·24 mT.* This is assigned to the *N*-t-butyl analogue of (3); the sum of the β-splittings is virtually the same in each case. We may employ the β-splittings expected for a fixed, half-chair conformation of the five-membered ring (4·9 and 2·1 mT—scaled up slightly to give the appropriate sum in this instance) to evaluate a weighting for the predominant conformation of the radical from *N*-t-butylpyrrolidine [*cf.* (4)] as 74%; the free-energy change associated with conformational interconversion into the species with t-butyl pseudoaxial [*cf.* (5)] is $+2{\cdot}6$ kJ mol^{-1}. That the conformational weighting of the *N*-t-butyl analogue of (4) is not 100% (in contrast, say, to t-butylcyclohexane[20]) is understandable in view of the reduced steric compression in the five-membered compared with the six-membered ring. The limited quantity of *N*-t-butylpyrrolidine available precluded investigation of the temperature dependence of splittings in the radical derived from it.

The non-equivalence of β-hydrogen hyperfine splittings which we have observed for the substituted pyrrolidinyl radicals provides confirmatory evidence for non-planarity in the five-membered-ring system. Our arguments also lend support to the interpretation, based on the invariance of couplings with temperature[23,24] and line-width alternation[24] observed for the related tetrahydrofuran-2-yl and its sulphur analogue, respectively, that these radicals also adopt half-chair geometries.

(b) *Radicals from Compounds with Six-membered Rings.*—(i) *Morpholine and* N-*alkylmorpholines.* Reaction of

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* Anomalous line-width effects indicate that the 4·24 mT triplet splitting is probably the mean value of two slightly inequivalent doublets [*cf.* the discussion for the radical (3)].

[22] R. O. C. Norman and B. C. Gilbert, *Advan. Phys. Org. Chem.*, 1967, **5**, 53.

[23] C. Corvaja, G. Giacometti, and M. Brustolon, *Z. Phys. Chem. (Frankfurt)*, 1972, **82**, 272.

[24] E. A. C. Lucken and B. Poncioni, *Helv. Chim. Acta*, 1972, **55**, 2673.

morpholine with the hydroxyl radical at pH *ca.* 1·5 generates an e.s.r. signal attributed to the radical (8), splittings being in good agreement with those reported previously[5] (see Table 1). The outer resonances alone of the (anticipated) 1 : 2 : 1 β-triplet are sharp, evidently as a result of rapid chair–chair flipping, but we could detect the broadened central lines [see Figure 1(a)]; as expected, these sharpen with increasing temperature (the measured splittings, however, do not vary appreciably). Moreover, we were able to simulate this broadening [Figure 1(b)] by allowing for the effects of conformational interconversion. The appropriate input parameters for the program could not be obtained from the morpholine spectra, since the slow-exchange limit was not attainable under our conditions. However, a realistic estimate of them was achieved in the following manner.

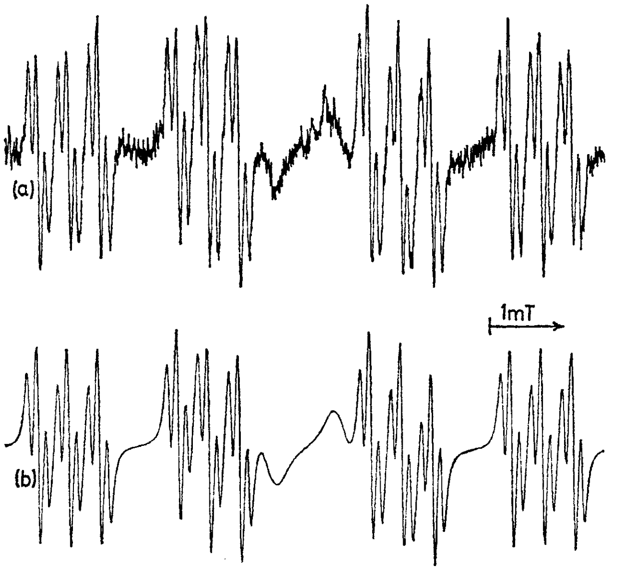
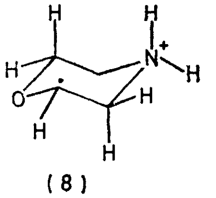
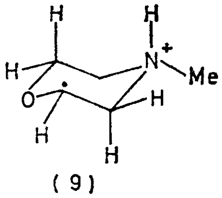


FIGURE 1 (a) E.s.r. spectrum of the radical (8) from morpholine at 20° and pH 1·8; (b) simulated spectrum obtained by using the parameters in Table 1 (see text) and a rate constant for exchange between equivalent conformations of $3{\cdot}5 \times 10^{9}$ s^{-1}

N-Methylmorpholine reacts with hydroxyl, under similar conditions, to produce the radical (9); see Table 1. This has an α-hydrogen and a nitrogen-splitting close to those of (8) but only a single γ-coupling, and the β-hydrogen hyperfine pattern also appears only to have a single splitting, of 4·30 mT. *N*-Ethylmorpholine behaves similarly (Table 1). It is expected that the *N*-methyl and -ethyl groups will favour, quite markedly, an equatorial conformation [such as (9)], with a weighting of about[20] 90% as in the parent molecules. This explains why spectra from the alkylated species resemble those anticipated for locked conformations with, evidently, two inequivalent β- and two inequivalent γ-hydrogens (although there should still be rapid interconversion). We conclude that, since (even with about 90% weighting of the conformation with an equatorial alkyl group) only one β-splitting is detected, in the fixed conformation (9) one of the β-hydrogens must have a very small splitting (less than the line-width) whilst that of the other must be very close to the observed sum; a similar argument holds for the γ-couplings. Thus, for the radical from *N*-methylmorpholine in the fixed conformation, $a(\beta_{ax}) \cong 4{\cdot}30$ and $a(\beta_{eq}) \cong 0$ mT. These values are as expected, since for a chair conformation the axial β C–H bond subtends a favourable torsion angle (30°) for hyperconjugative interaction with the unpaired electron, whereas an angle of 90° for the equatorial C–H bond should give rise to little or no splitting from this hydrogen atom.[22]



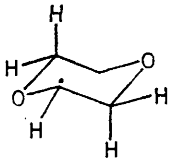
(8)



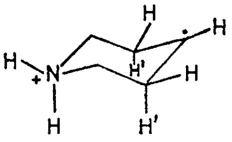
(9)

It seems likely, therefore, that the fixed conformation of the unsubstituted morpholine radical (8) has $a(\beta_{ax}) \cong 4{\cdot}44$ and $a(\beta_{eq}) \cong 0$ mT. Using these two values and other splittings observed (including two *equivalent* γ-couplings, since these are effectively averaged), we employed the simulation program with a rate constant (k) of $3{\cdot}5 \times 10^{9}$ s^{-1} for exchange between equivalent conformations to obtain the calculated spectrum in Figure 1(b). This represents optimum agreement with experiment. Exchange rates for the best matches with spectra at other temperatures are in Table 2. In view of the marked broadening of the central lines [*cf.* Figure 1(a)] we were unable to obtain more accurate values of k; however, we suggest that the reasonable agreement with experimental spectra which we have been able to achieve justifies the arguments advanced. An Arrhenius treatment of the rate data yields an energy of activation (barrier to ring-flipping) of $38{\cdot}7 \pm 3{\cdot}8$ kJ mol^{-1}, with $\log_{10} A = 16{\cdot}4 \pm 0{\cdot}7$.

(ii) 1,4-*Dioxan.* As reported previously,[6,7] the radical (10) mediates in the reaction between 1,4-dioxan and hydroxyl. Its e.s.r. characteristics (splittings $\pm 0{\cdot}005$ mT) are noted in Table 1; as for the morpholine-derived radical, the central lines of the 1 : 2 : 1 hyperfine patterns expected from the β-hydrogens in (10) are considerably broadened. This line-broadening has been investigated over the temperature range 6—42°, in which neither the slow- nor fast-exchange limits are realised; there is, however, a slight sharpening of the central resonances with increasing temperature. Reasonable accordance has been achieved between experimental spectra, including the broadened lines, and simulations incorporating rapid exchange between equivalent conformations which have values of 4·538 and 0 mT for the individual β-hydrogen couplings (by analogy with the result for the related morpholinyl radicals). Although γ-hydrogen fine structure became apparent on the broader lines in simulations at higher exchange rates, it was not comparably resolved in the experimental spectra (an extra line-broadening mechanism may be implicated). Matching was achieved on the basis of peak heights for the broader resonances. The other splittings employed in our calculations (for α- and γ-hydrogens) are those in Table 1; they show no appreciable temperature dependence. Table 2 includes the exchange rate constants utilised in conjunction with these parameters to obtain best fits to the experimental traces. An Arrhenius treatment of them gives $E_a = 28{\cdot}2 \pm 2{\cdot}7$ kJ mol^{-1} and $\log_{10} A = 14{\cdot}8 \pm 0{\cdot}5$ for the interconversion.



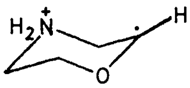
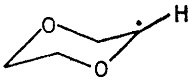
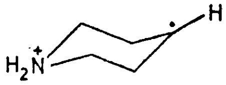
(10)



(11)

TABLE 2

Rate constants for conformational interconversion of six-membered heterocyclic radicals

Radical	T/°C [a]	$10^{-8}k$/s^{-1}
	7 20 44	14 ± 2 35 ± 5 100 ± 20
	6 14 19 26 31 42	35 ± 5 40 ± 5 60 ± 10 65 ± 10 90 ± 10 135 ± 20
	9 22 31 39	7 ± 1 11 ± 1 16 ± 2 25 ± 2

[a] ±2°.

(iii) *Piperidine and* N-*alkylpiperidines*. The hydroxyl radical reacts with piperidine at low pH to produce the radical (11) whose e.s.r. characteristics are listed in Table 1 (see Figure 2). This species exhibits a typical α-hydrogen splitting, and, at room temperature, a pattern from the β-hydrogens with intensities in the approximate ratio 1 : 4 : 1. The latter results typically [6] from chair–chair flipping of six-membered rings at intermediate rates such that, in this case, the two pairs of inequivalent β-splittings [a(H) and a(H')] are not completely averaged. The spectra also contain some additional broader lines. We find that the ratio of peak heights for the inner and outer sharp lines is temperature dependent; as expected, it becomes greater than 4 : 1 at higher temperatures and the broad lines sharpen such that the overall β-pattern approaches a 1 : 4 : 6 : 4 : 1 quintet [Figure 2(b)]. Within the temperature range attainable we were unable to reach either the high-temperature limit (a 1 : 4 : 6 : 4 : 1 pattern from the β-hydrogens) or the low-temperature limit (two 1 : 2 : 1 splittings). However, it was possible to simulate the observed spectra satisfactorily, including the broad resonances [see, *e.g.*, Figure 2(c)], by employing estimated values for the β-couplings in the fixed conformation (11). Again, the stratagem adopted involved the study of alkyl-substituted species.

Spectra were recorded for the radicals generated by oxidation of *N*-methyl- and *N*-ethyl-piperidine at various temperatures. In both cases it is clear that abstraction again occurs at the ring position furthest removed from the $-\overset{+}{N}HR-$ group, although the spectra are quite different in appearance from that of the parent (11). The alkylated species each show a doublet splitting from the α-hydrogen, together with two triplets from non-equivalent pairs of β-hydrogens (see Table 1 for the coupling constants); these do not appear as 1 : 2 : 1 patterns, however, but exhibit some broadening of the inner lines, evidently through fairly rapid interconversional processes.

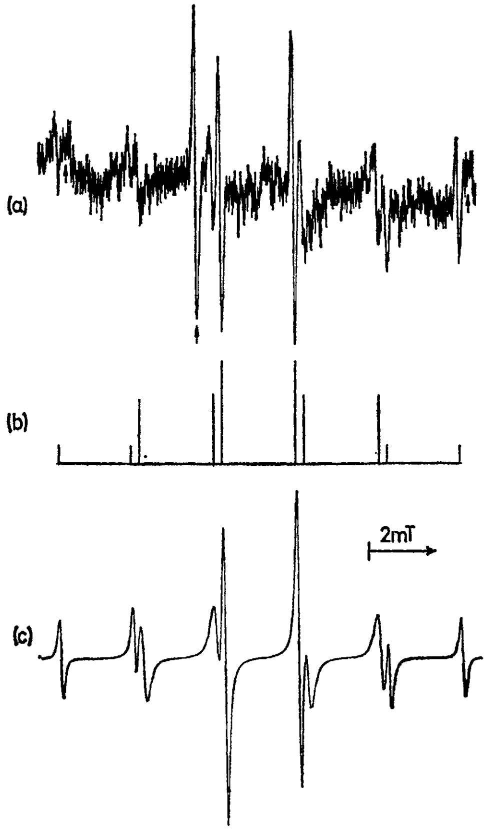
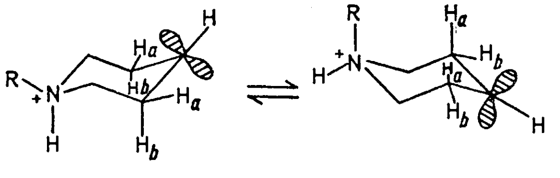


FIGURE 2 (a) E.s.r. spectrum of the radical (11) from piperidine at 39° and pH 1·6 (signals arrowed are spurious); (b) stick diagram of the spectrum expected in the fast-exchange region; (c) spectrum simulated by using hyperfine splittings of a(α-H) 2·18 mT, a(β-H) 3·94 mT (2H), and a(β'-H) 0·94 mT (2H) with a conformational interconversion rate constant of $2{\cdot}5 \times 10^{9}$ s^{-1}

Several further important points emerge from these spectra. For example, the magnitudes of the β-splittings (but not of the α-couplings) and also the widths of some absorptions vary with temperature; the sums of the β-hydrogen splittings, however, remain approximately constant. We propose the following explanation for these observations. The *N*-alkylated piperidinyl radicals must be rapidly interconverting (the line-width alternations indicate the occurrence of dynamic processes), presumably between conformations (12) and (13), the proportions of which will be unequal; for R = Me and Et we expect (12), with R equatorial, to be favoured. The observed spectra will then represent weighted averages of (12) and (13), having a predominant contribution from the former. With decreasing temperature, the weightings of (12) should increase and the *apparent* β-splittings will more closely approach those appropriate to a single conformation (the data in Table 1 provide confirmation of this). We might have anticipated that, at any given temperature, the weighting of (12) would be greater for R = Et than for R = Me, as a consequence of the increased steric requirements of an ethyl group. Unfortunately, the poor signal-to-noise ratio of spectra from the *N*-methylpiperidine-derived radical, compared with those from the ethyl analogue, precluded any comparative deductions.



(12) (13)

For these radicals, therefore, the apparent β-hydrogen splittings contain thermodynamic information, about the relative weightings of conformations (12) and (13), and the line-width effects contain kinetic information, about this interconversional process (we restrict our discussion to the *N*-ethylated radical). In order to extract this information we must know the splitting constants for the individual (fixed) β-hydrogens in (12) and (13). We therefore generated the analogous species from *N*-t-butylpiperidine (the splittings in Table 1 refer to 21°), and the absence of any line-broadening in its e.s.r. spectrum confirms the expected total preference for a locked conformation (*cf.* refs. 13 and 20); the β-splittings of 4·08 and 0·98 mT are thus appropriate to atoms H_b and H_a, respectively, in the fixed structure (12).

These couplings (adjusted slightly to give the appropriate sum) were used to derive weightings of (12) and (13) for the protonated *N*-ethylpiperidin-4-yl radical over the range of temperature investigated. The calculated proportions of (12) in the equilibrating mixtures of (12) and (13) are 97·1% at 8°, 95·2% at 27°, and 93·6% at 39°. At 300 K the conformational preference (ΔG°_{300}) for this radical is calculated as 7·5 kJ mol^{-1}, which is to be compared with the values (ΔG°_{298}) of 7·1 and 8·8 kJ mol^{-1} estimated [13,14] for the related 4-methyl- and 4-isopropyl-piperidine nitroxide radicals and coincides with that [25] of the ethylcyclohexane molecule at 303 K. Employing these conformational proportions in conjunction with the simulation program, we varied the exchange rates until good agreement was obtained with experimental spectra at the different temperatures investigated; the optimum rate constants for exchange between conformations (12) and (13) and the reverse process, respectively, were found to be $6{\cdot}4 \times 10^8$ and $9{\cdot}4 \times 10^9$ s^{-1} at 39°, $1{\cdot}9 \times 10^8$ and $3{\cdot}8 \times 10^9$ s^{-1} at 27°, and $3{\cdot}5 \times 10^7$ and $1{\cdot}2 \times 10^9$ s^{-1} at 8°.

Finally, spectra from the piperidine radical itself (11) were simulated quite closely [see, *e.g.*, Figure 2(c)] with estimated values of 3·94 and 0·94 mT for the axial and equatorial β-couplings (their ratio is the same as for the *N*-t-butyl species, the numbers being slightly reduced to give the appropriate sum) and suitable exchange rates at the different temperatures. The rate constants are in Table 2; from them we derive $E_a = 30{\cdot}4 \pm 3{\cdot}0$ kJ mol^{-1} and $\log_{10} A = 14{\cdot}5 \pm 0{\cdot}2$ for the conformational interconversion of (11). The activation energy barrier to ring-flipping compares reasonably well with that derived [9] from line-broadening in the e.s.r. spectrum of the structurally related cyclohexyl radical of $20{\cdot}5 \pm 2{\cdot}1$ kJ mol^{-1}.

The shape of the piperidinyl ring in the radicals studied is clearly similar to that for cyclohexyl; thus the individual β-hydrogen splittings for the fixed conformation in the former examples are *ca.* 4·1 and 1·0 mT, whereas for the latter the low temperature (−80°) limiting values are [8] *ca.* 4·0 and 0·5 mT. In both cases, and particularly for the piperidinyl radicals, there may be some degree of distortion from a perfect chair geometry (if the β-hydrogen splitting does follow a $B \cos^2 \theta$ dependence, the equatorial β-hydrogen with $\theta = 90°$ should have zero splitting). More appropriate values of θ for these radicals may be *ca.* 75 and 15° although a detailed analysis must await clarification of the exact angular dependence of β-hydrogen splittings in cyclic systems.

We thank the S.R.C. for a studentship to M. T.

[4/195 *Received*, 31*st January*, 1974]

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[25] A. H. Lewin and S. Winstein, *J. Amer. Chem. Soc.*, 1962, **84**, 2464.