Conformational Equilibria in *N*,3- and *N*,4-Dimethylpiperidine

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Summary The conformational equilibrium free energy difference for the *C*-methyl groups in *N*,3- and *N*,4-dimethylpiperidine, and therefore in 3- and 4-methylpiperidine to a good approximation, have been estimated to be 6·3 ± 0·3 and 8·3 ± 0·3 kJ mol^{-1} at 293 K in dodecane as solvent, using the ratios of diastereomeric ions formed by the kinetically controlled protonation of ^{13}C isotopically enriched derivatives.

KINETICALLY controlled protonation of *N*-methylpiperidines (Scheme) gives mixtures of ions of which the concentrations are related to the conformational equilibria in the amines.[1] When (**4**) or (**5**), < 0·2 M in dodecane, is vigorously stirred with sulphuric acid (81% is convenient for ^{13}C n.m.r. spectra and may be used at elevated temperatures, as may dodecane) conformers *EE* and *AA* (Scheme) give the more abundant ion [*cis*-(**8**) and *trans*-(**9**)] and conformers *EA* and *AE* the less abundant ion [*trans*-(**8**) and

TABLE. Ratios (R) of more to less abundant diastereomeric ions formed by kinetic protonation of the piperidines (**2**)—(**5**) (in dodecane) and derived conformational equilibrium constants (K_R and K_{NMe}) and free energy differences ($\Delta G°$) at 293 K.

Amine	Ions	R[a]	K_{NMe}	K_R	$\Delta G°$/kJ mol^{-1}
(**2**)	*cis,cis*-(**6**)/*trans,trans*-(**6**)	165 ± 20	0·006		12·5 ± 0·4
(**3**)	*trans*-(**7**)/*cis*-(**7**)	17·0 ± 20	0·006		12·5 ± 0·4
(**4**)	*cis*-(**8**)/*trans*-(**8**)	12·5 ± 1	0·074	0·074	6·3 ± 0·3
(**5**)	*trans*-(**9**)/*cis*-(**9**)	25·4 ± 2		0·033	8·3 ± 0·3

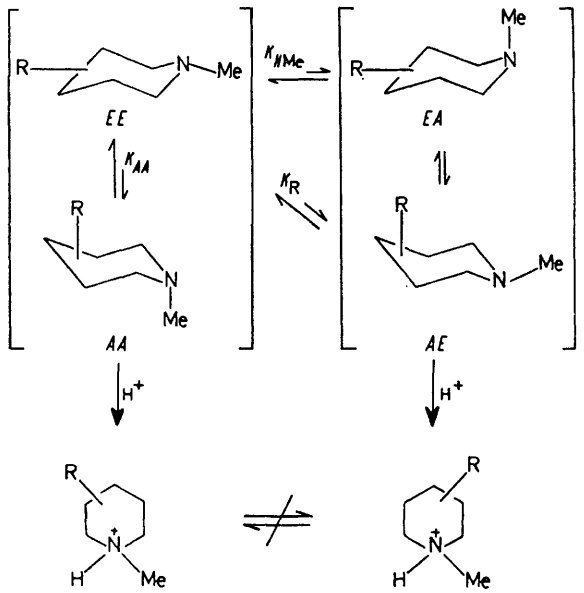
[a] Errors quoted for R and thence for $\Delta G°$ are based on experience of a large number of kinetically controlled protonations under varying conditions and are considerably greater than the reproducibility of the experiments reported here, which have been carried out under conditions believed to give strict control of protonation.

cis-(**9**)] in each diastereomeric pair (see also legend to Scheme). The mixtures of ions (**6**)—(**9**) were analysed using proton-decoupled ^{13}C n.m.r. spectra, in which separations of corresponding signals are usually large[2,3] compared with the line widths [see Figure for *N*-methyl signals in *cis*- and *trans*-(**7**)], in contrast to ^1H n.m.r. spectra of such ions. Adequate sensitivity ($<< 1\%$ of a minor component can be detected; see Figure) is readily achieved by ^{13}C isotopic enrichment. If, as is usual, it is assumed that conformational energies are additive for non-polar, non-vicinal groups on six-membered rings and that twist conformers may be neglected then the ratios (R) of concentrations of more to less abundant ions resulting from (**4**) and from (**5**) may be expressed (equations 1 and 2) in terms of the conformational equilibrium constants K_R and K_{NMe} for single substituents as given in the Scheme. The results

$$K_{3\text{-Me}} = (1 - K_{NMe} \times R)/R \quad (1)$$

$$K_{4\text{-Me}} = (1 - K_{NMe} \times R)/(R - K_{NMe}) \quad (2)$$

(Table) refine the earlier estimates for *N*-methylpiperidine[1] and show that conformational energies in 3- and 4-methylpiperidines, when the unshared pair is axial, are significantly different from that in methylcyclohexane in a non-polar solvent.[4] Since the orientation of an *N*-hydrogen atom should have a negligible effect on a 4-methyl group and only a small effect on a 3-methyl group the free energy differences for *C*-methyl groups in (**4**) and (**5**) should be good estimates for the parent 3- and 4-methylpiperidine.



R	Amine	Ions
H	(**1**)	
cis-3,5-Me$_2$	(**2**)	(**6**)
4-Bu^t	(**3**)	(**7**)
3-Me	(**4**)	(**8**)
4-Me	(**5**)	(**9**)

SCHEME. Conformational equilibria in *N*-methyl-*C*-alkyl-piperidines and their relation to the more abundant ($EE \rightleftharpoons AA$) and less abundant ($EA \rightleftharpoons AE$) diastereomeric ions formed by kinetically controlled protonation. It is assumed that (a) AE and AA may be neglected in (**2**) and (**3**), (b) AA may be neglected in (**4**), and (c) $K_{AA} = K_R.K_{NMe}$ in (**5**).

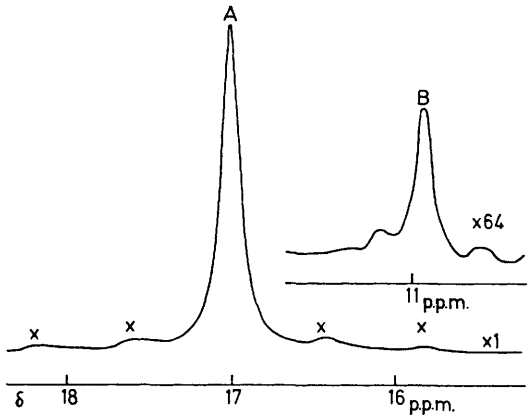


FIGURE. Part of the ^{13}C n.m.r. spectrum obtained after kinetically controlled protonation of (**3**) (88% ^{13}C in *N*-Me; 0·2M in dodecane; 2 ml) by sulphuric acid (81%; 1 ml) at 293 K (R = 159): A, *N*-Me in *trans*-(**7**); B, *N*-Me in *cis*-(**7**); X, spinning side band. Chemical shifts are relative to internal $Me_3CNH_3^+$. (Conditions: sweep width 2000 Hz; 4750 scans; 90° pulses at 10 s intervals; line broadening 3 Hz; 8K FID).

Preliminary results indicate that kinetically controlled protonation can be adapted to the determination of conformational equilibria in piperidines in the gas phase, in some polar solvents, and at high temperatures (up to 150 °C, at least). These results and the precautions taken in the use of ^{13}C n.m.r. spectra for this work will be reported in a full paper.[5]

Carbon-13 spectra were measured on a Brüker WH 90 pulse Fourier transform spectrometer and Nicolet B-NC 12 computer purchased with the aid of a grant from the S.R.C.

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[1] P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *J.C.S. Chem. Comm.*, 1974, 825.
[2] E. L. Eliel and F. W. Vierhapper, *J. Amer. Chem. Soc.*, 1975, **97**, 2424.
[3] M. J. T. Robinson, unpublished observations.
[4] J. A. Hirsch, in 'Topics in Stereochemistry,' ed. N. L. Allinger and E. L. Eliel, Wiley-Interscience, New York, vol. 1, ch. 4.
[5] P. J. Crowley, M. J. T. Robinson, and M. G. Ward, in preparation.