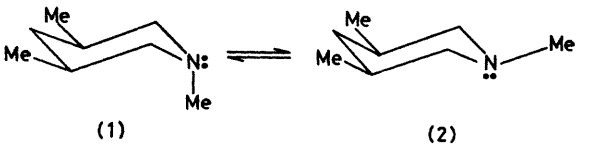
Conformational Equilibrium in 4-Methylpiperidine

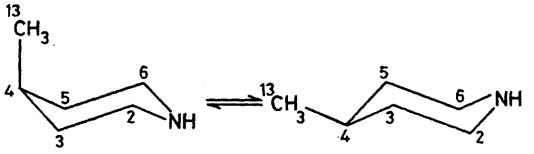
By Harold Booth and Jeremy R. Everett
(*Department of Chemistry, The University of Nottingham, Nottingham* NG7 2RD)

Summary Measurements at three low temperatures of the pulse Fourier transform ^{13}C n.m.r. spectrum of 4-methylpiperidine, enriched with ^{13}C in the methyl substituent, show that the conformational free energy difference

($-\Delta G°$) of the methyl group is 1·93 ± 0·02 kcal mol^{-1} (8·07 ± 0·08 kJ mol^{-1}).

A COMPARISON of the conformational free energy difference of a substituent in cyclohexane, with that of the same substituent in piperidine, is of considerable interest. The $-\Delta G°$ value of 1·74 kcal mol^{-1} for the methyl group in methylcyclohexane, obtained by a direct method,[1] contrasts remarkably with that of 2·7 kcal mol^{-1} obtained indirectly for the *N*-methyl substituent in the *N*-methylpiperidine (**1**⇌**2**).[2]





We have now applied the direct low-temperature method successfully to 4-[*Me*-^{13}C]methylpiperidine (**3**⇌**4**), synthesised from 1-benzyl-4-piperidone through a Wittig reaction with [*Me*-^{13}C]methyltriphenylphosphonium iodide, followed by hydrogenation and debenzylation. The noise-decoupled ^{13}C spectrum of (**3**⇌**4**), recorded at 173 K in $CFCl_3$–$CDCl_3$ (90:10 v/v) showed the enriched carbon at δ 23·03 (Me equatorial) and 17·03 p.p.m. (Me axial). The latter signal broadened at 183 K and was absent at higher temperatures. In the same spectrum the natural abundance ^{13}C carbon atoms of (**4**) gave signals at δ 46·7 [C-2 and -6, d, $^3J(^{13}C–^{13}C)$ 3·8 Hz], δ 35·17 (C-3 and -5, s), and δ 31·60 [C-4, d, $^1J(^{13}C–^{13}C)$ 35·0 Hz†]. Experimental conditions were chosen to ensure that signal areas reflected accurately the corresponding molecular proportions.[3] Spectra were recorded at 173, 162, and 153 K and the corresponding values of the equilibrium constant *K* were found to be 295, 418, and 544, respectively.‡ A plot of ln*K* against T^{-1}, incorporating the theoretical data pair $\ln K = 0$, $T^{-1} = 0$, (*i.e.* on the reasonable assumption that $\Delta S° = 0$) gave $-\Delta H°$ (and therefore $-\Delta G°$) as 1·93 ± 0·02 kcal mol^{-1}. Thus the methyl group in 4-methylpiperidine shows a *reduced* preference for the axial orientation, in comparison with the methyl in methylcyclohexane. Classical conformational analysis provides a reasonable, if oversimplified, explanation. The shortness of the C–N bonds, in comparison with the C–C bonds, causes the piperidine ring to be puckered around the nitrogen atom. As a consequence, the axial C–H bonds at C-2 and -6 are inclined inwards, causing the attached hydrogen atoms to suffer increased repulsions with an axial group at C-4. A similar explanation has been proposed to account for observed equilibria in decahydroquinolines[4] and in dialkylpiperidines.[5]

Interestingly, the $-\Delta G°$ value of 1·93 kcal mol^{-1} for 4-methylpiperidine is in good agreement with that of 1·98 kcal mol^{-1} obtained for 1,4-dimethylpiperidine (in dodecane) by the indirect method of Robinson,[6] who has developed a technique for rapid, irreversible protonation which is much superior to that originally employed.[7]

(*Received, 2nd October* 1978; *Com.* 1044.)

† Measured at 183 K.

‡ Measurements at 25·15 MHz used a JEOL P.S. 100 spectrometer interfaced to a NICOLET 1085 20 K 20-bit computer.

[1] H. Booth and J. R. Everett, *J.C.S. Chem. Comm.*, 1976, 278.
[2] P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *J.C.S. Chem. Comm.*, 1974, 825; *Tetrahedron* 1977, **33**, 915; see also D. C. Appleton, J. McKenna, J. M. McKenna, L. B. Sims, and A. R. Walley, *J. Amer. Chem. Soc.*, 1976, **98**. 292.
[3] *Cf.* H. Booth and M. L. Jozefowicz, *J.C.S. Perkin II*, 1976, 895.
[4] H. Booth, D. V. Griffiths, and M. L. Jozefowicz, *J.C.S. Perkin II*, 1976, 751.
[5] E. L. Eliel and D. Kandasamy, *Tetrahedron Letters*, 1976, 3765.
[6] M. J. T. Robinson, *J.C.S. Chem. Comm.*, 1975, 844.
[7] H. Booth, *Chem. Comm.*, 1968, 802.