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CONFORMATIONAL EQUILIBRIA OF C-METHYL GROUPS IN PIPERIDINES AND N-METHYLPIPERIDINES

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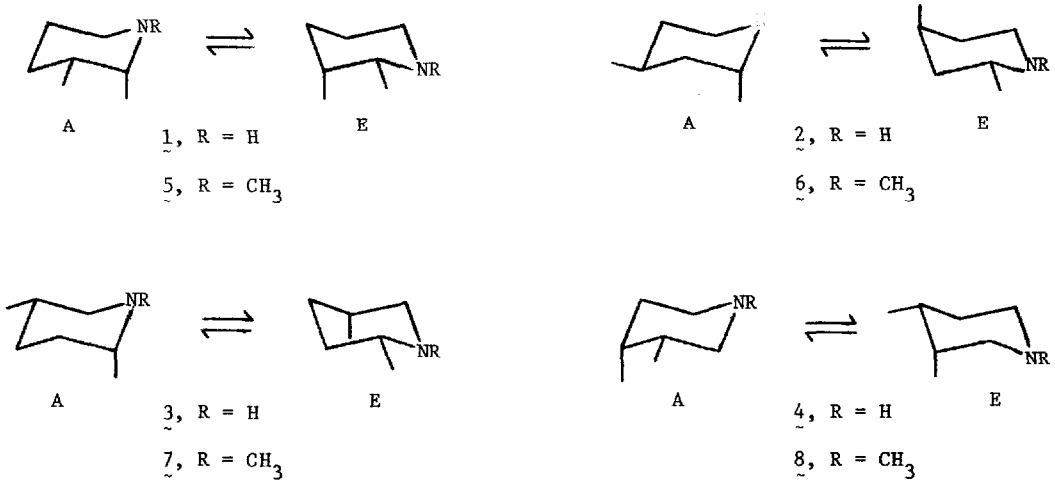
Booth[1] has recently demonstrated, through equilibrium measurements in 2β-methyl-cis-decahydroquinoline[2] and 9-methyl-cis-decahydroquinoline, that an axial methyl group at C(2) in the nitrogen-containing ring is disfavored, vis-à-vis the corresponding equatorial group, by over 2.7 kcal/mol. He also reports[1] that the methyl group at C(9) prefers the axial position in the carbon-containing ring by 1.4 kcal/mol which, assuming ΔG°_{Me} in that ring to be 1.7 kcal/mol,[3] would suggest a corresponding value of 3.1 kcal/mol for the nitrogen-containing ring.

We report here corresponding findings based on low-temperature C-13 NMR study of the conformational equilibria of 2,3-, 2,4-, 2,5- and 3,4-dimethylpiperidine (1-4) in contrast to those of their N-methyl homologs (5-8)(Scheme 1). The room-temperature C-13 spectra of a number of these compounds have previously been reported;[4,5] those as yet unknown will be included in our full publication. Low-temperature spectral data are shown in Table 1; while some of the (parametric) assignments are as yet preliminary (data shown in parentheses), there is little question, in most instances, as to which signals correspond to which conformer.



1, R = H
5, R = CH_3

2, R = H
6, R = CH_3

3, R = H
7, R = CH_3

4, R = H
8, R = CH_3

Scheme 1

Table 1

C-13 Chemical Shifts of Piperidines (1-4) and N-Methylpiperidines (5-8) at -80 to -95°C in CD_2Cl_2 (1-4) or $CHCl{=}CCl_2/CD_3COCD_3$ (5-8)[f]

Conformer	C(2)	C(3)	C(4)	C(5)	C(6)	Me_A[a]	Me_B[b]	N-Me
1E[c]	54.69	32.69	32.51	(20.88)	47.86	(20.66)	11.47	
1A[d]	51.91	34.85	(27.19)	(27.39)	38.94	12.22	19.94	
2E[c]	46.00	(41.34)	26.56	31.35	(40.12)	23.45	17.91	
2A[d]	47.27	(39.57)	25.17	35.60	(41.34)	[e]	22.96?	
3E[c]	(52.28)	30.43	(29.37)	(27.30)	(53.06)	23.29	16.96	
3A[d]	(46.18)	31.02?	27.69	32.90	(46.98)	[e]	20.11	
4E[c]	53.27	33.67	33.24	29.02	47.03	11.13	20.43	
4A[d]	46.48	(34.09)	(34.09)	31.06	39.53	17.44	11.36	
5E[c]	62.18	34.82	32.63	21.40	58.35	19.41	12.74	43.62
5A[d]	58.82	35.24	(26.13)	(26.22)	46.70	1.79	19.63	43.17
6E[d]	53.35	40.61	26.47	31.61	51.39	21.23	17.73	43.36
6A[c]	53.60	40.61	24.33	34.82	47.31	8.06	22.79	42.87
7E[c]	60.44	31.76	30.40	29.03	62.91	21.04	18.03	43.71
7A[d]	52.68	29.83	26.95	31.76	55.12	7.32	20.11	42.95
8E[c]	63.36	34.06	33.12	28.78	56.87	12.45	19.76	46.87
8A[d]	57.25	33.67	32.93	30.25	49.77	17.38	11.35	46.52

[a]Lower-numbered CH_3 group (Me_2 or Me_3). [b]Higher-numbered CH_3 group (Me_3, Me_4 or Me_5). [c]Major conformer. [d]Minor conformer. [e]Peak not clearly seen. [f]Shifts in ppm from TMS.

By integrating the underlined peaks in the major and minor isomer, taking the ratio and averaging (in those instances where several peaks were integrated), the equilibrium constants shown in Table 2 (with the corresponding free-energy differences) were computed. The underlying assumption that signal area ratios are proportional to the ratio of the corresponding nuclei (i.e. that no complications arise from unequal relaxation times and NOE's) has been defended elsewhere.[4,6] In Table 3 are shown absolute values of ΔG°_{Me}, in kcal/mol, at C(2), C(3) and C(4) in piperidine and N-methylpiperidine based on the equilibria of the 2,4- (2,6) and 2,5- (3,7) isomers, assuming additivity of ΔG's and taking ΔG°_{Me} for the 4-isomer as 1.98 kcal/mol, the reported[7] value for N,4-dimethylpiperidine. In the absence of contrary evidence it was assumed that the same value applies to 4-methylpiperidine itself.

The equilibria for the 2,3- (1,5) and 3,4- (4,8) dimethyl compounds support the values in Table 3. In the piperidine series, the calculated differences in conformational energies between Me-2 and Me-3, 0.87 kcal/mol, and between Me-3 and Me-4, 0.33 kcal/mol are virtually identical with the measured ΔG's: 0.84 kcal/mol for 1E/1A and 0.32 kcal/mol for 4E/4A. In the N-methyl series there are small discrepancies: 0.12 kcal/mol (calculated) vs. 0.22 (measured) for Me-2 vs. Me-3 and 0.21 kcal/mol (calculated) vs. 0.38 (measured) for Me-3 vs. Me-4. These discrepancies may be due to small differential vicinal interactions.

Table 2

Conformational Equilibria at Low Temperature

Conformers	1E/1A	2E/2A	3E/3A	4E/4A	5E/5A	6E/6A	7E/7A	8E/8A
K_{av}	10.0[a]	4.55[b]	9.7[c]	2.4[a]	1.76[c]	0.80[c]	1.36[c]	2.68[c]
$-\Delta G°$[d]	0.84	0.54	0.87	0.32	0.22	-0.09	0.12	0.38

[a]At -90°C. [b]At -95°C. [c]At -80°C. [d]In kcal/mol.

Table 3

Conformational Free Energies for Methyl Groups in Piperidines[a]

	Me-2	Me-3	Me-4
Piperidines	2.5	1.6$_5$	(1.98)[b]
N-Methylpiperidines	1.9	1.8[c]	(1.98)[7]

[a]In kcal/mol. [b]Assumed. [c]Reported[7] 1.51 kcal/mol.

The data in Table 3 agree with Booth's finding[1] that $\Delta G°$ for Me-2 in a piperidine ring is considerably larger than in cyclohexane (1.7 kcal/mol[3]) or at other positions in piperidine or N-methylpiperidine (Table 3).[8] It would also appear from our preliminary data that $\Delta G°_{Me-2}$ in an isolated piperidine ring is slightly smaller than it is in cis-decahydroquinoline, perhaps because of the greater flexibility of the former system.

Another interesting feature, hitherto unreported, emerges from Table 3. Although the difference of $\Delta G°_{Me}$ between the 3- and 4-positions in piperidine and N-methylpiperidine is nearly the same, the same is not true at C(2). $\Delta G°_{Me}$ at C(3) for both piperidine and N-methylpiperidine is smaller than at C(4), as one might expect based on the fact that a syn-axial hydrogen (for Me-4) is supplanted by a lone pair (for Me-3).[9] At C(2), however, whereas the value of $\Delta G°$ in piperidine is enhanced (see above), that for N-methylpiperidine is "normal", i.e. similar to the value for cyclohexane and for other positions in piperidine.

One possible explanation is that, at the concentrations required in the ^{13}C NMR experiment, 2-methylpiperidine (but not N,2-dimethylpiperidine) is substantially dimerized and that dimerization favors the isomer with equatorial Me-2.[10] This interpretation seems unlikely, however, in the light of published[11] findings regarding 3-hydroxypiperidine and the 6-methyl-3-hydroxypiperidines. The conformational equilibria in these compounds were assessed by infrared study of intramolecular hydrogen bonding and it was reported,[11] without explanation, that the results in the N-methylpiperidine series are in agreement with a $\Delta G°$ for Me-6 of ca. 1.7 kcal/mol whereas those in the N-H (piperidine) series require a much larger $\Delta G°_{Me-6}$ if additivity of ΔG's is assumed. These findings support ours and, since they were obtained at a concentration of 5.10^{-3} M, preclude dimer formation.

A more likely interpretation of our findings is that the conformations with axial 2-methyl groups in piperidine and N-methylpiperidine are equally destabilized by the nearby syn-axial hydrogen at C(6)[12] but that a compensating destabilization occurs for the equatorial Me-2 in N-methylpiperidine, though not in piperidine itself. An obvious source of that destabilization

the greater proximity of Me-2e compared to Me-2a to the N-Me, caused by the expected puckering of the piperidine ring in the vicinity of the nitrogen. It would be desirable to confirm this hypothesis by heat-of-formation and structural data for appropriately substituted piperidines.

The present findings are of interest in relation to the Wertz-Allinger hypothesis regarding instability of the axial conformation in methylcyclohexane.[13] We also draw attention, in passing, to the very high-field resonances of the axial Me-2 group in the N-Me derivatives 5A, 6A and 7A which is not seen in the NH compounds 1A and 2A.[14]

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References

1. H. Booth, D. V. Griffiths, and M. L. Jozefowicz, J. C. S. Perkin II, 751 (1976).
2. For nomenclature see F. W. Vierhapper and E. L. Eliel, J. Org. Chem., 40, 2734 (1975), footnote 2.
3. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience-Wiley, New York, 1965, p. 44.
4. H. Booth and D. V. Griffiths, J. C. S. Perkin II, 842 (1973).
5. D. Wendisch, H. Feltkamp, and U. Scheidegger, Org. Mag. Reson., 5, 129 (1973).
6. H. Booth and D. V. Griffiths, J. C. S. Perkin II, 111 (1975).
7. M. J. T. Robinson, J. C. S. Chem. Comm., 844 (1975).
8. The value of 1.9 kcal/mol for ΔG°_{Me-2} reported by R. R. Fraser and T. B. Grindley, Tetrahedron Lett., 4169 (1974) based on very indirect evidence is incompatible with our findings for the N-H compounds.
9. Cf. E. L. Eliel and M. C. Knoeber, J. Am. Chem. Soc., 88, 5347 (1966).
10. Cf. results for the 2-hydroxypyridine/2-pyridone equilibrium: P. Beak, F. S. Fry, Jr., J. Lee, and F. Steele, ibid., 98, 171 (1976) and P. Beak, personal communication.
11. S. Vašíčková, A. Vítek, and M. Tichý, Coll. Czechslov. Chem. Commun., 38, 1791 (1973).
12. As a result of the short N-C bond compared to C-C.
13. D. H. Wertz and N. L. Allinger, Tetrahedron, 30, 1579 (1974).
14. Cf. E. L. Eliel, V. S. Rao, F. W. Vierhapper, and G. Z. Juaristi, Tetrahedron Lett., 4339 (1975).