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CONFORMATIONAL EQUILIBRIA IN N-ALKYLPIPERIDINIUM SALTS

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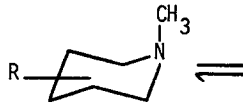
The conformational equilibrium in N-methylpiperidines (Scheme 1) has been the object of much recent interest.[1-7] Work by Booth[6] and by our own group[5] indicated that the values for $-\Delta G°$ of

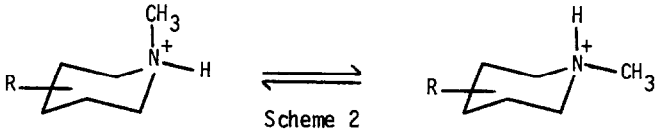


1 R = cis-3,5-di-Me

Scheme 1

less than 0.8 kcal/mol given in the earlier literature[8] (see also ref. 7) cannot be correct. Recent work involving freezing of the equilibrium shown in Scheme 1 (e.g. for N-cis-3,5-dimethylpiperidine, 1) by irreversible quenching of dilute solutions or dilute vapors of the amine by concentrated acid and NMR measurements of the composition of the salts so formed[1,2,4] supports a $-\Delta G°$-value as high as 3.0 kcal/mol. Although we have earlier espoused a somewhat lower value,[5] recent results from our own laboratories[9] and elsewhere[2] suggest that the 3.0 kcal/mol value is probably correct.

One remaining concern[5] with so large a $-\Delta G°$ value relates to its comparison with the corresponding value for N-methylpiperidinium salts (Scheme 2). Booth,[6] in earlier attempts to quench the equilibrium (Scheme 1) with acid, had obtained values considerably less than 3.0 kcal/mol for



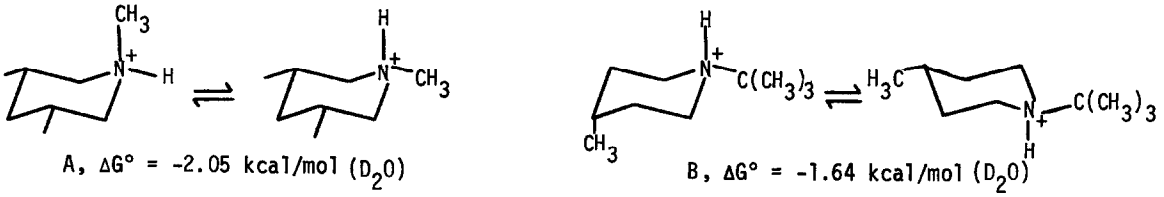
Scheme 2

$-\Delta G°$ and it is now clear[1] (see also ref. 11) that this was due to equilibration of the salts which occurred during quenching. The implication of this is that the salt equilibrium (Scheme 2) must be less on the side of equatorial N-CH_3 than the equilibrium of the free amines (Scheme 1) -- an implication which, at least at first sight, might not appear plausible. It is the purpose of the present report to place this finding on a firm footing.

Neither in Booth's work (which was directed to other ends) nor in earlier work[12-14] concerning equilibria of piperidinium salts was it clearly established that equilibrium had, in fact, been reached. Piperidinium salts presumably are conformationally stable as such and slowly

equilibrate (Scheme 2) by reversible deprotonation-protonation via the free piperidines. To assure that equilibrium was actually attained we first raised the pH of the salt (hydrochloride) solution to the point where the ^{13}C spectra of the two configurational isomers (clearly seen in solution) coalesce. At this pH (ca. 8), equilibration (Scheme 2) is fast on the NMR time scale. We then lowered the pH by about 2 units. At the new pH (ca. 6) the spectra of both isomers are sharp. However, since the exchange rate is lowered by only a factor of 100, it must still be fast on the laboratory time scale and one can thus be assured that equilibrium is maintained.

Using this method we determined the equilibria shown in Scheme 3.



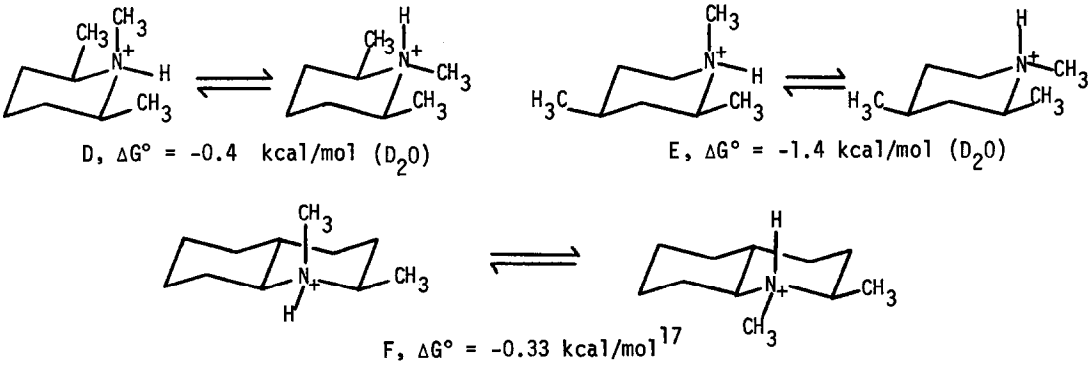
A, $\Delta G°$ = -2.05 kcal/mol (D_2O)

B, $\Delta G°$ = -1.64 kcal/mol (D_2O)

C, $\Delta G°$ = -1.40 kcal/mol (calc'd from A and B: -1.40 kcal/mol)(D_2O)

Scheme 3

It is clear from Scheme 3 that the $-\Delta G°$-value for an N-methylpiperidinium salt (Scheme 2, 2.05 kcal/mol) is, in fact, substantially smaller than that for the parent base (Scheme 1). (The $-\Delta G°$ data for B[15] and C, somewhat easier to determine, are consistent with those for A.) However, an even more clear-cut substantiation comes from the 2- and 2,6-disubstituted N-methylpiperidinium salts shown in Scheme 4.



D, $\Delta G°$ = -0.4 kcal/mol (D_2O)

E, $\Delta G°$ = -1.4 kcal/mol (D_2O)

F, $\Delta G°$ = -0.33 kcal/mol[17]

Scheme 4

The earlier literature[12-14] indicates equilibria containing 31-43% of the N-Me axial isomer for D[12,14] and 20% for N,2-dimethylpiperidinium.[13] Our data for D, E and F confirm substantial percentages, at equilibrium, of the configurational isomers with axial N-methyl. These high percentages probably reflect the much greater gauche repulsion of the N-Me group by the (more

proximate) C-2,6 equatorial Me groups as compared to that by the (more distant) axial Me groups, resulting from the puckering of the piperidine ring in the region of the hetero atom.[16,19]

It remains to be shown that the equilibria of the free amines corresponding to systems D and F are quite different from those of the salts. In the case of D, it has already been established by the quenching method[1] that $-\Delta G°$ (N-Me inversion) for the free N,cis-2,6-dimethylpiperidine (2) is 1.84 kcal/mol.[20] In the present work we confirmed that while cooling 2 to -95°C leads first to a broadening and then to a sharpening of the ^{13}C NMR signals, indicating that N-Me inversion is slow on the NMR time scale at -95°C, no signals for the minor isomer could be seen at this temperature. This was also true for 2β-methyl-trans-decahydroquinoline (3) (free amine corresponding to case F in Scheme 4) even though the spectrum was pulsed for 7 hr; we estimate less than 2% of the axial N-Me isomer to be present ($-\Delta G° > 1.3$ kcal/mol). Chemical shift measurements[18] and comparison with model compounds (cf.[5]) lead to a $-\Delta G°$ value of 1.65-1.84 kcal/mol for 3. Thus, even for systems such as D and F (Scheme 4) where very substantial amounts of the isomer with axial N-Me are present in the salt, very little of that conformer appears in the free amine (though somewhat more in the case of 2 than in the case of 1[1]).

It is evident from the foregoing that N-methylpiperidinium salts exist with the N-methyl group in the axial orientation to a considerably greater extent than the corresponding free piperidines. While the change in molecular geometry induced by protonation may play a part in this phenomenon, the most obvious explanation is solvation.[11,21,22] Indeed, Sudmeier and Occupati have stated[22] "... a sphere of tightly bound solvent increases the effective size of a substituent, in agreement with previous findings[23]" and it appears, from the classical work of Trotman-Dickenson,[21] that in the case of protonated amines solvation occurs principally on the side of the proton or protons. Thus the N-methylpiperidinium salt with axial CH_3 and (more open) equatorial H is solvated better than its diastereomer with equatorial CH_3 and (less open) axial H. This leads to the isomer with axial CH_3 being less disadvantaged (relative to the equatorial one) in the salt than in the free amine.

Data from the literature[6] as well as data from our own work (Table 1) confirm the expected existence of a solvent effect in the amine salt equilibria. However, contrary to expectations, the Me-axial salt is less preferred in water than it is in the case of organic solvents for N,cis-2,6-trimethylpiperidinium hydrochloride (D). This may indicate complicating effects of the C-methyl groups or of ion pairing in the organic solvents or it may indicate that the explanation in terms of solvation is not complete. Further studies are needed.

Table 1

Equilibrium Constant[a] for D (2·HCl) as a Function of Solvent

2.11 (D_2O)[b]	1.30 ($CDCl_3$)[c]	1.8 (m-cresol)

[a] K = N-Me(eq)/N-Me(ax). [b] Ref. 12 reports 1.94-2.23. [c] Ref. 6 reports 1.08.

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10. The data reported in ref. 5 ($-\Delta G°$ = 1.35-1.77 kcal/mol) have been reinterpreted in ref. 1 to support a $-\Delta G°$-value of $\geq$ 2.15 kcal/mol for the equilibrium in Scheme 1. Whether one agrees with the specific arguments presented[1] or not, one must concede that the chemical shift method used in our earlier investigation[5] is incapable of distinguishing between a $-\Delta G°$ of 1.5 kcal/mol and one of 3.0 kcal/mol or even larger because these differences are blurred, in cases of such one-sided equilibria, by small chemical shifts introduced by the substituents present in the compounds used to determine δ and δ_e.[5]
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15. The $-\Delta G°$-value for B, supported by the consistent value for C, is smaller than the value reported[3] for the 4-methyl group in N,4-dimethylpiperidine (1.98 kcal/mol). The latter value may be too high; we had noted previously[16] that it does not seem to be compatible with the $-\Delta G°$-value for Me-3 of -1.51 kcal/mol reported also in ref. 3. A value of -1.7 kcal/mol would be compatible with the data reported[16] for the N,C-trimethylpiperidines and with the data for the salts reported here.
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