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# CONFORMER POPULATIONS IN TROPANE, 4-METHYLMORPHOLINE AND 1,4-DIMETHYLPIPERAZINE [1]

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In collaboration with Anet and Robinson,[2] we recently produced evidence confirming the high equatorial preference ( $\Delta\underline{G}^{o}_{288}$ = 2.7 kcal mole$^{-1}$) for the methyl group in 1-methylpiperidine, as originally suggested by Robinson.[3] We now report results for tropane, 4-methylmorpholine and 1,4-dimethylpiperazine (Table).

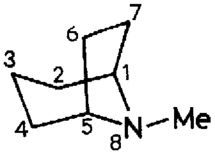
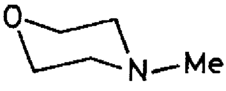
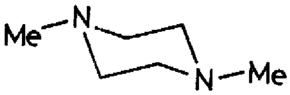
The conformation of tropane has been extensively studied previously: the predominant equatorial alkylation,[4] (itself contested[5] and later rigorously confirmed[6]), was originally taken to indicate the axial *N*-methyl conformation for the parent base,[7] but NMR[8] and dipole moments[9] support the preference of the equatorial *N*-methyl orientation (**1**). McKenna[10] has recently found $\Delta\underline{G}^{o}_{300}$ = 1.05 kcal mole$^{-1}$ by kinetically controlled protonation and 0.85 by the conceptually similar method of reaction with a nitrene. We have now applied the line broadening technique:[2] the 2-, the 7- and the *N*-methyl $^{13}$C signals of tropane all show maximum broadening at the same temperature which gives[11] $\Delta\underline{G}^{o}_{213}$ = 1.1 $\pm$ 0.15 kcal mole$^{-1}$, in excellent agreement with the kinetic protonation value. Assuming no significant entropy difference when extrapolating to 25°C, this implies 87% of the equatorial conformation at 298°.

4-Methylmorpholine has been investigated previously only by dipole moments[12] which gave $\Delta\underline{G}^{o}_{298}$ = 0.17 kcal mole$^{-1}$ (cyclohexane) which must now be considered unexpectedly low. However, the $^{13}$C broadening of the *N*-methyl peak now gives $\Delta\underline{G}^{o}_{178}$ = 1.6 $\pm$ 0.2 kcal mole$^{-1}$ implying 94% equatorial (**2**) at 298° (with $\Delta\underline{S}$ = 0).

X-Ray results[13] show that both the *N*-methyl groups of 1,4-dimethylpiperazine are diequatorial (**3**) and that the ring is flatter than that of cyclohexane. Dipole moment studies[14] yielded $\Delta\underline{G}^{o}_{298}$ = 1.28 kcal mole$^{-1}$ for benzene solution. We now find $\Delta\underline{G}^{o}_{208}$ = 2.0 $\pm$ 0.2 kcal mole$^{-1}$ from the broadening of the *N*-methyl $^{13}$C peak. The entropy of mixing for two equivalent minor conformers contributes RTln2 = 0.29 kcal mole$^{-1}$ at 208° and 0.41 kcal mole$^{-1}$ at 298°. Hence the corrected $\Delta\underline{G}^{o}_{298}$ = 1.88 kcal mole$^{-1}$, which implies 96% *N*-methyl equatorial at 298°. Anet[15] recently found 2.96 kcal mole$^{-1}$ by kinetic protonation: however this may well apply not to piperazine but to the equilibrium at the 4-methyl of 1-protonated 1,4-dimethylpiperazine.

All three compounds (1-3) show significantly less preference for the N-methyl equatorial ($\Delta G^{0}$ 1.1, 1.6 and 1.9 kcal mole$^{-1}$) than 1-methylpiperidine (2.7 kcal mole$^{-1}$). Steric interaction of an axial N-methyl group is evidently reduced for 4-methylmorpholine and 1,4-dimethylpiperazine. An equatorial N-methyl group experiences greater steric hindrance in tropane than in 1-methylpiperidine. The present work underlines the sensitivity of the conformational equilibria of N-methyl groups in six-membered rings to bond angle and length changes caused by heterosubstitution.

TABLE: FREE ENERGY DIFFERENCES FROM $^{13}$C COALESCENCE DATA AT 25.16 MHz

| | | | |
|---|---|---|---|
| Major conformer |  |  |  |
| | 1 | 2 | 3 |
| Temp (°K) of max. broadening | 213 | 178 | 208 |
| Broadening (Hz) | 11 | 1.5 | 1.5 |
| (%) Minor conformer at $T_c$ | 6.3 | 0.8 | 0.8 |
| $\Delta G_c^{\neq}$ (kcal mole$^{-1}$) | 1.1 | 1.6 | 1.9* ± 0.2 |

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11 Here and elsewhere the mean values for $\Delta G^{0}$ and population refer to $\Delta\nu$ = 7 p.p.m. and the range quoted covers $\Delta\nu$ 5 to 10 p.p.m. Anet found $\Delta\nu$ = 5 p.p.m. for 3-C in 1-methylcyclohexane[2], Eliel found[16] $\Delta\nu$ = 9-10 p.p.m. for the N-Me in condensed N-methylpiperidines: the present results demonstrate the insensitivity of this method to uncertainties in the value of $\Delta\nu$.

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* Corrected for entropy.