Non-additivity of the Conformational Free-energy Differences of 1-Substituted Cyclohexylamines

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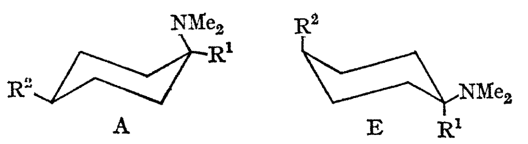
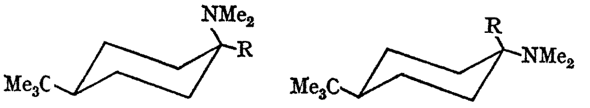
A NUMBER of examples[1] have demonstrated the non-additivity of the conformational free-energy differences of groups attached to the same carbon atom of cyclohexane. Here we examine some of the causes of non-additivity.

The syntheses and configurational assignments of the compounds used have been reported elsewhere.[2] Their $\mathrm{p}K_{\mathrm{MCS}}$ values measured in methylcellosolve[3] and their iodomethylation rate constants are given in the Table, as well as the conformational free-energy differences corresponding to amines (1) and (2) and their ammonium salts determined from their $\mathrm{p}K_{\mathrm{MCS}}$ values.[4]



	R^1	R^2	$\mathrm{p}K_{\mathrm{MCS}}$	$-\Delta G$ [a]	$-\Delta G^{+}$ [b]
(1)	H	$\mathrm{Pr^i}$	8·57[4]	0[4]	300[4]
(2)	Me	Me	8·72	−300	300
(3)	Me	H	9·02		



cis *trans*

	R	$\mathrm{p}K_{\mathrm{MCS}}$	*k*
(4) *cis*	H	8·45[4]	15·2[c]
(5) *trans*	H	8·67[4]	783[c]
(6) *cis*	Me	8·51	3·4[d]
(7) *trans*	Me	8·94	1460[d]

[a] Amine; [b] ammonium salt, cal./mole. [c] $k \times 10^{-4}$ l.mole^{-1}sec.$^{-1}$ in MeCN (ref. 5). [d] $k \times 10^{-3}$ min.$^{-1}$, pseudo-first-order rate constants in MeCN by conductivity measurements at 25° (ref. 6).

We calculate ΔG_2 and ΔG_2^{+} from the known ΔG values: $-\Delta G(\mathrm{Me})$ 1700 cal./mole,[7a] $-\Delta G(\mathrm{NMe_2})$ 2100 cal./mole,[4] and $-\Delta G(\mathrm{Me_2NH^+})$ 2400 cal./mole.[4] These values are −1300 and −1000 cal./mole, respectively, values definitely lower than those determined experimentally (see Table). These results show once more the non-additivity of conformational free-energy differences.

In order to understand the causes of this non-additivity, we have re-examined equation 1, suggested by Katritzky[8] to calculate ΔG_1, using the "fundamental interactions" (*b*: butane *gauche*, *pa*: propylamine *gauche*, *p*: propane *gauche*, and *ea*: ethylamine *gauche*) for the various rotamers of compound (1).

$$\Delta G_1 - \Delta G(\mathrm{Pr^i}) = 2100\ \text{cal./mole} = RT\ln(X + Y) \quad \text{(eqn. 1)}$$
$$X = \exp 2[(b - 2p) + (p - ea) - (b - pa)]/RT$$
$$Y = 2\exp[-2(b - pa) + (b - 2p) + (p - ea)]/\boldsymbol{RT}$$

Using the same reasoning, we obtain equation 2 for compound (2)

$$-\Delta G_2 + 1700\ \text{cal./mole} = 1400 = \boldsymbol{RT}\ln 3 - 2[(b - pa) - (p - ea)] \quad \text{(eqn. 2)}$$

The comparison of these two equations illustrates two consequences of geminal substitution:

(i) By using the experimentally determined value for ΔG_2, equation 2 yields $(p - ea) - (b - pa) = 375$ cal./mole. Since ΔG_2 and ΔG_1[4] were determined under identical experimental conditions, we can check whether this value of 375 cal./mole is compatible with equation 1.

By replacing $2(b - 2p) = -\Delta G(\mathrm{Me}) = 1700$ cal./mole[7a] and the value of 375 cal./mole in term *X*, the *Y* term becomes negative, which is impossible. This shows the incompatibility of the two equations, *i.e.* the fundamental interactions for compound (1) cannot be the same as for those for compound (2), at least in MCS system where solvation is important.†

The modification of the fundamental interactions, brought about by the methyl group at C-1, may be ascribed to a "buttressing effect"[5,9] which inhibits deformation in the *gem*-disubstituted cyclohexane ring. This must result in a marked decrease in the basicity and in the rates of iodomethylation of *gem*-disubstituted compounds with the amino-group in an axial position. The comparison of the difference in p*K* values and of the ratio of reaction rates for two pairs of amines [diastereoisomers (4) and (5); and (6) and (7)] supports this interpretation:
$\mathrm{p}K_5 - \mathrm{p}K_4 = 0{\cdot}22$ is less than $\mathrm{p}K_7 - \mathrm{p}K_6 = 0{\cdot}43$, and $k_5/k_4 = 51$ is much smaller than $k_7/k_6 = 429$.

(ii) There appears in eqn. 2 a simple entropy term ($\boldsymbol{RT}\ln 3$) due to the fact that the two possible rotational conformations (I′) and (II′) for the equatorial amine (2E)

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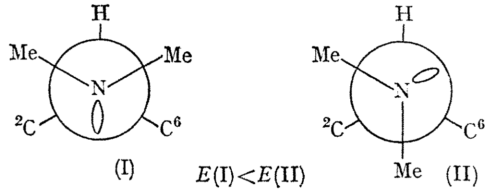
† Examination of the magnitude of the experimental error is necessary at this point. The p*K* values measured show a deviation of less than ±0·01 unit based on the statistical values of 8—10 independent p*K* determinations. The corresponding error in ΔG value for compound (2) is ±50 cal./mole. On assumption of the same precision for p*K* values of compound (1)[4] the error in ΔG for this compound is ±100cal./mole. [The p*K* differences of the 4-t-butylcyclohexylamines are important for the accuracy of ΔG: $(\mathrm{p}K_7 - \mathrm{p}K_6) = 0{\cdot}43$ is twice the difference $(\mathrm{p}K_5 - \mathrm{p}K_4) = 0{\cdot}22$].

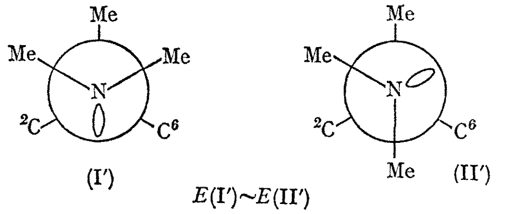
For a small, positive value for *Y* we have to assume accumulation of experimental errors: for example 2400 cal./mole in eqn. 1 instead of 2100 cal./mole, and in eq. 2, 300 cal./mole instead of 375 cal./mole, with these values, $(p - ea) = 560$ cal./mole becomes larger than $(b - pa) = 260$ cal./mole. These values are improbable;[8] we have to note, however, that even a very small variation in ΔG_1 and ΔG_2 produces a large variation of $(p - ea)$ and of $(b - pa)$. It seems to us that we can disregard experimental errors higher than our standard deviation. The ΔG value of cyclohexylamine measured in ethanol by other methods is in good agreement with ΔG_{MCS} (G. Ransbotyn, J. C. Celotti, R. Ottinger, J. Reisse, and G. Chiurdoglu, *Tetrahedron*, 1968, **24**, 3647). We acknowledge the constructive criticism of a referee on this point.

(or 3E) have approximately equal energies. On the other hand, the rotational conformations (I) and (II) for the equatorial amine (1E), have different energies.

The fact that conformation (II′) is equally favoured with respect to conformation (I′) has an important effect on the solvation of the corresponding ammonium salt. The steric strain resulting from the presence of solvent molecules around the ${}^{+}$N–H bond can, in this conformation, exercise a marked pressure on the methyl group. This energy of compression, which inhibits solvation, can be minimized by a flattening of the cyclohexane ring at C-3, C-4, and C-5. This flattening is certainly more difficult for compound (7), with its t-butyl group at C-4, than for compound (3), which is unsubstituted in that position. This is the reason why pK_3 is greater than pK_7.



(I) $E(\mathrm{I}) < E(\mathrm{II})$ (II)



(I′) $E(\mathrm{I'}) \sim E(\mathrm{II'})$ (II′)

This result is contradictory to the hypothesis of Winstein and Eliel,[7b] in that the 4-t-butyl group has an influence on substituents at C-1. Another exception to this hypothesis, implying an equilibrium reaction, has been reported.[10]

These results indicate, therefore, that the hypothesis of Winstein and Eliel is generally valid only if one admits that the stability of the *cis*- and *trans*-isomers, substituted by a 4-t-butyl group, is only approximately equal to that of the conformations A and E of the nonsubstituted cyclohexane compounds, respectively.

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