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CONFORMATIONAL ANALYSIS OF 4-KETOPIPERIDINES

THE CONFORMATIONAL ENERGY OF C_2 AND C_3 METHYL SUBSTITUENT OF N-METHYLPIPERIDONES-4

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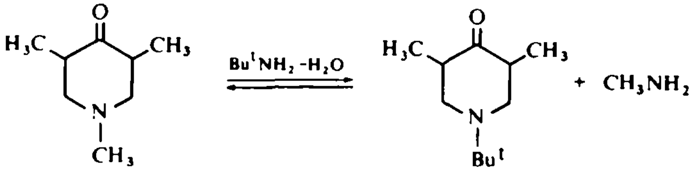
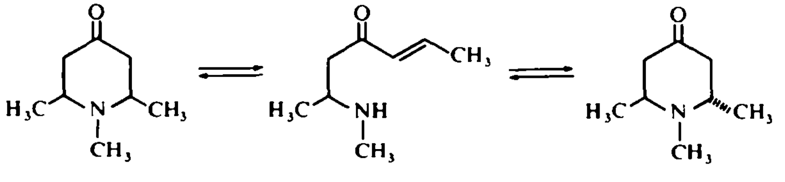
BY EQUILIBRATION in basic solution and VPC analysis of the resulting epimeric mixtures of 4-ketopiperidines having methyl groups as ring and heteroatom substituents (see Table I), the conformational energy of the methyl group at C_2 and C_3 has been evaluated.* All the listed ketones were equilibrated in t-$BuNH_2/H_2O$ solution (2:1 by volume) at 50°. This system does not cause any appreciable decomposition of the starting material even on prolonged heating (several weeks) and permits direct analysis by VPC. In contrast, the $NaOD/D_2O$ system recently used for a similar equilibration of N-t-butyl-3,5-dimethylpiperidones-4[1] leads to an extensive and eventually a complete fragmentation to low molecular weight products, probably via a retro-Mannich type reaction. The same is true of ion-exchange resin equilibrations.[2] The only detectable by-product of t-$BuNH_2/H_2O$ equilibrations is the product of amino-exchange.[3]



This amino-exchange with t-$BuNH_2$ is a reaction much slower than epimerization even at C_2 or C_6.† Formation of N-t-butyl derivatives is detectable only after 10–20 hours of heating at 50° (~1–2%). No amino-exchange was observed in case of 1,2,6-trimethylpiperidone-4(II). Here the equilibration may be conceived as proceeding via reversible ring opening.[4]



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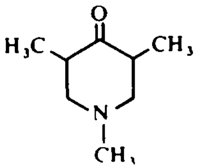
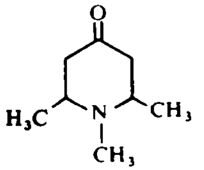
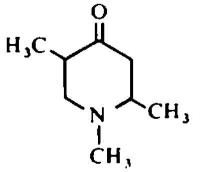
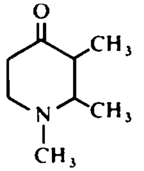
[*] For other N-substituents, ΔG° values may differ substantially from those listed in the table (in press).

[†] For C_3 or C_5-derivatives, equilibration is attained in 2 h at 50°; for C_2 or C_6-derivatives in 10 h. The tabulated data refer to the equilibrium composition after 20 hours of heating for ketones I, III and IV and after 48 hrs for ketone II.

TABLE I. EQUILIBRIUM OF THE COMPOUNDS I–IV AT 50°[a]

No	Formula	Ratio of epimers[b] e, e(%)	e, a(%)	K	$\Delta G^\circ \left(\frac{\text{kcal}}{\text{mole}}\right)$	$\Delta G^c_{corr} \left(\frac{\text{kcal}}{\text{mole}}\right)^c$
I		87	13	6·70	−1·23	−1·67
II		51	49	1·04	−0·03	−0·47
III		69	31	2·22	−0·51	—
IV		64	36	1·78	−0·37	—

[a] In t-$BuNH_2$ H_2O (2:1).

[b] Products were analysed by VPC on all-glass capillary apparatus with PEG 2000 as stationary phase.

[c] $\Delta G^\circ_{corr} = G\,50^\circ - RT \ln 2$.

Table I summarizes the composition of the equilibrium mixtures. The most salient features of these data are:

1. ΔG° value for C_3-methyl (as found for piperidone I) falls within the range of values found for 2-methyl substituted cyclohexanones (*e.g.* for 2,6-dimethylcyclohexanone 1·465–1·9 kcal/mole[4, 5]).

2. Almost equal stability of *cis*- and *trans*-isomers of 1,2,6-trimethylpiperidone-4 (II), *i.e.*, $e \rightarrow a$ transition of the methyl group adjacent to N—CH_3 function is of appreciably lower energy (−0·47 kcal/mole) than the corresponding transition of the methyl adjacent to carbonyl (−1·67 kcal/mole).

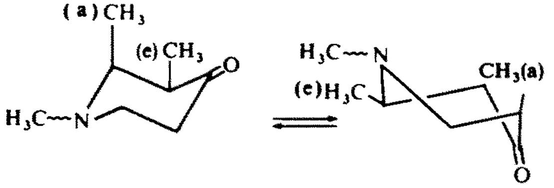
3. Greater stability of *cis*-epimers of ketones III and IV in comparison with the corresponding cyclohexanone derivatives.[2, 6] This fact also fits well with the low conformational energy of the C_2-methyl substituent.

4. The difference in stability of the *cis*- and *trans*-epimers of 1,2,5- and 1,2,3-trimethylpiperidones-4 (III and IV). This difference, although not great (0·14 kcal/mole), may indicate distortion of the piperidine ring resulting in closer proximity of *e*–*e* than *e*–*a* substituents.

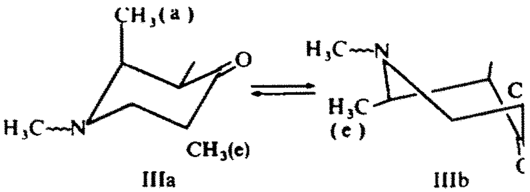
The unusually low ΔG° value of C_2-methyl deserves special comment. Two alternative explanations for the phenomenon may be suggested:

1. a unique "3-alkylketone" effect[7] for 4-ketopiperidines, and
2. steric interaction between the equatorial substituent on C_2 and the methyl on nitrogen.* That the second suggestion is true follows from experiments on the equilibration of the unsubstituted analogue of II† where the "normal" values for $e \rightarrow a$ transition were obtained.

In conclusion it may be added that, taking ΔG° for C_2 and C_3 methyls from the table, the estimated preponderance of the axial conformers IVa and IIIa in the equilibria should be about 90%, in accordance with the earlier chemical data.[8]



IVa IVb



IIIa IIIb

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* Probably this phenomenon reflects hindrance of nitrogen inversion by the equatorial C_2-methyl.

† In press.