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THE CONFORMATIONAL EQUILIBRIUM IN N,N'-DIMETHYLHEXAHYDROPYRIMIDINES

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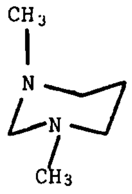
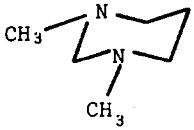
The hexahydropyrimidine system is of considerable interest in the theory of heterocyclic conformational analysis[1] because of the possibility of conformational equilibria at nitrogen. The position of the equilibrium should depend upon the relative magnitudes of non-bonded and dipolar interactions in conformations Ia and Ic. Eliel, on the basis of some nmr measurements reached the conclusion that a substantial proportion of the molecules exist in form Ia with one alkyl group axial.[2] Dipole moment studies led the group in Norwich to a similar conclusion, and they found a free energy difference between Ia and Ic of 0.54 ± 0.08 kcal/mole.[3] Because of our continuing interest in this system[4,5,6] we decided to investigate this equilibrium by nmr techniques that should enable a quantitative estimate of the equilibrium to be made.

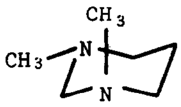
The study involved the preparation and examination of the model compounds II and III. In II the presence of a 5 axial methyl group constrains both N-methyls to equatorial positions. In the diazabicyclo[3,3,1]nonane III the nature of the molecule renders one N-alkyl group axial. Comparison of the chemical shift differences and coupling constants at C(2) enables one to



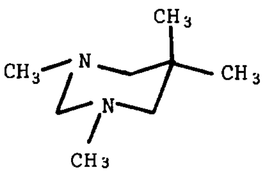
Ia



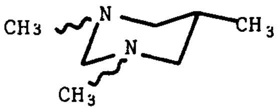
Ic



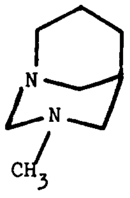
Ib



II



IV



III

estimate the position of the conformational equilibrium Ia $\rightleftharpoons$ Ic. We have previously used this method in the tetrahydro-1,3-oxazine series.[7] We also chose to study the conformational equilibrium at nitrogen in 1,3,5-trimethyl hexahydropyrimidine, for which there is compelling evidence of the C(5) methyl group preferring an equatorial conformation. Our results are presented in the table.

Compound	Solvent	C(2) proton data		Equilibrium constants (K) (IV eqeq $\rightleftharpoons$ IV eqax)	
		δΔ±0.01 ppm	J±0.2Hz	From δΔ	From J
I	$CDCl_3$(-73°)	1.26	8.9		
II	CH_2Cl_2(-60°)	1.68	7.9		
	CF_2Cl_2(-75°)	1.65	7.9		
III	$CDCl_3$	0.52	11.2		
	CH_2Cl_2	0.51	10.9		
	CD_3OD	0.53	11.0		
IV	$CDCl_3$	1.04	9.1	1.23	0.57
	CH_2Cl_2	1.00	9.1	1.39	0.67
	CD_3OD	1.17	9.2	0.80	0.72

values at 33.5° unless otherwise stated

These results indicate that the conformational equilibrium on nitrogen in compounds I and IV lies partway between the diequatorial and axial equatorial extremes. The equilibrium constants calculated from this data are presented in the table.

It seems clear that a reasonable estimate of K is 1.0 ± 0.5, from which it follows that $\Delta G = 0.0 \pm 0.4$. Correction for the entropy factor of Rln2 gives $\Delta G = -0.4 \pm 0.4$ kcals/mole for the equilibrium Ia $\rightleftharpoons$ Ic; a value which is satisfyingly in agreement with that found by Katritzky.[3] The 1.28 ppm difference observed for I at -73° is consistent with the expected shift of the equilibrium towards the diequatorial conformation at low temperatures.

It seems most probable that dipolar interactions ("rabbit ear effect") contribute to the low value of the free energy difference observed in this and similar systems.[7]

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