Quantitive Dependence of *N*-Methyl Inversion Barriers in Six-Membered Rings on Electronic and Steric Effects. Direct Observation of the Conformational Equilibria in Tetrahydro-1,3-oxazines and Hexahydropyrimidines

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Summary Low-temperature ^{1}H n.m.r. spectra of *N*-methyl and *N,C*-polymethyl derivatives of tetrahydro-1,3-oxazine and hexahydropyrimidine allow calculation of conformational equilibria and the rationalisation of steric and electronic effects on *N*-methyl inversion barriers.

WE have reported previously[1] that *N*-methyl inversions in hexahydropyridazines are high (*ca.* 12 cal mol^{-1}) if the *N*-methyl groups need to eclipse each other in the transition state and low (*ca.* 8 kcal mol^{-1}) if the inversion is unhindered by an adjacent *N*-methyl group. These conclusions have subsequently been confirmed by ^{13}C n.m.r.[2]

We have now observed that an adjacent equatorial *C*-methyl group raises the barrier to N-inversion in tetrahydro-2,3-dimethyl-1,3-oxazine by *ca.* 1 kcal mol^{-1} with respect to the parent tetrahydro-3-methyl-1,3-oxazine and that the buttressed equatorial *C*-methyl group in hexahydro-1,2,3-trimethyl-pyrimidine increases the *N*-methyl inversion barrier by *ca.* 1·2 kcal mol^{-1} with respect to the parent hexahydro-1,3-dimethylpyrimidine.

Unambiguous observations of *N*-methyl inversion in simple saturated six-membered heterocycles other than hexahydropyridazines have been reported only for tetrahydro-2-methyl-1,2-oxazine[3] and hexahydro-1,3,5-trimethyl-1,3,5-triazine.[4] These values together with our present

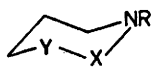
TABLE

The free activation energies and increments[a] (kcal mol^{-1}) for *N*-methyl inversion barriers in piperidines with additional hetero-atoms

Compound	$\Delta G_c^{\ddagger}$ kcal mol^{-1}	Ref.	α-O	β-O	α-*N*-Me(*ax*)	α-*N*-Me(*eq*)	β-*N*-Me	α-*C*-Me(*eq*)	α-*C*-Me(*eq*) buttressed by β-*N*-Me
Hexahydro-1,3,5-trimethyl-1,3,5-triazine	7·2 ± 0·1	4					0·4		
Hexahydro-1,2-dimethylpyridazine	*ca.* 12	1				5·6			
	ca. 8	1			1·6				
Tetrahydro-3-methyl-1,3-oxazine	6·8 ± 0·1	–		0·4					
Tetrahydro-2,3-dimethyl-1,3-oxazine	7·6 ± 0·1	–		0·4				0·8	
Hexahydro-1,3-dimethylpyrimidine	⩽6·7	–					0·3		
Hexahydro-1,2,3-trimethylpyrimidine	8·0 ± 0·1	–					0·4		1·2
Tetrahydro-2-methyl-1,4,2-dioxazine	10·2 ± 0·2	b	3·4	0·4					
Tetrahydro-2,3,3-trimethyl-1,4,2-dioxazine	11·0 ± 0·3	b	3·4	0·4				0·8	

[a] With respect to the barrier for *N*-methyl inversion (6·4 kcal mol^{-1}, J. M. Lehn and J. Wagner, *Chem. Comm.*, 1970, 414) in the seven-membered homopiperidine where unstrained bond angles give as close a resemblance to open-chain systems as can be afforded by simple cyclic systems. An alternative barrier (6·8 kcal mol^{-1}) has also been reported (J. B. Lambert, W. L. Oliver, jun., and B. S. Packard, *J. Amer. Chem. Soc.*, 1971, **93**, 933). [b] R. A. Y. Jones, A. R. Katritzky, A. R. Martin, and S. Saba, *J.C.S. Perkin II*, 1974, 1561.

data are shown in the Table which demonstrates that quantitative increments can be consistently assigned to the various steric and electronic effects on the *N*-methyl inversion barriers. [No allowance has been made for solvent effects; CF_2Cl_2 was used for all compounds except tetrahydro-2,3-dimethyl-1,3-oxazine (vinyl chloride)].



$X = CH_2$,	$Y = NR$	Hexahydropyrimidines
$X = CH_2$,	$Y = O$	Tetrahydro-1,3-oxazines
$X = NR$,	$Y = CH_2$	Hexahydropyridazines

The large increase in the barrier for *N*-inversion due to α-oxygen and α-nitrogen, and the smaller effect of β-oxygen and β-nitrogen is clear. α-*C*-Methyl (*eq*) has a modest steric effect on the barrier, somewhat increased by buttressing. The large difference in the effect between α-*N*-methyl (*eq*) and α-*N*-methyl (*ax*) is probably due partly to different electronic interactions in the transition state as well as the steric interaction of the eclipsed methyl groups. Differing electronic interactions in the transition state also account for the considerably greater effect of α-oxygen over α-*N*-methyl (*ax*); *cf.* the near equality of β-oxygen and β-nitrogen.

The results given should now allow the prediction of *N*-methyl inversion barriers in other six-membered heterorings; consequently we believe the barrier of 13·7 kcal mol^{-1} reported[3] for tetrahydro-2-methyl-1,2-oxazine should be assigned to ring inversion as the corresponding *N*-methyl inversion is expected to be *ca.* 9·8 kcal mol^{-1}.

Direct integration of the two *N*-methyl peaks for tetrahydro-3-methyl-1,3-oxazine at 128 K gave $K = 1·3$ corresponding to $\Delta G°_{128} = 0·16$ kcal mol^{-1}. The more intense upfield peak was assigned to the *N*-methyl equatorial by comparative low-temperature n.m.r. studies of the series 2-methyl, 2-ethyl, 2-isopropyl, and 2-t-butyl-tetrahydro-3-methyl-1,3-oxazine.[5] Assuming that ΔS is small for tetrahydro-3-methyl-1,3-oxazine, $\Delta G°_{298}$ is also *ca.* 0·16 kcal mol^{-1}. Previously published results from this laboratory gave $\Delta G°_{298} = 0·20$ kcal mol^{-1} from dipole moment measurements.[6] Similarly we have now obtained $\Delta G°_{298} = 0·14$ kcal mol^{-1} for tetrahydro-2,3-dimethyl-1,3-oxazine by integration of the n.m.r. peaks.

We have not yet frozen out *N*-inversion in hexahydro-1,3-dimethylpyrimidine. For the 1,2,3-trimethyl analogue the *N*-methyl peak splits at 139 K into two peaks of relative area 1·16:1. We assign the more intense peak to the equatorial *N*-methyl groups of both conformers and hence derive $\Delta G°_{139} = 0·63$ kcal mol^{-1} in favour of the axial/equatorial conformer relative to the diequatorial conformer. For symmetrical hexahydropyrimidines, $\Delta S = R\ln 2$ cal mol^{-1} K^{-1} for reasons of symmetry. Neglecting other ΔS terms, this gives $\Delta H° = 0·44$ kcal mol^{-1}. Extrapolation of our result then gives $\Delta G°_{298} = 0·85$ kcal mol^{-1}. Eliel *et al.* previously reported[7] $\Delta G°_{303} = 0·55$ kcal mol^{-1} by interpolation of ^{1}H n.m.r. chemical shifts, we have now calculated $\Delta G°_{298} = 0·62$ kcal mol^{-1} for hexahydro-1,2,3-trimethylpyrimidine from dipole moment measurements, both again in favour of the monoaxial/monoequatorial conformer.

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