The Barrier to Nitrogen Inversion in Six-membered Rings

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Summary *N*-Methyl inversion barriers of 13·5—13·8 kcal mol^{-1} in dihydro-1,2-oxazines and an empirical least-squares correlation of nitrogen inversion barriers in 20 six-membered rings, show that the process observed in *N*-methyltetrahydro-1,2-oxazine of 13·7 kcal mol^{-1} is nitrogen and not ring inversion.

In a recent communication Katritzky *et al.*[1] offer an empirical description of the barrier to *N*-methyl inversion in six-membered rings. Many serious discrepancies are immediately apparent in their scheme.

Firstly, the standard they choose for the nitrogen inversion barrier in six-membered rings is taken from a seven-membered ring. It is well known[2] that barriers to nitrogen inversion are very dependent on ring size, and that barriers found in seven-membered rings are almost invariably lower than in the corresponding six-membered ring. If it is desired to use the barrier in a seven-membered ring as a model for an 'unstrained' system, a factor should have been introduced into the analysis[1] to allow for 'strain,' *i.e.* the different restraints imposed on inversion at nitrogen by the six-membered ring, in the latter.

Secondly, the scheme proposed by Katritzky *et al.*,[1] against all literature precedent,[2] shows an α-nitrogen to have a greater barrier-enhancing effect than an α-oxygen.

Thirdly, the combination of the two errors above leads to a reassignation of the barrier to nitrogen inversion in the tetrahydro-1,2-oxazine series (**1**)[3,4] as a ring inversion, despite the strong evidence from solvent effects for the former assignment. As confirmation that the observed process in tetrahydro-1,2-oxazines is nitrogen inversion we present in Table 1 the barriers observed in the dihydro series (**2**). In these compounds, as in the previously measured 1,2-oxazolidine[3] (**3a**), ring inversion is expected to have a much lower activation energy than nitrogen inversion. The similarity of the barriers and the solvent effects between the dihydro- and tetrahydro-series supports the assignation of nitrogen inversion. Moreover the substituent effects in both series agree with expectations[2] if nitrogen- and not ring-inversion is the slow process.

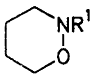
TABLE 1

Compound	R^1	R^2	R^3	Nitrogen inversion[a] barrier/kcal mol^{-1}		Ref.
(**1a**)	Me	—	—	(A) 13·7	(B) 15·0	3
(**1b**)	Pr^i	—	—	(A) 12·5		4
(**2a**)	Me	H	H	(C) 13·5		–
(**2b**	Et	H	H	(C) 13·3		–
(**2c**)	Pr^i	H	H	(C) 13·0		–
(**2d**)	Me	H	Me	(C) 13·8		–
(**2e**)	Et	H	Me	(C) 13·7		–
(**2f**)	Pr^i	H	Me	(C) 13·5	(B) 13·7	–
(**2g**)	Me	Me	Me	(C) 13·8	(B) 14·3	–
(**2h**)	Et	Me	Me	(C) 13·7	(B) 14·0	–
(**2i**)	Pr^i	Me	Me	(C) 13·4	(B) 13·5	–
(**3a**)	Me	—	—	(C) 15·6	(B) 16·9	3

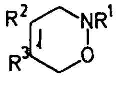
[a] Determined by the n.m.r. coalescence temperature method on either a Perkin Elmer R32 or a Varian A60 spectrometer. Solvents: (A) CH_2Cl_2; (B) D_2O–CD_3OD; (C) $CDCl_3$.

The key to constructing an empirical scheme of factors affecting nitrogen inversion barriers in six-membered rings is the value of the barrier in *N*-methylpiperidine. Since this value is not currently available, and it is virtually impossible to measure it by n.m.r. techniques[5] it must be treated as an unknown in the analysis of effects. Accordingly we have taken 20 examples of nitrogen inversion barriers in six-membered rings and performed a standard statistical least-squares analysis of those structural factors most likely to affect inversion rates. The results of this analysis are presented in Table 2. The barrier to nitrogen inversion in *N*-methylpiperidine is found to be 9·63 kcal mol^{-1} and the incremental factors fall into a very reasonable order

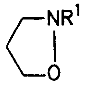
(α-O > α-NMe$_{eq}$ > α-CMe$_{eq}$ > β-NMe > β-O). The standard deviation of the fit is 0·23 kcal mol^{-1} making the 95% confidence limits on predictions *ca.* 0·5 kcal mol^{-1}. This standard deviation is comparable with the experimental errors in most of the determinations and to minor fluctuations in barrier height due to changes of solvent.[2] If compounds (**1a**) and (**1b**), for which it has been claimed[1] that ring inversion is the observed process, are omitted from the analysis the result is virtually unchanged. This indicates no anomaly in the assignment of this process as nitrogen inversion.



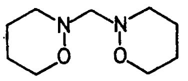
(1)



(2)



(3) a; R^1 = Me
b; R^1 = CH$_2$OMe



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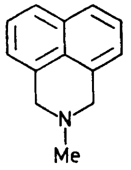

(5)

(6)

Interestingly the effects of β-heteroatoms are to lower the barrier. This is not without precedent[2] as the barrier in (**3b**) is 5·3 kcal mol^{-1} lower than in (**3a**).[3,4] Similarly the barrier in (**1c**; R^1 = CH$_2$OMe)[4] is 2·2 kcal mol^{-1} lower than in (**1a**)[3] whilst the barrier in (**4**) is 1·4 kcal mol^{-1} lower than in (**1a**).[6] These barrier-lowering effects of β-heteroatoms may result in part from relief of dipolar interactions in the transition state. Alternatively 'charge alternation,' the effect of a β-electronegative atom in raising the electron density, previously shown by quantum mechanical calculations,[7] may be implicated.

Two compounds have been studied that could act as reasonable models for the barrier in unhindered six-membered rings. In compounds (**5**)[8] and (**6**)[9] barriers of 9·7 and 9·5 kcal mol^{-1} have been reported. Whilst these are obviously not wholly ideal models for the barrier in *N*-methylpiperidine their agreement with that obtained independently by our least-squares analysis is very significant.

TABLE 2

Observed and predicted nitrogen inversion barriers in six-membered rings (kcal mol^{-1})[a]

Compound	Obs.	Calc.	Diff.
(**1a**)	13·7	13·30	+0·40
(**1b**)	12·5	12·77	−0·27
(**2a**)	13·5	13·51	−0·01
(**2b**)	13·3	13·36	−0·06
(**2c**)	13·0	12·97	+0·03
(**2d**)	13·8	13·89	−0·09
(**2e**)	13·7	13·75	−0·05
(**2f**)	13·5	13·36	+0·14
(**2g**)	13·8	13·83	−0·03
(**2h**)	13·7	13·69	+0·01
(**2i**)	13·4	13·30	+0·10
3-Methyltetrahydro-1,3-oxazine ..	6·8	6·94	−0·14
2-Methyltetrahydro-1,4,2-dioxazine	10·2	10·61	−0·41
1,3,5-Trimethylhexahydro-1,3,5-triazine	7·2	6·93	+0·27
1,2-Dimethylhexahydropyridazine	12·0	11·86	+0·14
1,2-Dimethyltetrahydropyridazine	12·0	12·06	−0·06
1,2,4,5-Tetramethyltetrahydropyridazine	12·3	12·38	−0·08
2,3-Dimethyltetrahydro-1,3-oxazine	7·6	7·19	+0·41
2,3,3-Trimethyltetrahydro-1,4,2-dioxazine	11·0	10·86	+0·14
1,2,3-Trimethylhexahydropyrimidine	8·0	8·54	−0·54

[a] Calculated values obtained from the following parameters: *N*-methylpiperidine, 9·63; *N*-ethylpiperidine, 9·49; *N*-isopropylpiperidine, 9·10; α-O, +3·67; α-*N*-Me (*eq.*), +2·22; β-O, −2·70; β-*N*-Me, −1·35; 4,5-double bond, +0·20; 5-methyl-4,5-double bond, +0·59; 4,5-dimethyl-4,5-double bond, +0·53; α-*C*-Me (*eq.*), +0·26.

Kessler and Liebfritz[10] have estimated the barrier in *N*-methylpiperidine to be 7·8—8·0 kcal mol^{-1}. This value, although lower than ours, is substantially greater than that arbitrarily chosen in ref. 1, and would also give a negative β-effect for a heteroatom.

We conclude that the scheme published recently[1] contains several major flaws, that the process observed in the oxazines is most probably nitrogen inversion, and that our parameters should allow fairly reliable predictions of barriers to be made for several similar systems.

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[5] See for example J. B. Lambert and W. L. Oliver, *J. Amer. Chem. Soc.*, 1969, **91**, 7776.

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