N-Methyl Inversion Barriers in Six-membered Rings[1]

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Summary *N*-Methyl inversions should be considered in terms of two half-barriers, *ax* → *ts* (increased in piperidine by β-heteroatom substitution) and *eq* → *ts* (lowered by β-heteroatoms); this resolves previous controversy and rationalises literature data.

We have published[2,3] alternative, and apparently mutually incompatible, incremental schemes for the computation of *N*-methyl inversion barriers in six-membered rings from the heteroatoms present. In particular the Norwich group ascribed to β-heteroatoms a *barrier raising* effect,[2] while the Stirling workers considered that β-heteroatoms *lowered* the barrier.[3]

Detailed consideration of the literature data,[4] and further extensive work from both our groups particularly using ^{13}C n.m.r. spectroscopy on saturated six-membered rings containing three heteroatoms,[1,5] now clearly indicates that *N*-inversions in six-membered rings must be discussed in terms of half-barriers *ax* → *ts* and *eq* → *ts*, which differ by the ΔG^0 for the conformational equilibrium of the *N*-substituent.† Thus for *N*-methylpiperidine we now consider the best estimates are $\Delta G^{\ddagger}$ (*ax* → *ts*) = 6·0 kcal mol^{-1} (*cf.* previous suggested value of 6·8 kcal mol^{-1})[2] and $\Delta G^{\ddagger}$ (*eq* → *ts*) = 8·7 kcal mol^{-1} (*cf.* previous value of 9·6 kcal mol^{-1}).[3]‡

β-Heteroatoms *increase* the *ax* → *ts* half barrier (as suggested by the Norwich group[2]), but *decrease* the *eq* → *ts* half barrier (as suggested by the Stirling group[3]). These β-heteroatom effects show considerable regularity; a β-equatorial-*N*-methyl group increases the *ax* → *ts* barrier by 1·0 kcal mol^{-1}; for β-oxygen and β-sulphur the effect is somewhat greater (1·6—1·8 kcal mol^{-1}). These three hetero-substitutions lower the *eq* → *ts* half barriers by 0·8, 1·2, and 1·6 kcal mol^{-1}, respectively.

The effects of α-heteroatoms appear to be less regular. α-Axial-*N*-methyl groups decrease the *eq* → *ts* barrier by *ca.* 1·1 kcal mol^{-1}, but change little the *ax* → *ts* barrier. In contrast, α-equatorial-*N*-methyl groups and α-oxygen each significantly increase both the *ax* → *ts* and *eq* → *ts* barriers (2·9—6·6 kcal mol^{-1}); the α-*eq*-*N*-Me effect is greatest on *ax* → *ts* and the α-*O* greatest on *eq* → *ts*.

γ-Heteroatoms have small effects only on both half

† In the full paper over 60 experimental barriers for some 45 six-membered saturated heterocyclic ring systems with up to four heteroatoms will be considered and the component half barriers deduced taking into account the ΔG°. A conformational route map will be considered for each heterocycle and this correlated to that of *N*-methylpiperidine.

‡ 1 cal = 4·184 J.

barriers ($\ngtr$ 0·2 kcal mol^{-1}). α-*C*-Methyl groups show small effects on inversion half barriers unless there are either three methyl groups on adjacent ring atoms or a geminal dimethyl group.§

It is now clear that the earlier confusion and controversy arose largely because the work carried out at Norwich[2] referred to *ax* → *ts* half barriers whereas that carried out at Stirling[3] referred to *eq* → *ts* half barriers. It is clearly important for future discussions of inversion barriers in non-symmetrical systems that the ground state be clearly defined; for *N*-inversions in conformational analysis both half barriers should preferably be given.

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§ A detailed discussion will be given in the full paper.

[1] *Cf.* our Series 'Conformational Analysis of Saturated Heterocycles;' see A. R. Katritzky and R. C. Patel, *Heterocycles*, 1978, **9**, 263, for the most recently published part.

[2] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Chem. Comm.*, 1975, 255.

[3] F. G. Riddell and H. Labaziewicz, *J.C.S. Chem. Comm.*, 1975, 766.

[4] *Cf.* R. C. Patel, Ph.D. Thesis, University of East Anglia, 1977.

[5] A. R. Katritzky, V. J. Baker, I. J. Ferguson, and R. C. Patel, *J.C.S. Perkin II*, 1979, 143; A. R. Katritzky, R. C. Patel, and D. M. Read, *Tetrahedron Letters*, 1977, 3803; A. R. Katritzky and R. C. Patel, *J.C.S. Perkin II*, in the press; A. R. Katritzky, R. C. Patel, F. M. S. Brito Palma, F. G. Riddell, and E. S. Turner, unpublished results; A. R. Katritzky, V. J. Baker, and F. M. S. Brito-Palma, unpublished results; F. G. Riddell, M. H. Berry, and E. S. Turner, *Tetrahedron*, 1978, **34**, 1415; F. G. Riddell and J. E. Anderson, *J.C.S. Perkin II*, 1977, 588; F. G. Riddell, E. S. Turner, and A. Boyd, *Tetrahedron*, 1979, 259; F. G. Riddell and E. S. Turner, *J. Chem. Research* (*S*), 1978, 476; *Heterocycles*, 1978, **9**, 267.