The Conformational Analysis of Saturated Heterocycles. N-Inversion in Hindered Piperidines

By FRANK A. L. ANET* and ISSA YAVARI
(*Department of Chemistry, University of California, Los Angeles, California* 90024)

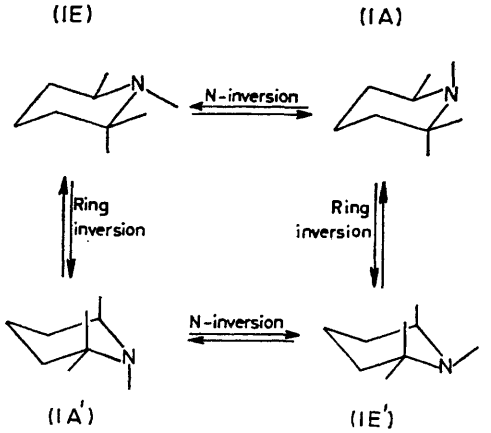
IAN J. FERGUSON and ALAN R. KATRITZKY*
(*School of Chemical Sciences, University of East Anglia, Norwich* NR4 7TJ)

MARCIAL MORENO-MAÑAS
(*Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Barcelona, Spain*)

and MICHAEL J. T. ROBINSON*
(*Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford* OX1 3QY)

Summary Results from a new dynamic n.m.r. method, applicable to heavily biased equilibria, and kinetically controlled protonation studies agree when applied to 1,2,2,6-tetramethylpiperidine, giving the free energy difference for *N*-inversion [ΔG° (**1E** → **1A**)] as 1·9 ± 0·2 at 213 K (d.n.m.r.) and 1·95 ± 0·1 kcal mol^{-1} at 293 and 373 K (kinetic protonation); the free energy of activation [$\Delta G^\ddagger$(**1E** → **1A**)] is 11·0 ± 0·3 kcal mol^{-1} at 213 K.

N-METHYLPIPERIDINE occupies a special place in the conformational analysis of saturated heterocycles and like piperidine it has been the subject of several conformational studies;[1] in particular dipole moments,[2] chemical shifts in relation to model systems,[1] and kinetically controlled protonation[3] have resulted in a wide range of values for the free energy difference between the *N*-methyl equatorial and axial conformers (namely 0·59, 1·35—1·77, and 2·7 kcal mol^{-1}). The methods used have not included dynamic n.m.r. (d.n.m.r.) spectroscopy, which is accepted as conclusive when it is applicable, because the equilibrium in *N*-methylpiperidine is too biased. We have sought, therefore, a related piperidine which would have a lower free energy difference and which could be studied by d.n.m.r. spectroscopy and kinetically controlled protonation. We have recently observed that adjacent equatorial methyl groups in *N*-methyl-heterocycles *raise* the barrier to *N*-inversion and *lower* the free energy difference,[4] both factors increasing the possibility of detecting axial *N*-methyl; multiple substitution is expected to lead to a non-additive enhancement of both effects. Consequently we prepared 1,2,2,6-tetramethylpiperidine[5] where there are two adjacent equatorial methyl groups and where ring inversion should not be an important process as it would give rise to conformers with highly unfavourable 1,3-*syn* diaxial interactions (**1E′**, **1A′**). Thus any spectral changes will only be a consequence of slowing N-inversion.



SCHEME 1

The variable temperature ^{1}H n.m.r. spectra of 1,2,2,6-tetramethylpiperidine showed no observable changes in the range 307—123 K. A concurrent ^{13}C d.n.m.r. study was also carried out on the piperidine. The spectrum was assigned on the basis of an undecoupled spectrum which also revealed a sharp quartet for the *N*-methyl (no *anti* vicinal couplings) and deshielding β-effects and shielding γ-effects. The d.n.m.r. study again showed no large spectral changes in the range 307—97 K. However a careful examination of the spectra in the range 243—183 K showed that a dynamic n.m.r. effect is undoubtedly present. Three lines, due to the C-2 methyl (*trans* to the C-6 methyl) and to C-3 and the C-5 broaden significantly in this temperature range and then become sharper at lower temperatures. These are exactly the resonances that are expected to broaden if the minor form has the axial *N*-methyl structure (**1A**) and the major form has the equatorial *N*-methyl structure (**1E**). The C-3 and C-5 carbon atoms each gain a γ-effect contribution [on going from (**1E**) to (**1A**)] and the C-2 axial loses one γ-contribution while all the other carbons maintain their respective number of γ contributions. Thus the lines that should broaden do so. The broadening is greatest for the C-2 methyl and at 213 K is *ca.* 4 Hz greater than the sharp lines of the spectrum. The lines from C-2 and C-6 might have been expected to broaden because the β-effect of the *N*-methyl group should differ for the axial and equatorial orientations but this is probably a small effect and its magnitude is difficult to predict.

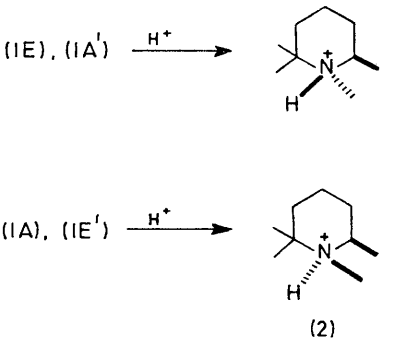
This general type of broadening behaviour has been extensively studied in the case of methylcyclohexane[6] and

has led to equations (1) and (2).† Assuming that the γ-effect is *ca.* 5 p.p.m. (300 Hz) then equation (1) gives *P ca.* 1% at 213 K. Equation (2), in the case of the piperidine (**1A** → **1E**), gives $k = ca.\ 2000\ s^{-1}$ at 213 K and consequently $\Delta G^{\ddagger}$ (**A** → **E**) = 9·1 ± 0·3 kcal mol^{-1}. At 213 K also, $\Delta G^{\circ} = 1{\cdot}9 \pm 0{\cdot}2$ kcal mol^{-1} and $\Delta G^{\ddagger}$ (**E** → **A**) = 11·0 ± 0·3 kcal mol^{-1}. The free activation energy of inversion is relatively high owing to the strain energy arising from the need for the methyl groups to be eclipsed in the transition state.

$$\nu(\tfrac{1}{2}\text{max.}) = P \times \Delta\nu \quad (1)$$

$$k = 2\pi\Delta\nu \quad (2)$$

The piperidine (**1**) (*ca.* 0·25 M solutions in n-dodecane‡) was also submitted to kinetically controlled protonation by 64% sulphuric acid at 293 and 373 K giving mixtures of diastereomeric ions *cis*- and *trans*-(**2**) (Scheme 2). The minor component, *cis*-(**2**), was measured quantitatively using the high-field half of the *N*-methyl doublet and the low field *C*-methyl singlet in the ^{1}H n.m.r. spectrum, giving $\Delta G^{\circ}_{293} = 1{\cdot}94 \pm 0{\cdot}06$ and $\Delta G^{\circ}_{373} = 1{\cdot}97 \pm 0{\cdot}04$ kcal mol^{-1} (error limits are extremes for four measurements, two using *N*-Me and two using *C*-Me signals, at each temperature), in excellent agreement with the estimate from d.n.m.r. studies, *cis*-(**2**) was identified qualitatively from the ^{1}H n.m.r. spectrum of a *ca.* 1 : 1 mixture of *cis*- and *trans*-(**2**) obtained by protolysis of an equilibrated mixture of borane–amine adducts obtained from (**1**) and BH_3–Me_2S,[7] a general method for preparing solutions containing high concen rations of the *less* stable of two diastereomeric alkylp i ridinium ions.[8]



SCHEME 2

These results for the *hindered* system (**1**) indicate that the parent *N*-methylpiperidine must have a very high preference for the *N*-methyl equatorial conformer and that the value of 2·7 kcal mol^{-1} from kinetically controlled protonation[3] is most probably of the correct order. Very recently other evidence both for[9] (using a kinetically controlled reaction and therefore based on similar assumptions to protonation[3]) and against[10] this value has appeared.

(*Received, 5th December* 1975; *Com.* 1355.)

† In equation (1) ν(½ max.) is the maximum broadening at the half height of the signal, *P* the population in the minor form, and Δν the chemical shift difference in Hz. In equation (2) *k* in s^{-1} is the rate constant at the temperature of maximum broadening for the direction minor to major. These equations are applicable for conformer ratios greater than 10 : 1 and can be obtained mathematically from the Gutowsky–Holm line-shape equation for two sites. The exact value of the γ-effect is not particularly crucial to our results; in equation (2) a 200 Hz range in the value of the chemical shift results in only *ca.* 0·3 kcal mol^{-1} variation in the free energy of activation.

‡ As a comparison of free-energy differences obtained in such differing solvent systems (CF_2Cl_2 and n-dodecane) might not be strictly comparable, solutions of the piperidine (**1**) in CH_2Cl_2 or C_6H_6 were submitted to the same protonation procedure and gave $\Delta G^{\circ} = 1{\cdot}73 \pm 0{\cdot}05$ and $1{\cdot}90 \pm 0{\cdot}02$ kcal mol^{-1}, respectively. These results are also in good agreement with the estimate from d.n.m.r. studies.

[1] E. L. Eliel and F. W. Vierhapper, *J. Amer. Chem. Soc.*, 1975, **97**, 2424 and references therein.
[2] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 122.
[3] P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *J.C.S. Chem. Comm.*, 1974, 825.
[4] (a) R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, *J.C.S. Perkin II*, 1974, 406; (b) I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Chem. Comm.*, 1975, 255.
[5] H. K. Hall, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 5444.
[6] F. A. L. Anet and V. J. Basus, results to be published.
[7] *Cf.* R. E. Lyle, E. W. Southwick, and J. J. Kaminski, *J. Amer. Chem. Soc.*, 1972, **94**, 1413.
[8] M. J. T. Robinson, to be published.
[9] D. C. Appleton, J. McKenna, J. M. McKenna, L. B. Sims, and A. R. Walley, *J. Amer. Chem. Soc.*, 1976, **98**, 292.
[10] V. M. Gittins, P. J. Heywood, and E. Wyn-Jones, *J.C.S. Perkin II*, 1975, 1642.