Conformational Equilibrium in *N*-Methylpiperidine

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Summary Kinetically controlled protonation of piperidines has been developed into a reliable method for studying conformational equilibria in piperidine and its alkyl derivatives; in *N*-methylpiperidine (**1**) the equatorial conformer **1*E*** is more stable than the axial **1*A*** by 11·3 ± 0·8 kJ mol^{-1} in cyclohexane and by ≮ 12·5 kJ mol^{-1} in the gas phase, at 288 K.

MANY methods have been used to study the very mobile inversion equilibria at the nitrogen atom in piperidine and its *N*-alkyl derivatives. The results, summarised by Katritzky[1,2] and by Eliel[3] are often startlingly diverse for a given system. Unfortunately the methods used have usually depended on indirect estimates of the properties of individual conformers or have relied on unproven assumptions. We have reinvestigated the equilibrium at nitrogen for (**1**) in the gas phase and in solution by kinetically controlled protonation of the anancomeric derivatives (**2**) and (**3**). This method, first used by Booth for piperidine itself,[4] is in principle very simple and direct but we believe that previous results have been invalidated by the use of inappropriate reaction conditions.

The reaction between piperidines and concentrated strong acids is effectively irreversible once a homogeneous solution has been formed.[4,5] When diastereomeric ions E–H$^+$ and A–H$^+$ result from the protonation of two conformers E and A of a piperidine the ratio of their concentrations $R = [A\text{–H}^+]/[E\text{–H}^+]$, estimated from n.m.r. spectra, is a measure of the conformational equilibrium constant K if protonation is (a) much faster than inversion at nitrogen so that the Curtin-Hammett principle does not apply, (b) stereospecific with retention of configuration, and (c) irreversible at the interface of the acidic and basic

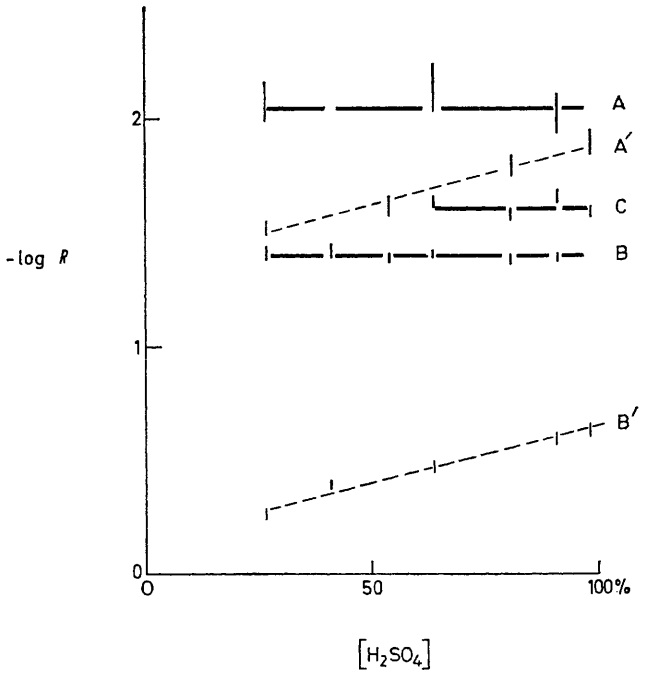
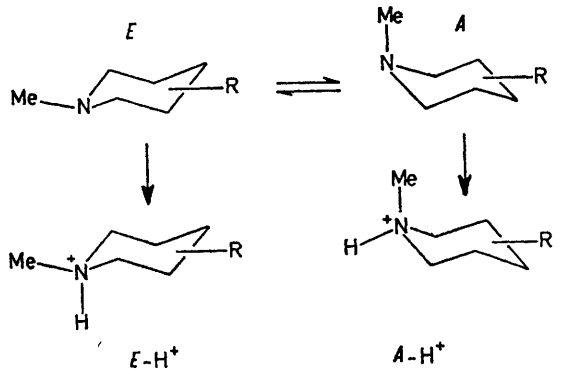


FIGURE. R (= $[A\text{–H}^+]/[E\text{–H}^+]$) as a function of the concentration of sulphuric acid used to protonate (**2**) and (**3**). Lines A and B: (**2**) and (**3**) extracted from 0·2M solutions in cyclohexane; A′ and B′: (**2**) and (**3**), undiluted, mixed with acid (straight lines have been drawn through points determined under standardised conditions but have no special significance because R depends on the method of mixing as well as on the concentration of acid); C: (**3**), vapour.

phases during the mixing process, as well as when the mixing is complete. Booth's method,[4,5] the mixing of an undiluted liquid amine with an excess of a strong acid



(**1**) R = H. (**2**) R = *cis*-3,5-Me_2. (**3**) R = *cis*-2,6-Me_2.

(trifluoroacetic acid), has been criticised[2,6,7] and defended.[5] We have now proved that it is invalid because R varies with the acid used (see lines A′ and B′ in the Figure), presumably because condition (c) is not satisfied so that partial equilibration occurs in the liquid–liquid interface. This partial equilibration is eliminated by separating the amine molecules by dilution with an inert solvent or by vaporisation.

When a tertiary amine, *e.g.*, (**2**) or (**3**) (other examples will be given in our full paper), is extracted by an excess of a strong acid from a sufficiently dilute solution in an inert immiscible solvent (cyclohexane was used for the data summarised in the Figure) the value of R is independent of the concentration of the amine and of the acid (27—98% sulphuric acid for lines A and B) and therefore corresponds to K for the amine in the solvent. In a similar way the gas phase value of K may be determined by allowing the amine vapour to diffuse slowly through air to the surface of an involatile strong acid [see line C for (**3**) in the Figure]; unfortunately only an upper limit to K for (**2**) in the gas phase can be given at present.

Taking (**2**) as a model for *N*-methylpiperidine itself we find that $\Delta G°_{288} = 11{\cdot}3 \pm 0{\cdot}8$ kJ mol^{-1} in cyclohexane, much higher than previous estimates,[2,3] and $\lesssim 12{\cdot}5$ kJ mol^{-1} in the gas phase. The results show that the equilibria at nitrogen in *N*-methylpiperidines are much more strongly in favour of equatorial methyl than previously believed.

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