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THE CONFORMATIONAL EQUILIBRIUM IN PIPERIDINE: EVIDENCE FROM DEUTERONATION OF MODEL COMPOUNDS

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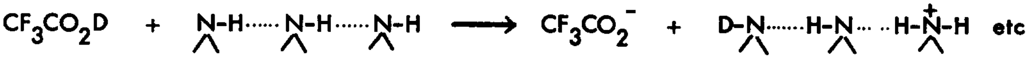
The conformational equilibrium in piperidine ($1E \rightleftharpoons 1A$) has been studied for 20 years with surprising changes in the balance of evidence.[1] This Letter concerns the kinetically controlled, stereospecific conversion of conformers of piperidine derivatives into analysable mixtures of diastereomeric ions. Booth[2,3] attempted to deuteronate the model piperidine 2 kinetically to give 4b and 4c by mixing the liquid amine with an excess of CF_3CO_2D. Diffusion of the ammonium ion 4 into the acid, however, will be slower than H (or D) exchange between the ammonium ion, as it is formed at the interface of the two liquids, and the amine molecules hydrogen bonded to it, since such exchanges are at the diffusion controlled limit in homogeneous solution.[5] If, therefore, the conjugate base of the acid is very weak H—D scrambling may take place among the nitrogen species at the liquid-liquid interface, thereby giving 4a-d and invalidating the results, without exchange between the acid and amine,[6] e.g.:



$$CF_3CO_2D + N\text{-}H\cdots N\text{-}H\cdots N\text{-}H \longrightarrow CF_3CO_2^- + D\text{-}N\cdots H\text{-}N\cdots H\text{-}\overset{+}{N}\text{-}H \quad \text{etc}$$

We have reinvestigated the deuteronation of ring-biased piperidines (2,3) using ^1H NMR spectra with ^{14}N decoupling[7,8] to analyse the resulting mixture of isotopically distinct ions (Fig. 1).

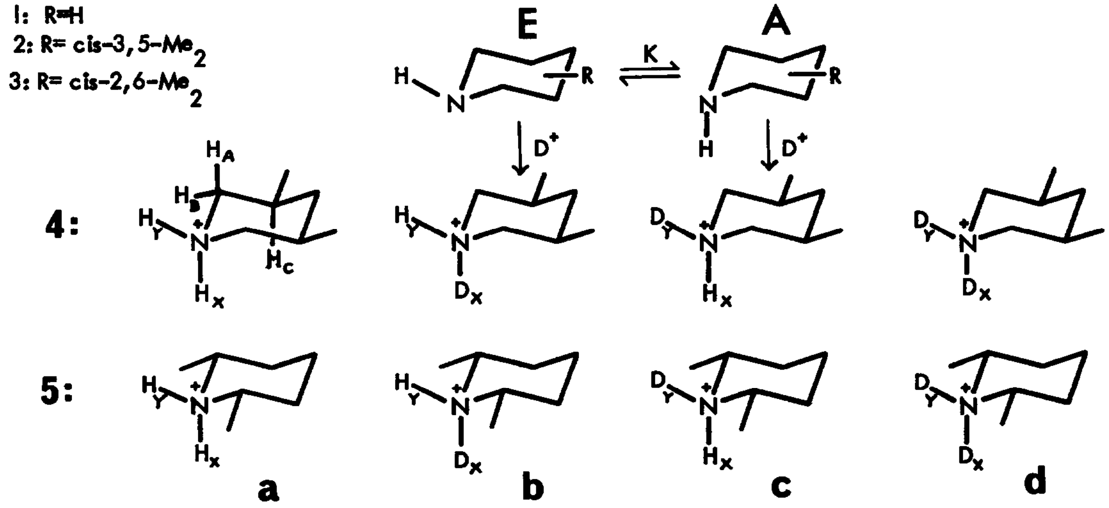


Figure 1. Ions resulting from deuteronation of piperidines 2 and 3

Figure 2 shows parts of the ^{1}H NMR spectra[7] of solutions of 4 and 5 prepared by five different methods; Ia–e are the N-H resonances from the following solutions:

(a) 4a chloride in CF_3CO_2D;

(b) A statistical mixture of 4a–d chlorides, prepared by crystallisation of 4a from H_2O-D_2O (1: 1), in CF_3CO_2D;

(c) A mixture of liquid 2 and excess CF_3CO_2D (Booth's method[2]);

(d) A solution prepared by allowing the vapour of 2 to diffuse to the surface of D_2SO_4;[4,10]

(e) A solution prepared by extracting 2 from a dilute solution in cyclohexane with D_2SO_4.[4,10]

Spectra IIa–e show the resonances of the 2(6)-axial protons (H_A) in the five samples of 4, while spectra IIIa–e show the N-H resonances of five solutions, prepared analogously to (a)–(e) above, of 5. Deuteronation may be used to determine the conformational equilibrium in secondary amines if the reaction is (i) irreversible,[2] (ii) stereospecific and (iii) kinetically controlled. The stereospecificity is probable by analogy with tertiary amines,[4] although multiple labelling experiments would be required to elucidate the possible role of proton (or deuteron) tunnelling. Spectra IId and IIe (see below) strongly suggest that deuteronation, as in tertiary amines, is kinetically controlled under suitable conditions, as in (d) and (e) above.

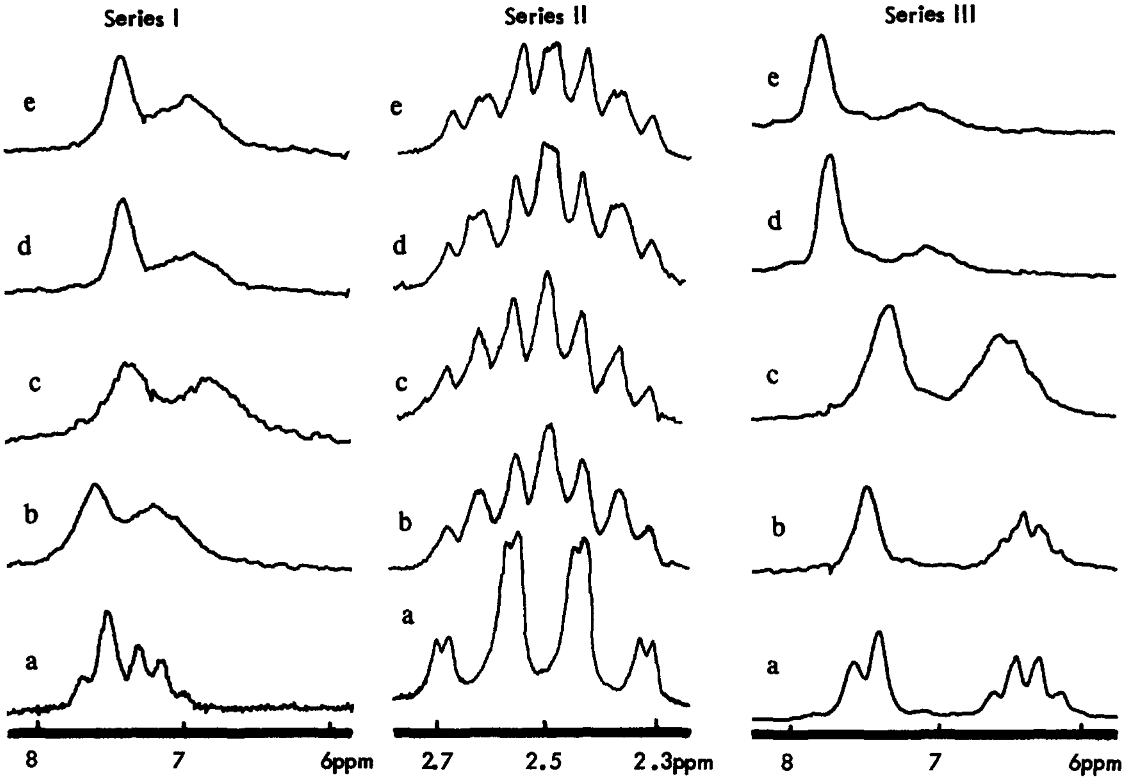


Figure 2. Parts of the proton spectra of 4 and 5: Series I, $\overset{+}{N}H$ (with ^{14}N-decoupling), and Series II, 2(6)-axH(H_A)[11] resonances for solutions (a)–(e) for 4 ; Series III, $\overset{+}{N}H$ (with ^{14}N-decoupling) resonances for solutions of 5 analogous to (a)–(e).

TABLE Ratios of integrals $\underline{R} = H_X/H_Y$ for ions **4** and **5** and derived values of K and ΔG^o (kJ mol^{-1}) at 293K for **2** and **3**

4	$\underline{R}$	K(**2**)[a]	ΔG^o(**2**)	**5**	$\underline{R}$	K(**3**)[a]	ΔG^o(**3**)
Ia	1.03			IIIa	1.04		
Ib	1.04			IIIb	1.06		
Ic	0.97			IIIc	0.96		
Id	0.86	0.82	0.5 ± 0.2	IIId	0.43	0.41	2.1 ± 0.2
Ie	1.02	0.98	0.0 ± 0.2	IIIe	0.50	0.48	1.8 ± 0.2

[a] The average value, 1.04, of $\underline{R}$ for Ia, b and IIa, b has been used to correct the observed values of $\underline{R}$ in deriving K: the correction lowers ΔG^o by <0.1 kJ mol^{-1}.

In ion **4**a the proton H_A (see IIa in Fig. 2) appears as a quartet due to approximately equal couplings to H_B, H_C and H_X ($11._7$ Hz, first order analysis); each component is further split into a doublet by coupling to H_Y ($2._7$ Hz).[11] In the spectrum of **4**d (not shown), the couplings to D_X and D_Y are unresolved and H_A appears as a triplet. In the remaining spectra IIb-e from mixtures of ions H_A gives seven lines, consisting of a quartet (from **4**a and **4**b) and a triplet (from **4**c and **4**d). There is, however, an important difference between IIb or IIc, in which there is broadening but no resolved coupling to H_Y in the triplets, and IId or IIe, in which the triplets show a clear coupling to H_Y in spite of broadening by D_X. Since IIb comes from a mixture of all four ions **4**a-d and matches IIc almost exactly, we conclude that IIc does not correspond to a mixture of **4**b and **4**c only, as claimed by Booth,[2] and cannot be the result of kinetically controlled deuteronation of **2**. In contrast IId and IIe, from solutions prepared by methods which avoid amine-ion reactions and consequent isotopic scrambling at the acid-amine interface, are consistent with a mixture of **4**b and **4**c resulting from kinetically controlled deuteronation.

The ^{14}N decoupled spectra Ia-e of the N-H protons of **4** were integrated; the ratios of areas $\underline{R} = H_X/H_Y$ (Table) are a reliable measure of [**4**c]/[**4**b] for spectra Id and Ie and so lead directly to K and ΔG^o for the equilibrium $\mathbf{2}E \rightleftharpoons \mathbf{2}A$ in the gas phase and in cyclohexane. Spectra of mixtures of ions **5**a-d do not allow the presence of **5**a and **5**d to be determined at the available ^{14}N decoupling power and resolution (spectra IIIa-e). Qualitatively, however, it is striking that the value of $\underline{R}$ for IIIc is close to unity (as for Ic) and that the H_Y resonance is relatively broad, as is that of IIIb, which must correspond to a mixture of **5**a-d, whereas IIId and IIIe show lower values of $\underline{R}$ and narrow H_Y resonances. These differences suggest that IIId and IIIe arise from kinetic deuteronation, while IIIc shows isotopic scrambling.

If the ratios $\underline{R} = H_X/H_Y$ for ions **4**c and **4**b (from spectra Id and Ie) are accepted as a measure of the equilibrium constant K(**2**) then our results (Table) indicate little or no conformational preference, in the gas phase and in a non-polar solvent, in **2** and by analogy in piperidine (**1**) itself. This conflicts with the recent conclusion[1a] that there is a clear preference for the equatorial conformer **1**E under similar conditions and emphasises the need for still further investigation of this system.

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2. H. Booth, Chem.Comm. 802 (1968); H. Booth and J. H. Little, *J.Chem.Soc.Perkin II* 1846 (1972).
3. Booth's technique for protonation (deuteronation) has been extensively discussed (ref. 1) and has been shown to be invalid for N-methylpiperidines.[4]
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6. Aqueous acids, even with acidity greater than CF_3CO_2D, e.g. 80% D_2SO_4, allow H-D exchange between acid and amine during mixing because the relatively strong base D_2O is formed temporarily in the mixing region.
7. ^{1}H NMR spectra were measured with a Perkin Elmer R32 (90 MHz) and Varian CFT-20 spectrometers, the latter modified to allow ^{14}N decoupling.
8. B. Bianchin and J. J. Delpuech, *Tetrahedron* **30**, 2859 (1974).
9. The amines were distilled twice from excess BaO *in vacuo* immediately before use.
10. Solutions were diluted with CF_3CO_2D in order to lower the viscosity of the solutions; the varying solvents and anions lead to the variations in chemical shifts of H_X and H_Y apparent in Fig. 2.
11. Booth[2] observed a broadening which he attributed to coupling with H_Y and, probably, ^{14}N. ^{14}N-decoupling had no detectable effect on IIa-e.