A Variable Temperature Nuclear Magnetic Resonance Spectroscopy Study of Nitrogen Inversion in Medium-ring Monocyclic and Bicyclic Systems[1]

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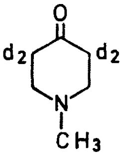
Summary Nitrogen inversion barriers and structural effects on the barriers have been studied by variable temperature n.m.r. spectroscopy in monocyclic (six- and seven-membered ring) and bicyclic (bicyclo[2,2,2]octane and bicyclo[3,2,2]nonane) amines.

THE study of nitrogen inversion in unstrained systems is made difficult by two factors: (i) the ambiguity in identifying the observed process,[2] as hindered rotation or hindered ring inversion may occur together with nitrogen inversion; (ii) the relatively low energy barriers expected for such processes in the absence of electronegative hetero-atoms. We report the barriers to nitrogen inversion in compounds (I)—(VII), determined by variable-temperature n.m.r. spectroscopy. The results are listed in the Table.† In these systems there is no hindered rotation problem.

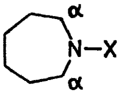
Spectral data and activation parameters for nitrogen inversion in compounds (I—VII)[a]

Compound	Signal observed (at $T°$)	J_{AB} (Hz)	$\Delta\nu_{AB}$ (Hz)	T_c (°)	$\Delta G_c^\ddagger$ (kcal/mole)
(I)	CH_2 (−126)	11·4 ± 0·3	49·7 ± 0·5	− 94 ± 3	8·6 ± 0·3
(II)	CH_2 (α) (−165)	9·0 ± 1·0	27·0 ± 2	−140 ± 5	6·4 ± 0·5
(III)	CH_2 (α) (−120)	13·0 ± 0·5	25·0 ± 1	−100 ± 3	8·4 ± 0·3
(IV)	CH_2 (α) (−127)	8·6 ± 0·5	51·8 ± 1·0	−98 ± 3	8·4 ± 0·3
(V)	CH_2 (α) (−115)	11·0 ± 0·5	38·5 ± 1·0	−54 ± 2	10·6 ± 0·2
(VI)	CH_2 (α) (−122)	11·0 ± 0·3	32·0 ± 0·8	−92 ± 3	8·8 ± 0·3
(VII)	CH_2 (α) (−112)	10·5 ± 0·3	38·4 ± 0·5	−65 ± 2	10·1 ± 0·2

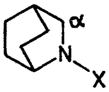
[a] Measured at 60 MHz using a Varian A-60 spectrometer; solvent, $CHFCl_2$, except for (II) (CHF_2Cl).



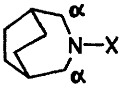
(I)



(II; X = CD_3)
(III; X = Cl)



(IV; X = CD_3)
(V; X = Cl)



(VI; X = CD_3)
(VII; X = Cl)

In compound (I), the barrier to ring inversion is expected to be lowered with respect to *N*-methylpiperidine by the introduction of the carbonyl group, as cyclohexanone (< 5·2 kcal/mole[4]) has a much lower inversion barrier than cyclohexane (10·8 kcal/mole[5]). Thus ring inversion should not interfere with nitrogen inversion. In the seven-membered-ring compounds (II) and (III) pseudo-rotation is expected to present a barrier of the order of 2—3 kcal/mole.[6] Ring inversion is precluded by the bicyclic nature of systems (IV)—(VII). Inversion of the three-atom bridge in (VI)—(VII) also occurs, but the substituent effect on barrier height produced by replacing N–CD_3 (VI) by N–Cl (VII) is similar to that obtained for (II) and (III) and (IV) and (V), thus favouring nitrogen inversion as the observed process.‡

The following preliminary conclusions may be drawn from the results listed in the Table and from the literature data: (i) the barriers to nitrogen inversion in cyclic tertiary amines depend on ring size (n) and decrease in the order: $n = 3$ (*ca.* 20 kcal/mole[7]) $> n = 6$ [*ca.* 8·5 kcal/mole, (I)] $\sim n = 4$ (*ca.* 8·5 kcal/mole[8]) $> n = 5$ (*ca.* 8 kcal/mole[1,3]) $> n = 7$ [*ca.* 6·5 kcal/mole, (II)[3]]; (ii) the inversion barrier is the same in the bicyclo[2,2,2]-system (IV) as in the monocyclic system (I), but it is appreciably higher in (VI) and (VII) than in (II) and (III). There may be a special barrier-raising effect in some bicyclic systems§; (iii) the replacement of the CH_3 group by a chlorine atom on nitrogen leads to a barrier increase, in agreement with the effect found in other systems.[1,2,8] The magnitude of the effect depends on the structure of the molecule[1] but its generality may help to distinguish nitrogen inversion from other processes.

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† An activation free energy of *ca.* 7 kcal/mole has been reported recently for compound (II) (ref. 3).

‡ In addition, if bridge flipping were the observed process it should also be present in the secondary amine (CH_3 replaced by H) corresponding to (VI). This compound has a temperature independent n.m.r. spectrum down to −135°.

§ The reality of such a "bicyclic effect" seems to be confirmed by recent findings of higher barriers than expected on the basis of angle-strain effects, in bicyclo[2,2,1]- (refs 9 and 10) and bicyclo[3,3,1]-systems (ref. 10).

[1] Previous paper in the series: J. M. Lehn and J. Wagner, submitted for publication.
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