Ring Inversion in Morpholine and Piperazine Derivatives, studied by Nuclear Magnetic Resonance

By R. K. HARRIS and R. A. SPRAGG

(*School of Chemical Sciences, University of East Anglia, Norwich*)

MUCH work has been published[1] concerning ring-inversion in cyclohexane derivatives (and some heterocyclic systems containing six-membered rings) as studied by the temperature variation of nuclear magnetic resonance spectra. It has not proved possible to observe the spectrum of a single chair form of 1,4-dioxan, since the rate of inversion appears to be large with respect to the n.m.r. time scale even at −100°c. On the other hand Reeves and Strømme[2] succeeded in observing the spectrum of the "fixed" chair form of *NN'*-dimethylpiperazine (I) using only a moderate decrease in temperature.

Since we found the relatively high inversion barrier in *NN'*-dimethylpiperazine surprising, we have investigated the spectra of *N*-methylmorpholine (II) and morpholine (and re-examined that of *NN'*-dimethylpiperazine) as a function of temperature down to −60°c, the lowest temperature at present attainable with our spectrometer.† Previously reported low-temperature experiments on morpholine derivatives have failed to detect any slowing of ring inversion.[3,4] The results are presented in the Table. The Figure shows the spectra of *N*-methylmorpholine at (A) room temperature and (B) −60°c; the low-temperature spectrum is clearly that of the "fixed" chair form.

At temperatures intermediate between +30° and −60°c the spectrum is complex but the coalescence of the signals from the axial and equatorial protons α to the nitrogen at −31°c is quite clear cut and gives the value quoted in the Table for the free energy of activation, ΔG^*, for the ring-inversion.

† Spectra were recorded on a Varian instrument operating at 100 Mc./sec.

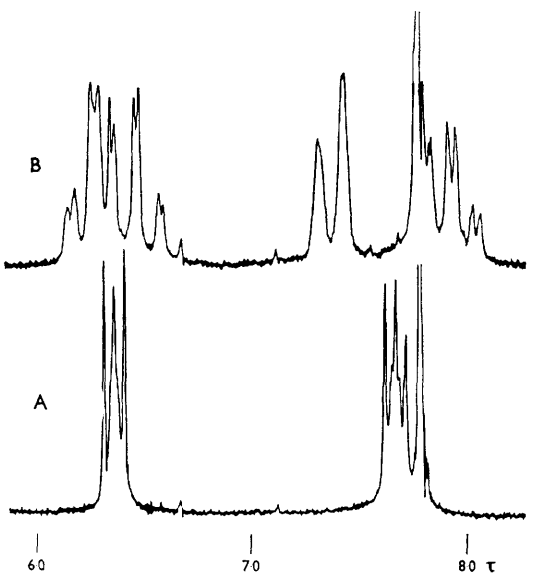
Our value of $\Delta G^* = 12{\cdot}6$ kcal./mole for (I) is in agreement with the result of Reeves and Strømme[2] ($\Delta G^* = 13{\cdot}04$ kcal./mole). However, our value of δ_{ae}, 0·63 p.p.m., is much larger than that reported by those authors, 0·27 p.p.m., in the same solvent. The spectrum at −58°c is rather simple because of a coincidence of lines. It is consistent with the parameters given by Harris[5] for the room-temperature spectrum of the molecule containing ^{13}C in natural abundance, $J_{aa} + J_{ee} = 13{\cdot}6$, $J_{ae} = 3{\cdot}2$ c./sec.

barrier.§ This effect may be due to the size of the methyl group as opposed to a hydrogen atom, although for cyclohexane, methylation does not appear to affect the barrier greatly (in 1,1-dimethylcyclohexane, for example, $\Delta G^* = 10{\cdot}5$ kcal./mole,[6] very close to the value in cyclohexane itself). At −60°c, morpholine itself still gives an averaged spectrum, although the signal from the OCH_2 is very considerably broadened. Morpholine therefore has a considerably lower coalescence temperature than *N*-methylmorpholine. However the inversion barriers in the two molecules need not be different if the values of δ_{ae} differ greatly.

TABLE. *N.m.r. results for the compound studied* (20% *solutions in* CH_2Cl_2)

Compound	Axial/equatorial chemical shift difference (p.p.m.), δ_{ae}, at −60°c	Coalescence temperature T_c	ΔG^*(kcal./mole)
Morpholine	—	< −60°c	—
N-Methylmorpholine	N–CH_2‡ *ca.* 0·49	−31°c	11·5
	O–CH_2‡ *ca.* 0·22	?	—
NN'-Dimethylpiperazine	0·63	−8·5°c	12·6

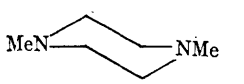
‡ Obtained from an approximate (first-order) analysis.



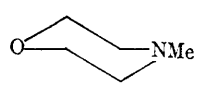
FIGURE

The n.m.r. spectrum of N*-methylmorpholine at* (A) + 30°c *and* (B) −60°c. *The strong band at* $\tau = 7{\cdot}8$ *is due to* NMe *protons; the low-field group of lines is from* OCH_2 *protons* (*impurity at* $\tau = 6{\cdot}7$).

It seems from these results that the presence of an *N*-methyl in place of CH_2 or O in a six-membered ring markedly increases the inversion



(I)



(II)

As this Communication was in process of preparation a Paper by Lambert and Keske[7] was published which gave details of the low-temperature spectra of piperidine and *N*-methylpiperidine. These authors report values of δ_{ae} for protons α to nitrogen of 0·436 p.p.m. for piperidine and 0·942 p.p.m. for *N*-methylpiperidine in methanol, with similar values in cyclopropane solution. This is said to result from the different conformational preferences of the methyl group and the hydrogen atom in relation to the lone pair. Our values for δ_{ae} of protons α to nitrogen in *N*-methylmorpholine and *NN'*-dimethylpiperazine suggest that choice of solvent is very important when using δ_{ae} as a test of conformational preference. Both solvents chosen by Lambert and Keske[7] may produce specific effects, arising for instance from hydrogen bonding or anisotropic shielding.

These nitrogen-containing compounds undergo a second type of conformational change, namely inversion at the nitrogen atom which might affect

§ Assuming that the failure to observe T_c for 1,4-dioxan is due to a low value of ΔG^*, and not to a small δ_{ae}.

the ring-inversion characteristics. Ring inversion must in fact be accompanied by inversion at the nitrogen atom if an equivalent conformation is to be achieved. The effect of symmetry and statistical weights of supposed transition states on the entropies of activation also need to be considered.

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