Barriers to Nitrogen Inversion in Six-membered Rings. Ring and Nitrogen Inversion in Some Methylene Bridged Bisheterocycles

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A complete temperature dependent line shape analysis of 2,2'-bistetrahydro-1,2-oxazinylmethane and coalescence temperature measurements on 2,2'-bis-3,6-dihydro-1,2-oxazinylmethane, 2,2'-bis-1,2-oxazolidinylmethane and 3,3'-bistetrahydro-1,3-oxazinylmethane are reported. Joining the nitrogen atoms in the two heterocyclic rings *via* a methylene bridge has a negligible effect upon the ring inversion barrier, but substantially lowers the nitrogen inversion barrier. The relevance of these results to the current controversy over the barrier to nitrogen inversion in six-membered rings is discussed.

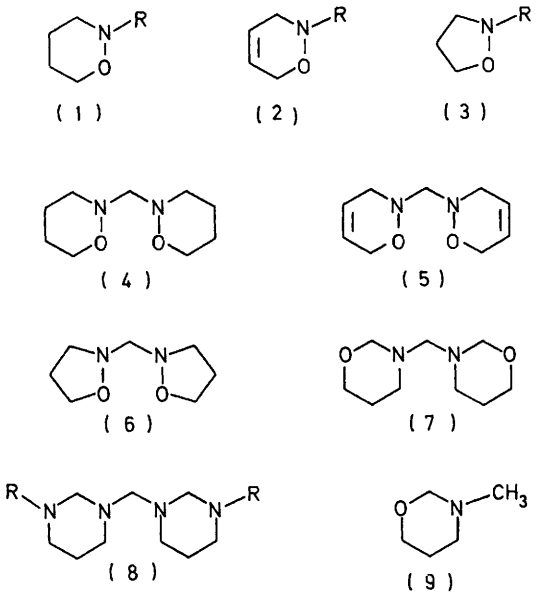
THERE is currently a controversy over several aspects of nitrogen inversion and ring inversion in six-membered rings.[1,2] This paper considers two of these aspects, the nature of the process observed to have a barrier of *ca.* 13 kcal mol^{-1} in tetrahydro-1,2-oxazines (1) and the effect of β-heteroatoms on nitrogen and ring inversion.

Katritzky and his co-workers (KCO) [1] have considered the possibility that nitrogen inversion barriers in such

[1] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Chem. Comm.*, 1975, 255.

[2] F. G. Riddell and H. Labaziewicz, *J.C.S. Chem. Comm.*, 1975, 766.

rings can be derived from the barrier in the simplest such ring, *N*-methylpiperidine,[3,†] by assigning increments to



the various significant structural features which make a given ring different from *N*-methylpiperidine. Such procedures are fraught with difficulties, particularly since there is no *a priori* reason why the effects of structural modification on nitrogen inversion barriers should be additive. On the contrary, it might seem that one structural modification should interact with and modify the effect of another one to the extent that the effects of such modifications should not be additive. For example, in the analysis of ^{13}C chemical shifts in cyclic compounds by such an additivity scheme it is frequently necessary to introduce 'joint parameters' which represent the interaction between the effects of two structural modifications.[4] We thus feel that such schemes of additivity should be approached with some scepticism, and before accepting them they should be examined from several aspects.

The most important point to consider, since almost any limited set of data can be made to fit an equation with a few constants, is whether the solution proposed is unique. Do the data lead inexorably to the scheme proposed or could another scheme accommodate the facts equally well? Other points to consider are the various predictions that can be made on the basis of a scheme, and the soundness of any statistical techniques used to derive it.

One of us has shown [2] that an alternative scheme to that proposed by KCO [1] is possible, based on a standard statistical least squares analysis. Whilst we are not as a result fully convinced proponents of this alternative scheme it does have the merit of giving to the two important points of controversy mentioned in the opening paragraph, a coherent explanation which agrees with our previous deductions from stepwise arguments.

Thus we have deduced from comparisons of similar compounds and from solvent effects that the *ca.* 13 kcal mol^{-1} process in tetrahydro-1,2-oxazines [5] is due to nitrogen inversion and that the effect of a β-heteroatom is to lower the nitrogen inversion barrier.[2] KCO have concluded,[1] on the basis of their empirical scheme that the former process is due to ring inversion and that the effect of a β-heteroatom is to raise the barrier to nitrogen inversion.

We now reconsider these questions and present new evidence, supporting our earlier interpretation.[2] If we keep in mind the logical precept that a prediction proven to be true is not necessarily conclusive support for a scheme, we should also remember that a proven fact incapable of explanation in one scheme necessarily invalidates that scheme.

The main evidence that nitrogen inversion is the observed process in the tetrahydro-1,2-oxazines (1) is that the barrier measured (13.7 kcal mol^{-1}) is very similar to that measured for the dihydro-oxazines (2) (*ca.* 13.5 kcal mol^{-1}) and the oxazolidines (3) (15.6 kcal mol^{-1}).[5] Certainly in the five-membered ring, and most probably in the cyclohexene analogue, one expects ring inversion to be so much more rapid than nitrogen inversion that there is little doubt that these barriers are for nitrogen inversion. Secondly, though perhaps less convincingly, the effects of hydrogen bonding solvents are to raise the barriers in all these compounds.[2,5] It is clear that only during nitrogen inversion must a hydrogen bond to nitrogen be broken.

In addition to this evidence, a third method of assigning the process in (1) can be suggested. If all three series show a consistent set of substituent effects on the observed barrier the web of circumstantial evidence favouring nitrogen inversion is considerably strengthened. To perform this experiment we have condensed the parent compound in each series (1—3; R = H) with formaldehyde to form the bisheterocycles (4)—(6). We can, in these compounds, not only test the substituent effect upon the barrier, but also check the assertion of KCO that a β-nitrogen atom increases the nitrogen inversion barrier.

The argument can be strengthened further by the preparation and examination of the bistetrahydro-1,3-oxazinylmethane (7). In this compound, as closely related to (1)—(6) as possible, the observed process should be ring inversion,[6] and therefore the effect of bridging two ring nitrogen atoms by a methylene group can be measured.

Compounds (4)—(7) are stereochemically intriguing.

† In all this work nitrogen atoms in the ring skeleton bear alkyl substituents avoiding the complication of hydrogen exchange in the NH compounds. The simplest compound in this series is therefore *N*-methylpiperidine.

[3] See for example J. B. Lambert and W. L. Oliver, *J. Amer. Chem. Soc.*, 1969, **91**, 7776.

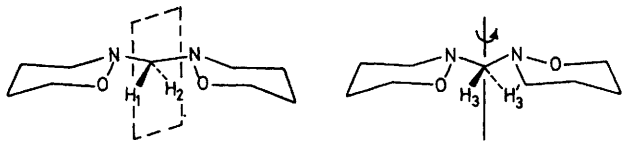
[4] G. M. Kellie and F. G. Riddell, *J. Chem. Soc.* (*B*), 1971, 1030.

[5] F. G. Riddell, J. M. Lehn, and J. Wagner, *Chem. Comm.*, 1968, 1403.

[6] J. M. Lehn, P. Linscheid, and F. G. Riddell, *Bull. Soc. chim. France*, 1968, 1172.

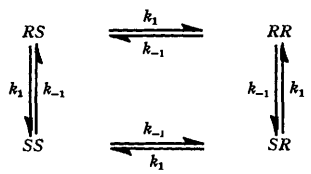
If either nitrogen or ring inversion becomes slow on the n.m.r. time scale then the nitrogen atoms or the rings respectively become chiral and two diastereoisomers are observed. This phenomenon has previously been reported by one of us in the bishexahydropyrimidylmethane series [7] (8) where the diastereoisomerism is due to slow ring inversion.

For (4), when nitrogen inversion is slow on the n.m.r. time scale, two sets of conformations are expected, a *meso*-set (4a), with a time-averaged plane of symmetry, and a racemic set (4b) with a time-averaged two-fold



axis of symmetry. From these symmetry elements it is simple to deduce that the spectrum of the bridging methylene in (4a) should be an AB quartet and in (4b) a singlet.

The exchange process can be drawn as in the Scheme



SCHEME

where *R* and *S* refer to the absolute configuration on nitrogen. As a consequence H_1 interconverts with H_2 *via* $H_3 + H_3'$ [reaction (1)]. The relative proportions of

$$H_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H_3 \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} H_2 \qquad (1)$$

the *meso* and racemic sets are of course determined by the ratio $k_1 : k_{-1}$.

We hoped that one or more of the three compounds (4)—(6) would provide lineshape changes suitable for a complete lineshape analysis, and thus give reasonably accurate kinetics for the process. In the event the only one that fulfilled our hopes was (4) in $CFCl_3$ solution. We therefore report in Table 1 accurate kinetics for this system, but only report coalescence temperature measurements for the others (Table 2) where the line shape changes were obscured by overlapping coalescences.

RESULTS

Compounds (4)—(7) have temperature-dependent n.m.r. spectra which are reported in detail in the Experimental section. The most striking feature is that in each case, the methylene group joining the two rings appears as one singlet at room temperature and as two signals of different intensity, a singlet and an AB quartet, at low temperature, usually *ca.* −80°. In the case of (5)—(7), approximate coalescence temperatures were determined. Approximate rate constants for the processes concerned, at these coalescence temperatures were then calculated, by treating the two signals as if they were singlets or AB quartets.

TABLE 1

N.m.r. rate data for (1)

T/°C	Racemic (%)	k/s^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}
−48	30.4	5.2	12.32
−46	30.7	8.0	12.24
−44	30.9	9.6	12.27
−42	31.26	12.2	12.28
−40	31.54	14.8	12.29
−38	31.80	19.2	12.28
−36	32.06	23.9	12.28
−34	32.50	33.7	12.22
−32.5	32.66	42	12.00
−28.5	33.20	59	12.25
−23.5	33.82	78	12.37
−18.5	34.56	123	12.37
−9	36.16	180	12.67

Full lineshape computer fitting of (4) was carried out using the DNMR 3 program of Binsch. Appropriate chemical shifts and populations (see Table 1) for each temperature were determined by interpolation from high and low temperature measurements. Visual matching of spectra was carried out in the range where broadening of spectra gave line-widths greater than three times the line-width in the absence of exchange.

Rate constants shown in Table 1 are those for the inversion of one nitrogen in the racemic form; that is the form whose n.m.r. spectrum is a singlet; values of $\Delta G^{\ddagger}$ are calculated from these rate constants using the Eyring equation with transmission coefficient 1. The rate constant for nitrogen inversion in a *meso*-form will be about one-half that of the racemic form (precisely, the rate constants will be related by a factor $p_r/100 - p_r$ where p_r is the percentage of racemic form as given in Table 1). The barrier to nitrogen inversion in a *meso*-form will as a result be *ca.* 0.35 kcal mol^{-1} higher than in the racemic form.

Table 3 shows the barriers determined and several other relevant barriers [7,9] for compounds (1)—(7) and (9). The effect of bridging two rings by a methylene group on barriers to ring inversion is shown by comparing results for (7) and (9). That the barrier observed in (9) is a ring inversion [6] has not been questioned in the literature, and the observed barrier for (9) falls into line with other barriers widely accepted to arise from ring inversion.[8] In fact, bridging has a negligible effect on ring inversion. This may also be seen in comparing the barriers of the bridged hexahydropyrimidines (8) [7] with those of the unbridged compounds.[9]

In contrast, for the three rings of types (1)—(3) the effect of joining two such rings by a methylene group [*i.e.* compare (1) and (4), (2) and (5), and (3) and (6)] produces a markedly lower barrier for the process involved. These results suggest first that the process in

[7] F. G. Riddell, *J. Chem. Soc.* (*B*), 1971, 1028.
[8] J. E. Anderson, *Topics Current Chem.*, 1974, **45**, 140.
[9] F. G. Riddell, *J. Chem. Soc.* (*B*), 1967, 560.

compounds (1)—(6) is not ring inversion, *i.e.* it is probably the other likely process, nitrogen inversion, and secondly that the effect of a β-heteroatom is to lower the barrier to this nitrogen inversion process.

It is ill advised in the field of heterocyclic conformational analysis to draw general conclusions from specific examples, but these results, taken with the comparison of compounds (1)—(3) and the effect of hydrogen bonding solvents on barriers which we discussed in the introduction, together suggest that the process with a barrier of *ca.* 13 kcal mol^{-1} in the 1,2-oxazines is nitrogen inversion, and that the effect of β-heteroatoms is to lower such barriers.

In accord with the logical precept outlined earlier, whilst these results do not prove our proposed scheme [2] to be correct, they cast very grave doubts on the alternative suggestions of KCO.[1]

EXPERIMENTAL

The compounds were prepared either by reaction of the parent amine with paraformaldehyde in benzene solution in a Dean and Stark apparatus, in which case the progress of the reaction was monitored by n.m.r. spectroscopy, or by reaction of an aqueous solution of the amine with excess of 40% aqueous formaldehyde solution as described previously.[9] B.p.s are: (4), 51° at 0.1 mmHg; (5), 60° at 1 mmHg; (6), 95° at 5 mmHg; and (7), 90° at 0.5 mmHg. The compounds were identified by their n.m.r. spectra (Table 4) and by their mass spectra which showed the expected molecular ions and fragmentation patterns.

Spectra were recorded at 90 MHz on a Perkin-Elmer R32 spectrometer equipped with a standard variable temperature probe and frequency counter. Measurements of temperature (made separately from the experimental runs) proved the temperature settings to be accurate to within 1°.

Plots of chemical shifts *versus* temperature were made for the methylene bridge hydrogens in $CFCl_3$ solutions of (4) and (6). These graphs, given in Supplementary Publication No. SUP 21937 (3 pp.),* were used to estimate T_c for these systems and obtain estimates of chemical shifts and relative populations where required.

TABLE 2

Kinetic data for compounds (4)—(7) †

	Compound (solvent)	Resonance observed	Δν(T/°C)	J/Hz	T_c/°C	$\Delta G^{\ddagger}$/kcal mol^{-1}
(4)	($CFCl_3$)	Bridge *	18.0		−28 ± 2	12.4
(5)	($CFCl_3$)	6-H	44.5 (−95)	15	−66 ± 2	10.2
		3-H	29 (−95)	14	−72 ± 3	9.8
(6)	$CFCl_3$	Bridge *	17.5		−51 ± 2	11.2
	$CDCl_3$	3-H	63		−32 ± 4	11.6
	CD_3OD	5-H	*ca.* 6		−48 ± 5	11.9
(7)	CD_2Cl_2–$CFCl_3$	2-H	24 (−90)	10	−66 ± 3	9.9

* Data taken from graphs in SUP 21937. † Transmission coefficient taken as 1 in all cases.

TABLE 3

Comparison of ring and nitrogen inversion barriers (kcal mol^{-1})

Compound	Monocyclic Barrier	Solvent	Ref.	Compound	Bridged Barrier	Solvent
(1; R = Me)	13.7	CH_2Cl_2	5	(4)	12.3	$CFCl_3$
(2; R = Me)	13.5	$CDCl_3$	2	(5)	10.0	$CFCl_3$
(3; R = Me)	15.6	$CDCl_6$	5	(6)	11.6	$CDCl_3$
(9)	10.0	CF_2Cl_2	6	(7)	9.9	CD_2Cl_2–$CFCl_3$

TABLE 4

Room temperature ^{1}H chemical shifts (δ)

Compound	Solvent	Bridging methylene	CH_2N	CH_2O	OCH_2N	Other
(4)	$CFCl_3$	3.49(s)	2.78(t)	3.82(t)		1.60(m)
(5)	$CDCl_3$	3.81(s)	3.38(m)	4.34(m)		5.80(m)
(6)	$CFCl_3$	3.69(s)	2.98(t)	3.78(t)		2.18(m)
	$CDCl_3$	3.76(s)	3.16(t)	3.93(t)		2.23(m)
(7)	CD_2Cl_2	3.63(s)	2.94(t)	3.78(t)	4.30(s)	1.58(m)

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* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index Issue. Items less than 10 pp. are supplied as full-size copies.