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BARRIERS TO NITROGEN INVERSION IN 6-MEMBERED RINGS

NITROGEN INVERSION IN TETRAHYDRO-1,2-OXAZINES

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Abstract—A study of the nitrogen inversion process in the bicyclic oxazine, N-methyl-2-oxa-3-azabicyclo[2,2,2]octane, by ^{13}C NMR spectrocopy reveals a free energy of activation of 14.9 kcal mole^{-1}. Detailed examination of the kinetics of the process observed in the ^1H spectra of N-methyl tetrahydro-1,2-oxazine shows $\Delta H^{\neq}$ 15.1 ± 0.4 kcal mole^{-1} and $\Delta S^{\neq}$ 2.3 ± 1.5 cal mol^{-1} K^{-1}. It is concluded from the similarity in the activation parameters that both processes arise from nitrogen inversion.

There has recently been some controversy over the question of nitrogen inversion barriers in 6-membered rings.[1–3] One compound that is central to the whole problem is N - methyltetrahydro - 1,2 - oxazine (1). When we first investigated this system we suggested that the origin of the kinetic process observed in the ^1H NMR spectra was nitrogen inversion.[4] Subsequently Katritzky *et al.* suggested that ring inversion might equally account for our observations.[1]

Studies on methylene bridged heterocycles of general type 2 produced strong circumstantial evidence in favour of our view point, which now appears to be generally accepted.[5] To finalise the matter we now produce further evidence to support our views from a study of the bicyclic oxazine (3) and from a detailed study of the kinetics of the process in 1.

Bicyclo[2.2.2]octane derivatives, which have boat-like 6-membered rings, cannot possibly undergo ring inversion.[6] There is therefore no ambiguity as to the origin of any process observed in 3 which must arise from slowing of nitrogen inversion. Thus observation of a process in 3 with activation parameters similar to those in 1 would finally confirm the nature of the process in 1.

The principal difficulties in obtaining an accurate activation energy for the process in 1 are the overlap of the coalescing NCH_2 group with the N-Me resonance, and the presence of additional couplings to the C(4) methylene group.[4] The effect of additional small couplings has been studied by Drakenburg[7] and is to lower the apparent coalescence temperature thus lowering the apparent free energy of activation. To avoid these difficulties we first tried removing the Me resonance by deuteriation and removing the spin couplings by homonuclear decoupling. The results were unsatisfactory for kinetic measurements. We therefore chose to study the heptadeuterio derivative (4) with heteronuclear deuterium decoupling.

There is a distinct lack in the literature of high quality studies of activation parameters for nitrogen inversion to compare with, for example, Anet and Bourn's study of the kinetics of inversion of the cyclohexane ring,[8] or the more recent work of Binsch *et al.* on nitrogen inversion in an aziridine, and ring inversion in cyclohexane derivatives.[9] This lack provided an additional stimulus to our work. Such studies of sufficient quality as do exist, indicate that the entropy of activation for nitrogen inversion in a 6-membered ring should be small and possibly positive.

In the inversion of a 6-membered nitrogen-containing ring such as tetrahydro - 1,2 - oxazine, in which the equatorial conformation is overwhelmingly favoured,[10,11] both ring and nitrogen inversion processes are required to complete the inversion process (e→e* in Fig. 1). We and others have generally assumed that in multiple step processes of this kind, to go from e to e* requires two distinct processes, nitrogen inversion N (or N*) and ring inversion R (or R*) and that there are two distinct transition states on the route.

An alternative mechanism deserves consideration involving synchronous inversion of the nitrogen and ring with only one transition state. This mechanism implies that the N atom inverts at or near the point on the potential energy surface where ring inversion occurs and that the two relevant vibrational modes of the molecule

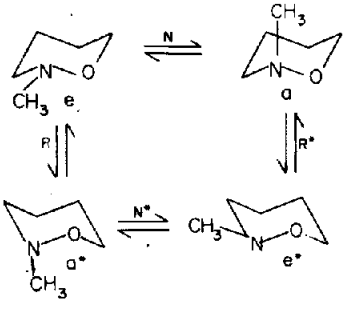


Fig. 1.

are coupled. The simplest transition states for such a process would require five of the seven heavier atoms in the skeleton to be coplanar (**5**). This implies a greater degree of order in the transition state than for the earlier discussed mechanism and would thus probably give rise to a somewhat lower entropy of activation. The strain involved in a transition state such as **5** implies that the enthalpy of activation should be greater than for a two step process.

RESULTS

The ^1H decoupled ^{13}C spectrum of **3** at 0° shows seven lines, consistent with slow inversion of the N atom. On warming, the signals attributed to the N-Me group and the two bridgehead carbons remain sharp, but the signals from the four C atoms in the ethylene bridges broaden. Coalescences for these lines are at 22 ± 3° and 50 ± 5°. At 120° the spectrum consists of five lines consistent with rapid nitrogen inversion (Table 1). The free energies of activation calculated from the coalescences are 14.93 ± 0.1 and 14.89 ± 0.2 kcal mole^{-1} respectively. *The free energy of activation for nitrogen inversion in* **3** *is therefore* 14.9 ± 0.1 *kcal mole*$^{-1}$.

The ^1H spectra of the C(3) H atoms in the heptadeuterioxazine (**4**) were studied at varying temperatures with deuterium decoupling. Full line shape analysis of the coalescing AB spectrum gave the rate data recorded in Table 2, from which the Eyring activation parameters were determined to be $\Delta H^{\neq}$ 15.1 ± 0.4 kcal mole^{-1}, $\Delta S^{\neq}$ + 2.3 ± 1.5 cal mole^{-1} K^{-1}.

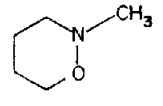
The agreement between the activation parameters for **3** and **4** is within the quoted 95% confidence limits. There can be no doubt remaining therefore that the process observed in the oxazines arises from slowing of nitrogen inversion.

DISCUSSION

Nelsen and Weisman[6] studied the nitrogen inversion process in the aza bicyclo[2.2.2]octane derivative (**6**) and recorded a barrier of 6.6 kcal mole^{-1}. Addition of the α oxygen to give **3** considerably increases the barrier, in accord with our views on α effects of heteroatoms.[2] It is interesting that the chair-boat change on going from **4** to **3** does not affect the inversion barrier by very much. We therefore conclude that the dihedral angle about the N–O bond, *ca.* 67° in **4**,[12] and much smaller than this in **3**, does not drastically affect the nitrogen inversion barrier.

Table 1. ^{13}C NMR data for N - methyl - 2 - oxa - 3 - azabicyclo[2.2.2]octane (ppm downfield from TMS for *ca.* 20% soln in $CDCl_3$)

Atom Number	Temperature	
	-0.5°	121°
1	66.38	67.12
4	50.97	52.13
$3CH_3$	41.96	42.38
Bridge	23.93	24.62
	23.40	(Tc+22±3°)
Bridge	24.88	20.89
	15.05	(Tc+50±5°)



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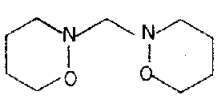

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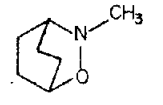

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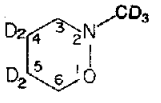

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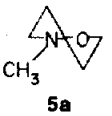

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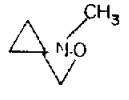

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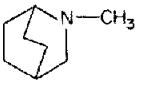

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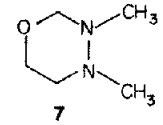

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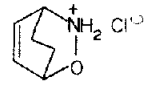

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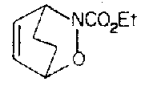

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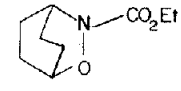

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Table 2. Rate data for compound (**4**)

Temp (°C)	k_{obs} from fitting	k_{calc} from activation parameters
-5	7.5	8.0
0	14	13.7
5.5	24	23.4
10	36	38.2
15	59	62.1
20	105	99.2
24	140	142.8

The data lead to $\Delta H^{\neq}$ 15.1±0.4 kcal mole^{-1}, $\Delta S^{\neq}$ + 2.3±1.5 cal mole^{-1}K^{-1}. For a ca 5% solution in $CDCl_3$.

The entropy of activation in **4** is small and slightly positive. Its magnitude +2.3 cal mole^{-1} K^{-1} is identical within experimental error with that found earlier for 3,4 - dimethyltetrahydro - 1,3,4 - oxadiazine **7** (+2.8 eu)[13] and is consistent with the two step mechanism discussed earlier.

EXPERIMENTAL

Preparation of 2 - *oxo* - 3 - *azabicyclo*[2.2.2]*oct* - 5 - *ene hydrochloride* (**8**). A soln of 1 - chloro - 1 - nitrosocyclohexane (27.6 g; 0.19 mol) cyclohexa - 1,3 - diene (30 g; 0.375 mol) in anhyd benzene (175 ml) containing EtOH (20 ml) was stored at +4° for two days. The solid product was collected by filtration, washed with a little cold benzene and dried *in vacuo*. The crude yield of **8** was 13.7 g (49%). This light brown crystalline material was used without further purification for the preparation of **9**. A small sample of material was recrystallized from isopropanol to give colourless needles m.p. 162–163° (dec). (Found: C, 49.01; H, 6.90; N, 9.36; Cl, 24.03. $C_6H_{10}ClNO$ requires: C, 48.82; H, 6.83; N, 9.49; Cl, 24.02%).

Preparation of N - *ethoxycarbonyl* - 2 - *oxa* - 3 - *azabicyclo*[2.2.2]*oct* - 5 - *ene* (**9**). A stirred suspension of **8** (32.7 g) in ether (400 ml) and water (5 ml) was treated alternately with K_2CO_3 (30 g) and ethyl chloroformate (26.5 g) in portions. The mixture was stirred under reflux for 1 hr then stood at room temp. overnight. The ether layer was decanted, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was distilled to give **9** (24 g), b.p. 120–124°/2 mm. (Found: C, 58.81; H, 6.99; N, 7.56. $C_9H_{13}NO_3$ requires: C, 59.00; H, 7.15; N, 7.65%).

Preparation of N - *ethoxycarbonyl* - 2 - *oxa* - 3 - *azabicyclo*[2.2.2]*octane* (**10**). A soln of **9** (8 g) in MeOH (30 ml) containing Pd–C (10%; 150 mg) was stirred under H_2 at room temp. and one atmosphere until all H_2 uptake had ceased, (<1 hr). The catalyst was removed by filtration, the solvent removed under reduced pressure and the product distilled to give **10** (7.35 g), b.p. 88–90°/0.6 mm. (Found: C, 58.16; H, 8.04; N, 7.48. $C_9H_{15}NO_3$ requires: C, 58.36; H, 8.16; N, 7.56%).

Preparation of N - *methyl* - 2 - *oxa* - 3 - *azabicyclo*[2.2.2]*octane* (**3**). This compound was prepared by LAH reduction of **10** following the literature,[15] b.p. 70–72°/15 mm. (Found: *m/e* 127.1004. $C_7H_{13}NO$ requires: *m/e* 127.0998).

The preparation of **4** was accomplished by standard methods as outlined below. Diethylacetylenedicarboxylate was reduced by Pd/C and deuterium to tetradeuterio diethylsuccinate. This succinate ester was reduced by LAH to the diol, and then converted to the tetradeuterio - 1,4 - dibromobutane. Reaction with N-hydroxyurethane and reduction with LAD gave the heptadeuterio derivative (**4**).[14] Monitoring of the H/D ratio at various stages showed >97% incorporation of D at each site on the ring and >99% D incorporation in the N-Me group.

Variable temp spectra were recorded on the Edinburgh University Varian XL100 spectrometer. For **4** D decoupling and ^{19}F internal lock (C_6F_6) were employed. Below the low temp. slow exchange limit (−10°) there was a negligible change in the chemical shift difference and coupling constant, which were therefore used for the computations. The effective value of T_2 was extrapolated from the low and high temp. limit line widths. Computations were performed using the program DNMRS on the Stirling University computer.

The same spectrometer was used in its ^{13}C mode for the spectra of **3**.

In both cases temps. were measured by a copper constantan thermocouple positioned in the gas stream approximately 1 cm below the sample tube and recorded on a digital thermometer. Measurements of temp. are estimated to be accurate to ±0.5° and reproducible to ±0.5°.

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REFERENCES

[1]I. J. Ferguson, A. R. Katritzky and D. M. Read, *J. Chem. Soc.* Chem. Comm. 255 (1975).
[2]F. G. Riddell and H. Labaziewicz, *Ibid.* Chem. Comm. 766 (1975).
[3]F. G. Riddell and J. E. Anderson, *Ibid.* Perk II, 588 (1977).
[4]F. G. Riddell, J. M. Lehn and J. Wagner, *Chem. Comm.* 1403 (1968).
[5]A. R. Katritzky, personal communication.
[6a]J. M. Lehn and J. Wagner, *Chem. Comm.* 414 (1970); [b]S. F. Nelsen and G. R. Weisman, *J. Am. Chem. Soc.* **98**, 1842 (1976).
[7]T. Drakenburg and R. E. Carter, *Organic Magn. Res.* **7**, 307 (1975).
[8]F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.* **89**, 760 (1967).
[9a]D. Hofner, I. Tamir and G. Binsch, *Organic Magn. Res.* **11**, 172 (1978); [b]D. Hofner, S. A. Lesko and G. Binsch, *Ibid.* **11**, 179 (1978).
[10]R. A. Y. Jones, A. R. Katritzky, S. Saba and A. J. Sparrow, *J. Chem. Soc.* Perk. II, 1554 (1974).
[11]F. G. Riddell, M. H. Berry and E. S. Turner, *Tetrahedron* **34**, 1415 (1978).
[12]F. G. Riddell, P. Murray-Rust and J. Murray-Rust, *Tetrahedron* **30**, 1087 (1974).
[13]F. G. Riddell and A. J. Kidd, *J. Chem. Soc.* Perk. II, 1816 (1977).
[14]F. G. Riddell and D. A. R. Williams, *Tetrahedron* **30**, 1083 (1974).