Conformational Analysis of 3,4-Dimethyltetrahydro-1,3,4-oxadiazine

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Contrary to a recent report, the diequatorial conformation makes no appreciable contribution to the title compound. Evidence is presented that the preferred conformation is 3-axial-4-equatorial. The activation parameters or the conformational process in this compound are: $\Delta H^{\ddagger}$ 13.25 ± 0.14 kcal mol^{-1}, $\Delta S^{\ddagger}$ +2.8 ± 0.6 cal mol^{-1} K^{-1}, possibly owing to slowing of a nitrogen inversion process.

KATRITZKY and his co-workers (hereafter referred to as KCO) have recently reported on the conformational analysis of some tetrahydro-1,3,4-oxadiazines.[1] For the *NN'*-dimethyl derivative (1) they give a free energy of activation of 12.6 kcal mol^{-1} at the coalescence temperature (*ca.* 256 K) for a process which they describe as slow ' non-passing ' ring inversion. They suggest, on the basis of comparison of *N*-methyl conformational free energy differences in related compounds, that the major conformation is (1ae), and they assign a minor doublet in the low-temperature, slow-inversion-limit spectrum, to the (1ee) conformation. Although this doublet would, on their interpretation, arise from *ca.* 20% of the minor conformation, no other lines attributable to this conformation were observed.

RESULTS

A full lineshape analysis of the ^{1}H n.m.r. spectrum of the coalescing AB quartet of the C-2 protons in compound (1) over a range of temperatures gives the activation parameters $\Delta H^{\ddagger}$ 13.25 ± 0.14 kcal mol^{-1}, $\Delta S^{\ddagger}$ +2.8 ± 0.6 cal mol^{-1} K^{-1} (Table). These agree well with the approximate free energy of activation measured by KCO (12.6 kcal mol^{-1}), attributed to slowing of ' non-passing ' ring inversion.[1] However, as shown below, slow nitrogen inversion cannot be ruled out as the origin of these observations, and may indeed be responsible for the observed changes.

Rate data * for compound (1)

Temp. (°C)	k_{obs} from fitting	k_{calc} from activation parameters
+5	1 000	934
−5	340	368
−16	125	122
−24	54	51
−32	20	20.4
−40	8.0	7.6
−45	4.0	3.98

* These data lead to $\Delta H^{\ddagger}$ 13.25 ± 0.14 kcal mol^{-1} and $\Delta S^{\ddagger}$ +2.8 ± 0.6 cal mol^{-1} K^{-1}. For a *ca.* 10% solution in CDCl_3

We agree with the assumption of KCO that the preferred conformation is (1ae). Experimental proof may be found in the C-2 proton geminal coupling constant at slow exchange, found to be 10.1 Hz at *ca.* −80 °C. This coupling is much closer to that found in the model compound (2) with an axial *N*-alkyl group (*J* 10.5 Hz) than in the model compound (3) with the *N*-methyl group constrained to be equatorial (*J* 7.5 Hz).[2] In addition, the chemical shift of the C-2 proton in the 2-*p*-nitrophenyl derivative (4) (δ 5.70) is much closer to that of the model (5) (δ 5.62) than to that of (6) (δ 4.21).

The minor doublet in the low-temperature spectra of compound (1) does not however arise from the diequatorial conformation as suggested by KCO. It comes from the equatorial C-5 proton. The triplet observed at ambient temperature for the C-5 protons at δ *ca.* 2.47 broadens as the temperature is lowered, and reappears at δ *ca.* 2.91 and 2.11 (Figure 1). Decoupling of the resonances due to the C-6 protons or the axial C-5 proton produces the expected changes in the equatorial C-5 proton signal [Figure 1(e)]. There is no broadening and resharpening of the methyl peaks as the temperature is lowered, as would occur were the explanation of KCO correct. Moreover, the value of the supposed equilibrium constant can be calculated to be 0.17, in reasonable agreement with that reported (0.22). Finally, the non-appearance of any other lines due to a diequatorial conformation in such a simple spectrum must argue against its presence. An upper limit of 5% can be placed on the proportion of the diequatorial conformation on the basis of our estimate of detectability, giving a free energy difference at 250 K of >1.5 kcal mol^{-1}.

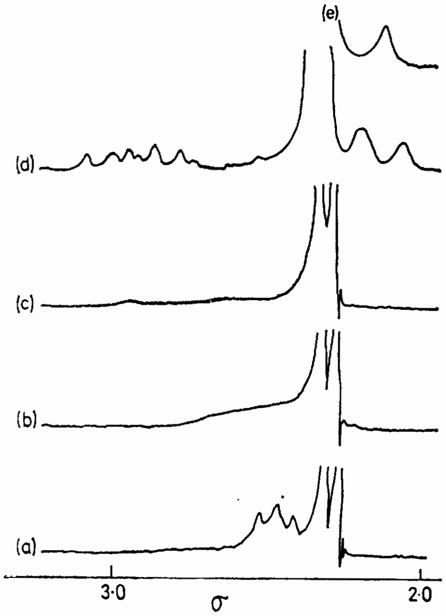

FIGURE 1 90 MHz ^{1}H N.m.r. spectra of 3,4-dimethyltetrahydro-1,3,4-oxadiazine: (a) 33.5 °C; (b) 0 °C; (c) −20 °C; (d) −65 °C; (e) −65 °C with decoupling at δ *ca.* 2.91

DISCUSSION

Our purpose in preparing and examining this compound was two-fold: to determine its preferred conform-

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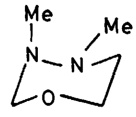
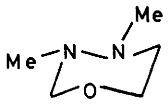
[1] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Perkin II*, 1976, 1861.

[2] F. G. Riddell and J. M. Lehn, *J. Chem. Soc.* (*B*), 1968, 1224.

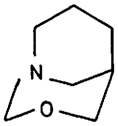
ation(s), and to see if its conformational energetics could shed any light on the problem of ring and nitrogen inversion processes in six-membered rings.[3,4] The observed conformation is that expected from comparison of free energy differences in related systems. The large conformational free energy difference in *N*-methylpiperidine (7) (2.7 kcal mol^{-1}) [5] is reduced to *ca.* 0 in *N*-methyltetrahydro-1,3-oxazine (8) [2] owing to reduction of non-bonded interactions and a favourable anomeric effect. The free energy difference between the diequatorial and axial equatorial conformations in *NN'*-dimethylhexahydropyridazine (9) is small (*ca.* 0.4 kcal mol^{-1}),[6] and so much smaller than in *N*-methylpiperidine as to indicate a tendency (*ca.* 2.3 kcal mol^{-1}) for the pairs of electrons on nitrogen to be *gauche* rather than *trans*. Given that the β-oxygen atom in tetrahydro-1,3-oxazine reduces the free energy difference to zero with respect to piperidine, we should expect the axial-equatorial conformation in the 1,3,4-oxadiazines to be *ca.* 2.3 kcal mol^{-1} more stable than the diequatorial. This, it should be emphasised, is an extremely rough estimate (possibly ± 0.5 kcal mol^{-1}).



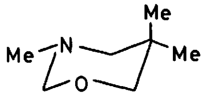
(1ae)



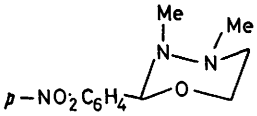
(1ee)



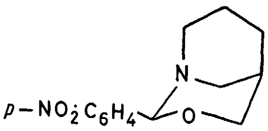
(2)



(3)



(4)



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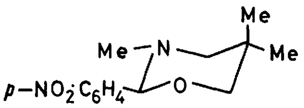

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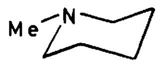
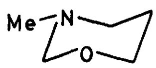
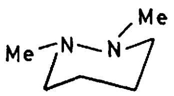


(7)



(8e)



(9ee)

The conformational route map for compound (1) is shown in Figure 2. Calculation on the basis that all the processes shown are of equal probability gives a transmission coefficient of 0.4 for the observed process leading to an entropy of activation of -1.8 cal mol^{-1} K^{-1}. The observed entropy of activation of $+2.8 \pm 0.6$ cal mol^{-1} K^{-1} is significantly greater (by *ca.* 5 cal mol^{-1} K^{-1}) than this prediction. It is necessary for at least two of the processes shown in Figure 2 to be slow to account for the observed spectral changes. Studies on the hexahydropyridazines have enabled the magnitude of each barrier to be assigned.[6,7] The most rapid processes in the hexahydropyridazines are nitrogen inversions involving the diaxial conformation ($\Delta G^{\ddagger}$ *ca.* 7.5 kcal mol^{-1}). It is likely that this will also be the case in the oxadiazine series. The only combinations of slow processes compatible with our results are then, in the nomenclature of Figure 2, 1,2; 1,2,3; 1,2,4; 1,3,4; and 1,2,3,4. Any other combinations of slow processes lead to no observable change. The only concrete conclusion to be drawn therefore is that the barrier to process 1, ' passing ring inversion,' is greater than or equal to the observed barrier.

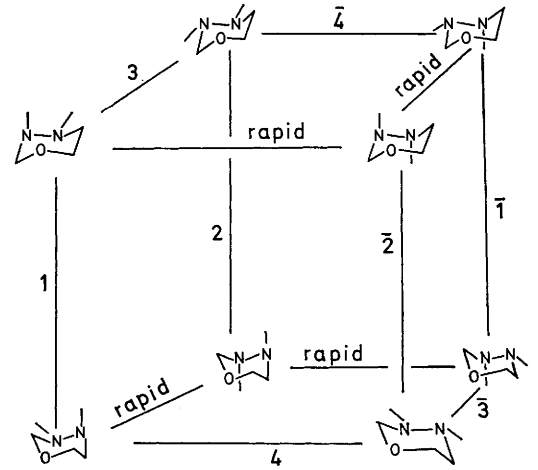


FIGURE 2 Route map for ring and nitrogen inversion in 3,4-dimethyltetrahydro-1,3,4-oxadiazine

It is possible however to speculate further. The barriers in the hexahydropyridazines, related to the diequatorial conformation as zero energy, and using the nomenclature of Figure 2 are 1, 11.5; 2, 10.2; 3, 12.6; and 4, 12.6 kcal mol^{-1}. Transposing these values to the oxadiazines, relative to the diequatorial oxadiazine as zero energy, requires a reduction in the value for 3 of *ca.* 1.8 kcal mol^{-1} (negative β-oxygen effect) * and little or no adjustment to the other barriers. If we now readjust our zero energy point to the axial-equatorial conformation, which is 0.4 kcal mol^{-1} higher in energy than the diequatorial in the hexahydropyridazine series, but probably as much as 2.3 kcal mol^{-1} lower in the

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* This represents a modification of the β-oxygen effect of -2.7 kcal mol^{-1} suggested in ref. 3, when the correct nitrogen inversion barrier in 1,4,2-dioxazines is taken into account (F. G. Riddell, M. H. Berry, and E. S. Turner, in preparation).

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

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

[5] P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *J.C.S. Chem. Comm.*, 1974, 825.

[6] S. F. Nelsen and G. R. Weisman, *J. Amer. Chem. Soc.*, 1974, **96**, 7111; S. F. Nelsen and J. M. Buschek, *J. Amer. Chem. Soc.*, 1974, **96**, 6987.

[7] F. G. Riddell, unpublished work.

oxadiazines, we must add 2.3 — 0.4 = 1.9 kcal mol^{-1} to each barrier.* Thus, probable barriers in the oxadiazine series become 1, 13.4; 2, 12.1; 3, 12.7; and 4, 14.6 kcal mol^{-1}. The order in which they would be expected to ' freeze out ' is therefore 4, 1, 3, 2. Thus, possibility 1, 3, 4 for the observed process mentioned above becomes a likely contender, and the activation energy of the most rapid process and the last to be frozen out, 3, is 12.7 kcal mol^{-1}, in good agreement with the experimental results.

EXPERIMENTAL

Preparation of 3,4-*Dimethyltetrahydro*-1,3,4-*oxadiazine* (1).—1,2-Dimethylhydrazine (1.42 g) was added to a solution of ethylene oxide (1.1 g) in ethanol (10 ml) at 0 °C. The solution was allowed to warm to room temperature overnight. Removal of volatile material yielded crude 1-(2-hydroxyethyl)-1,2-dimethylhydrazine (1.98 g, 81%) as an oil, which was used without further purification. This product (0.67 g) and paraformaldehyde (0.19 g) were heated under reflux in benzene (10 ml) for 2.5 h. Distillation yielded 3,4-dimethyltetrahydro-1,3,4-oxadiazine as a liquid, b.p. 119° (0.4 g, 55%) (Found: *m/e* 116.0953. Calc. for $C_5H_{12}N_2O$: *M*, 116.0950).

Preparation of 3,4-*Dimethyl*-2-p-*nitrophenyl*-1,3,4-*oxadiazine* (4).—*p*-Nitrobenzaldehyde (0.36 g) and the crude hydroxyethyldimethylhydrazine (0.25 g) were heated under reflux in benzene (10 ml) for 2 h. Evaporation yielded a solid which was recrystallised twice from light petroleum (b.p. 60—80°); yield 0.18 g (32%), m.p. 94—97° (Found: *m/e* 237.1091. Calc. for $C_{11}H_{15}N_3O_3$: *M*, 237.1114).

N.m.r. spectra were recorded with a Perkin-Elmer R32 spectrometer operating at 90 MHz fitted with the standard variable-temperature equipment and frequency counter. Calibration of the temperature control unit over its entire range revealed all temperatures to be within ±1.5 °C of the control settings and reproducible to within ±0.5 °C. The temperature in the sample was uniform to within ±0.5 °C over the bottom centimetre of the tube. The effective chemical shifts and coupling constants were obtained by extrapolation of values obtained down to −90 °C (supercooled solution) and were calibrated with the frequency counter. The effective transverse relaxation times were obtained from measurements of linewidth at half height ($W_{\frac{1}{2}}$) in the regions of slow (−50 to −90 °C) and rapid (+20 to +40 °C) exchange, by assuming a linear variation of $W_{\frac{1}{2}}$ with temperature.

Computations were performed on the University Elliott 4130 computer using the program DNMRS. Errors on the enthalpy and entropy of activation are 95% confidence limits from a least-squares fit of the Eyring rate equation.

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* This only alters the magnitudes of the barriers, not their relative values.