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CONFORMATIONAL EQUILIBRIA AND NITROGEN INVERSION IN TETRAHYDRO-1,2,5-OXADIAZINES

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Abstract—Conformational equilibria and nitrogen inversion barriers in some tetrahydro-1,2,5-oxadiazines have been investigated by ^{1}H NMR spectroscopy and by chemical equilibration. The conformational free energy differences obtained are: 4-methyl, 1.2 ± 0.2; 6-*p*-nitrophenyl, 1.4 ± 0.2 kcal mole^{-1}. Barriers to inversion of the N atom at position 2 are in the region 14.1–15.6 kcal mole^{-1}. The conformational behaviour of the tetrahydro-1,2,5-oxadiazine ring is shown to be composed of aspects of the behaviour of the tetrahydro-1,2-and 1,3-oxazine rings.

The conformational analysis of saturated heterocyclic systems containing three heteroatoms is proving to be a matter of considerable interest and fascination.[1] This is particularly true where the new heterocyclic ring contains fragments from other heterocycles whose conformational analysis is well documented, because the different conformational tendencies of these fragments must be reconciled in the new heterocyclic system being studied. This proved to be the case in the tetrahydro-1,4,2-dioxazine series (**1**) where the conflicting conformational properties of the tetrahydro-1,2- and 1,3-oxazine[6–10] rings (**2** and **3**) were shown to combine together.[1] Another closely related case is the tetrahydro-1,2,5-oxadiazine series (**4**) where comparison with the same two simpler heterocyclic systems should permit interesting and instructive comparisons to be drawn.

Previous preliminary reports of the tetrahydro-1,2,5-oxadiazine ring have been made by ourselves[11,12] and the Norwich group.[13,14] The activation parameters for inversion of the 2-N-Me group were found to be ΔH^+ 14.4 ± 0.1 kcal mole^{-1}, ΔS^+ −1.2 cal mol^{-1} K^{-1}, ΔG_c^+ 14.7 kcal mole^{-1} (+22°).

The synthesis of the compounds reported here were all carried out by previously outlined procedures.[11–14] ^{1}H NMR data at various temperatures are reported in Table 1.

The 2,4,5-trimethyl derivative (**5**) shows the expected but somewhat broadened spectrum at ambient temperature. On lowering the temperature certain resonances broaden further, notably the lower-field C-6H doublet. By −50° this resonance has resharpened into 2 doublets in the ratio *ca.* 14:1 ($\Delta G° = 1.2 \pm 0.2$ kcal mole^{-1}). Maximum broadening of the doublet occurs at +15 ± 5° (ΔG^+ *ca.* 15.5 kcal mole^{-1}). The coupling constant in the minor doublet is 10.8 ± 0.3 Hz and that in the major doublet is 9.2 ± 0.2 Hz. The corresponding couplings in the tetrahydro-1,3-oxazines (**3**) are 7.5 Hz (N-alkyl equatorial) and 10.5 Hz (N-alkyl axial),[7] and in the tetrahydro1,4,2-dioxazines (**1**) 8.3 Hz and 11.2 Hz (equatorial and axial respectively).[1] It seems clear that in our compound the minor conformation has its 5-N-Me largely axial whilst the major conformational set contains both equatorial and axial 5-N-Me groups.

The route map for conformational inversion of **5** is shown in Scheme 1. Since the process we observe corresponds almost certainly to slowing of inversion of the hydroxylamine nitrogen (N-2) the observed species at slow exchange must be **5a** + **5b** (major set) ⇌ **5c** (minor conformer). By going into the axial position the N-5 Me group in **5c** can relieve the *gauche* interaction present in **5d**. The free energy difference for an N-Me group in tetrahydro-1,3-oxazine is *ca.* 0 kcal mole^{-1}, therefore this change here relieves the *gauche* interaction at little, if any, extra cost in energy.

For comparison, the corresponding conformational free energy difference in 4-methyltetrahydro-1,2-oxazines (**2a** ⇌ **2b**) is 1.7 ± 0.2 kcal mole^{-1}.[3,4] The free energy difference in our system might have been expected to be greater than this due to the shortening of the C-4 to C-6 distance by replacing two C–C bonds with shorter C–N bonds. When allowance is made for the *gauche* interactions present in **4a** and **4b**, but not in **4c** this is indeed seen to be the case. Taking 0.8 kcal mole^{-1} as the value of the *gauche* interaction one can estimate a free energy difference for the 4-Me group in the absence of the 5-Me group of 1.2 + 0.8 = *ca* 2.0 kcal mole^{-1}.

For the 6-*p*-nitrophenyl derivative (**6**) a broadening and resharpening of resonances was observed on cooling the sample. At −30° a small peak has appeared *ca.* 0.46 ppm to low field of the main C–6H resonance. For reasons similar to those outlined above for **5** we attribute this signal to the minor conformer (**6a**) with the 6-aryl and 5-methyl groups axial. The free energy difference is found to be 1.4 ± 0.2 kcal mole^{-1}. The corresponding free energy difference for a 6-Me group in the 1,2-oxazine series is 2.4 ± 0.4 kcal mole^{-1}. Again we might have expected a higher value in the oxadiazines due to shortening of trans-annular distances. However relief of the *gauche* interaction and the possibility of phenyl going axial more readily than Me,[15] account for the lower value observed. The free energy of activation for the observed process (equatorial aryl → axial aryl) is 15.6 ± 0.4 kcal mole^{-1}.

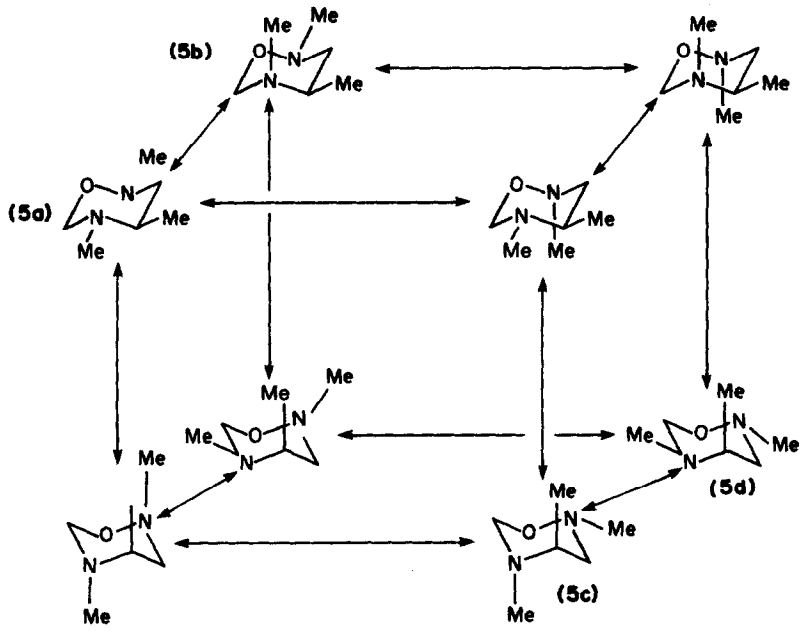
When 2,4,5-trimethyl-6-*p*-nitrophenyltetrahydro-1,2,5-oxadiazine (**7**) is made under kinetically controlled conditions a roughly equimolar mixture of *cis* and *trans* isomers is formed. These isomers are separable by preparative tlc on sodium hydroxide treated plates. Normal untreated plates catalyse the epimerisation of the *trans* to the *cis* isomer.

The *cis* isomer (**7a**) shows no evidence of any kinetic process in its ^{1}H spectrum between +60° and −60° although there is some evidence of viscosity broadening at the lower temperatures. This is good confirmatory

Table 1. ^{1}H NMR data†

Compound No.	Temp. (°C)	N2Me	N5Me	C6H	C4Me
5	+64	2.56	2.26	4.27 4.44 J = 9.0 Hz	1.09
	−40	2.66 Major	2.28 Major	4.32 4.46 Major J = 9.2 4.94 lowfield doublet J = 10.8 of minor	1.10 major
6	+35	2.68	2.07	5.07	
	−30	2.73 major	2.02 major	4.98 major 5.44 minor	
7a	+30	2.65	1.93	5.05	1.17
7b	+56	2.64	2.29	5.66	1.31
	−45			5.56	1.12
				5.83	1.15

†Chemical shift data in ppm downfield from TMS for *ca* 10% w/v solutions in $CDCl_3$.



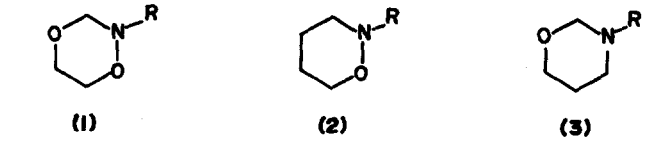
Scheme 1.

evidence that the process observed in 6 is not from an axial-equatorial equilibrium of the 2-N Me group. Had this been the case it should have been observed in **7a** also.

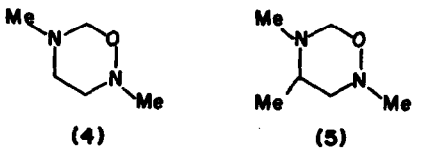
The *trans*-isomer (**7b**) shows a kinetically broadened spectrum at ambient temperature. The spectrum broadens further on lowering the temperature and the C–6H singlet splits into an approximately equal doublet ($Tc + 6 \pm 3°$; $\Delta G_c^{\ddagger}$ 14.1 ± 0.3 kcal mole^{-1}). Again we believe that the process being "frozen out" is slowing of inversion at N-2 separating **7bi** from **7bii**. The approximately equal amounts of both conformers arise because of the near equality of the conformational free energy differences for 4-Me and 6-*p*-nitrophenyl groups in this system as shown above.

Solutions of either isomer in $CDCl_3$ equilibrate slowly at +36° ($T_{1/2} < 24$ hr). When equilibrium was approached from both sides at +36° both samples gave solutions containing a *cis*: *trans* ratio of 6.82 (±1): 1 ($\Delta G°$ 1.18 ± 0.10 kcal mole^{-1}). Assuming that the *cis* → *trans* free energy difference arises solely from changing the 4 or 6 substituents from equatorial to axial a *cis*: *trans* ratio of 4.13:1 may be calculated from our conformational free energy data. Taking the upper error limits on the free energy differences of the 4-Me and 6-aryl substituents the ratio would be 5.75:1 and $\Delta G°$ 1.07 kcal mole^{-1}. In view of the approximations and assumptions† involved the agreement is very satisfactory.

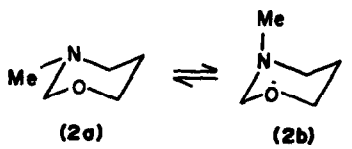
†The principal assumptions are that $\Delta S = 0$ in all cases, that conformational energies are additive, and that therefore energies can be transposed from tri- to tetra-substituted rings.



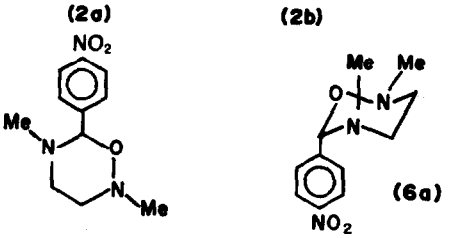
(1) (2) (3)



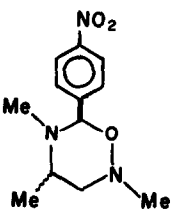
(4) (5)



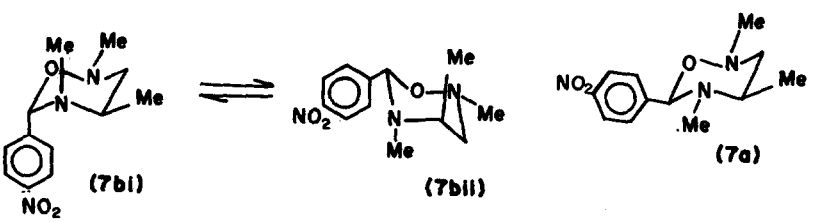
(2a) (2b)



(6) (6a)



(7)



(7bi) (7bii) (7a)

EXPERIMENTAL

N - *Methyl* - N - (2 - *methylaminoethyl*) - *hydroxylamine.* A soln of N-methylhydroxylamine (2.13 g), N-methylaziridine (2.58 g) and ammonium chloride (100 mg) in MeOH (20 ml) was maintained at room temp. for 48 hr. The solvent was removed by rotary evaporation and the residue distilled to give N-methyl-N-(2-methylaminoethyl)-hydroxylamine (1.45 g; 30%) b.p. 80°/5.5 mm.

N - *Methyl* - N - (2 - *methylaminopropyl*) - *hydroxylamine.* This compound was prepared as above from N-methylhydroxylamine (1.9 g), N-methylpropyleneimine (2.8 g) and ammonium chloride (100 mg) in MeOH (20 ml), yield (2.19 g; 47%) b.p. 140°/12 mm.

2,5 - *Dimethyltetrahydro* - 1,2,5 - *oxadiazine* (4). N-methyl-N-(2-methylamino-ethyl)-hydroxylamine (660 mg) and paraformaldehyde (200 mg) in dry benzene (5 ml) was heated under reflux for 1 hr. Careful distillation gave 2,5-dimethyltetrahydro-1,2,5-oxadiazine (550 mg; 75%), b.p. 140–5°/750 mm. (Found: M^+, 116.0954. $C_5H_{12}N_2O$ requires: M^+, 116.0950).

2,4,5 - *Trimethyltetrahydro* - 1,2,5 - *oxadiazine* (5). This compound was prpared as above from N-methyl-N-(2-methyl-aminopropyl)-hydroxylamine (650 mg) and paraformaldehyde (200 mg) in dry benzene (5 ml), yield (490 mg; 68%), b.p. 90–95°/100 mm. (Found: M^+, 130.1139. $C_6H_{14}N_2O$ requires: M^+, 130.1107).

2,5 - *Dimethyl* - 6 - p - *nitrophenyltetrahydro* - 1,2,5 - *oxadiazine* (6). A soln of N-methyl-N-(2-methylamino-ethyl)-hydroxylamine (800 mg) and *p*-nitrobenzaldehyde (1.15 g) in dry benzene (10 ml) was heated under reflux with azeotropic removal of water for 1 hr. The dark-red oil obtained on removal of the solvent was purified by thick layer chromatography on silica gel (40% EtOH, 60% petroleum ether) to give 2,5-dimethyl-6-*p*-nitrophenyl-tetrahydro-1,2,5-oxadiazine (720 mg; 40%) as a light-yellow gum which rapidly darkened on standing in air. (Found: M^+, 237.1106. $C_{11}H_{15}N_3O_3$ requires: M^+, 237.1114.)

cis- *and* trans - 2,4,5 - *Trimethyl* - 6 - p - *nitrophenyl* - *tetrahydro* - 1,2,5 - *oxadiazine* (7a) *and* (7b). A soln of N-methyl-N-(2-methylaminopropyl)-hydroxylamine (0.57 g), *p*-nitrobenzaldehyde (0.73 g) and toluene-*p*-sulphonic acid (5 mg) in dry benzene (15 ml) was heated under reflux for 0.5 hr and evaporated to give a red oil. The ^1H NMR spectrum of this crude material indicated that it was a mixture of "*cis*" and "*trans*" isomers in the approximate ratio of 1:1. Separation was achieved by thick layer chromatography on silica impregnated with KOH (KOH: silica = 1:13) and developed with a mixture of EtOAc (47.5%), petroleum ether (47.5%) and triethylamine (5%). Visualisation under UV revealed two bands. The lower band was stripped with a mixture of dichloromethane and triethylamine and the solid residue obtained on evaporation was recrystallised twice from petroleum ether to give *cis*- 7a (0.32 g; 26%) m.p. 60–61°. (Found: M^+, 251.1244. $C_{12}H_{17}N_3O_3$ requires: M^+, 251.1270.)

The higher running band yielded *trans*- 7b (0.18 g; 15%) as a

pale-yellow gum. (Found: M^+, 251.1272. $C_{12}H_{17}N_3O_3$ requires: M^+, 251.1270.)

Equilibration of **7a** *and* **7b**. Solns of each isomer in $CDCl_3$ (*ca.* 10% w/v) were allowed to stand in the sample preheating block of the NMR spectrometer at 36°. The progress of the equilibration was followed by NMR spectroscopy. After one week both samples had reached the same equilibrium position ($T_{1/2}$ < 24 hr). Planimetry of the C(6) H signals allowed measurement of the equilibrium constant ($K = 6.82 \pm 1$ for *trans* $\rightleftarrows$ *cis*).

NMR spectra. NMR spectra were run on a standard Perkin Elmer R32 spectrometer as described previously.[1]

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