The Conformational Analysis of Saturated Heterocycles. Part 92.[1] Conformational Equilibria of 1,2-Dioxa-4,5-diazacyclohexanes

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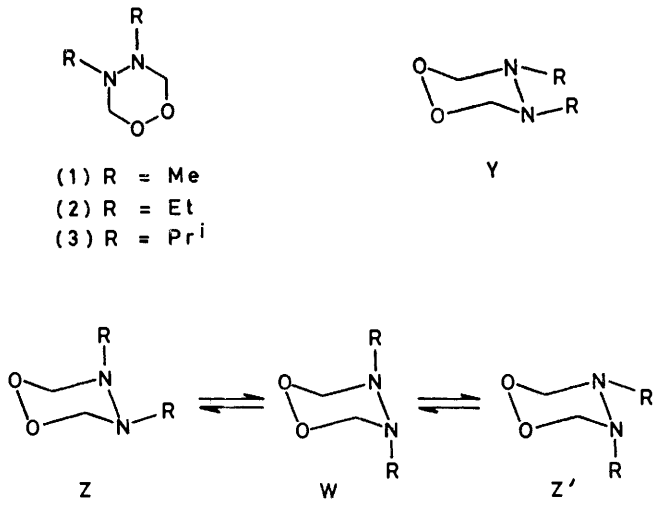
Proton and ^{13}C n.m.r. spectra indicate that 4,5-dimethyl- and 4,5-diethyl-1,2-dioxa-4,5-diazacyclohexanes exist very predominantly in the equilibrating *ax–eq* and/or *ax–ax* conformations: for the di-isopropyl analogue this coexists with *ca.* 20% of the *eq–eq* conformer.

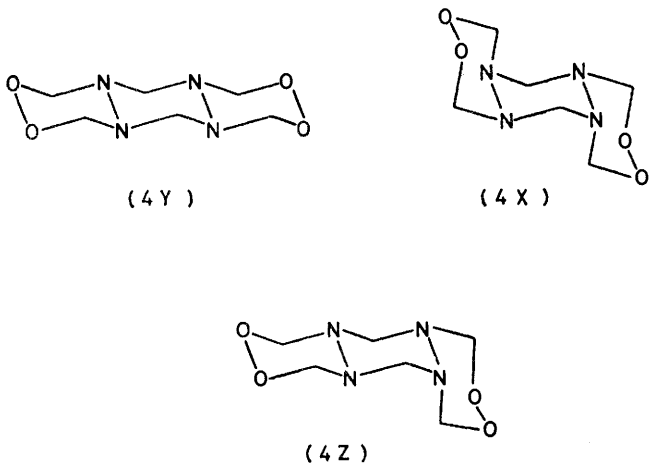
FOLLOWING our recent rationalisation of the conformational equilibria of 1,2,4,5-tetra-azacyclohexanes (hexahydro-1,2,4,5-tetrazines),[2] we have now studied the three monocyclic 1,2-dioxa-4,5-diazacyclohexanes (1)—(3), and the tricyclic analogue (4). The tricycle (4) was prepared in 1921,[3] but its correct structure only given later.[4] The monocyclic analogues (1)—(3) were then prepared [4] from CH_2O, H_2O_2, and RNHNHR, but little [5] has since been published on this class of compounds and nothing on their conformational analysis.

The monocyclic compounds (1)—(3) could exist in three chair conformers: the barrier separating the diequatorial conformer Y is expected to be considerably higher (passing interaction) than that dividing the two identical *eq–ax* conformations Z and Z′ from the diaxial form W (non-passing interactions) [2,6,7] (Scheme 1). Hence for the monocyclic compounds (1)—(3) we expect two sets corresponding to Sets I and III for the analogous monocyclic tetra-azacyclohexanes (Scheme 3). The tricyclic derivative could exist in the three conformations (4X), (4Y), and (4Z) (Scheme 2).

N.m.r. Spectra of Monocyclic Compounds.—At 253 K, in the ^1H spectrum all the compounds show the CH_2 split into peaks for the axial (δ 4.32—4.69) and equatorial protons (δ 5.56—5.77) with a geminal coupling of 12.0—12.9 Hz, showing that ring-inversion is slow. This regularity applies to the sole AB patterns of the methyl (1) and ethyl (2) derivatives, and to the major (78%) AB for the isopropyl derivative (3). The minor AB pattern for (3) shows a much lower geminal HH coupling of *J* 5.4 Hz. The ring-reversal barrier is expected to be high in such a heavily hetero-substituted ring; for examples see *inter alia* 1,2-diazacyclohexanes,[7] 1,3,4-oxadiazacyclohexanes,[8] and 1,2,4-triazacyclohexanes.[9]

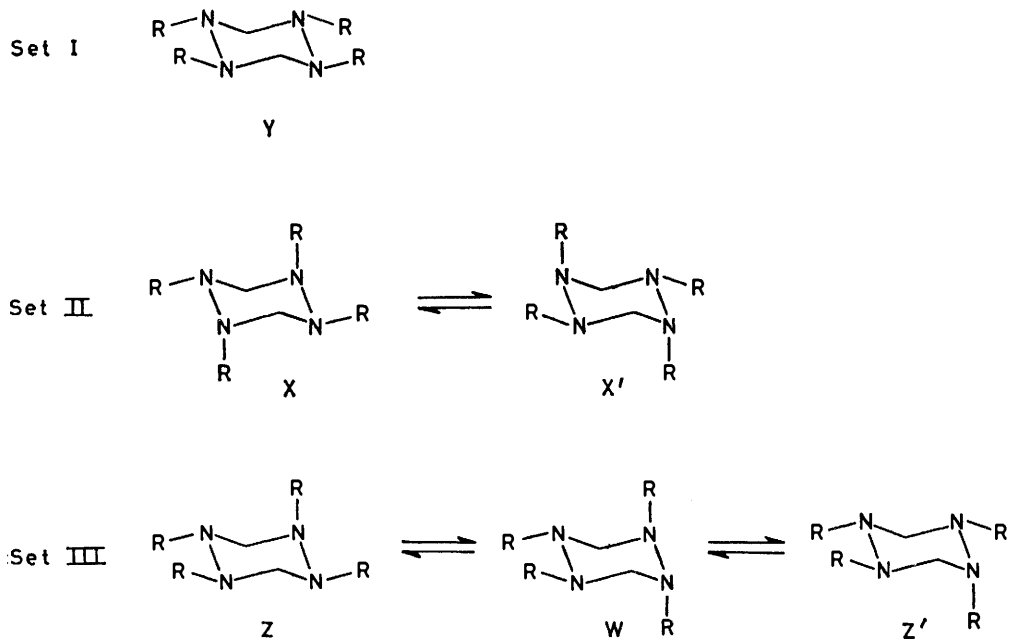


SCHEME 1 Conformational sets for monocyclic 1,2-dioxa-4,5-diazacyclohexanes



SCHEME 2 Conformations of tricyclic dioxadiazacyclohexane (4)

The chemical shifts of the substituent hydrogen atoms in comparison with those of the corresponding tetra-azacyclohexanes give some evidence for the predominant conformation of the ethyl compound (2). The chemical shifts of the ethyl methylene peaks in 1,2,4,5-tetraethyltetra-azacyclohexane are at δ 3.2 and 2.8 (AB quartet, on decoupling from methyl) in the symmetric axial equatorial pairs, but δ 3.9 and 3.6 in the diequatorial pair.[2] This compares with δ 3.2 and 2.7 found in (2) (Table 1). The assignment is therefore Z ⇌ W ⇌ Z′. The conformations of the methyl (1) and isopropyl derivatives (3) cannot be assigned unequivocally from proton spectra since the chemical shifts are not sufficiently distinguished. The *N*-substituents show the expected patterns in the proton n.m.r. spectra for the methyl, ethyl, and isopropyl groups in (1), (2), and (3) respectively (Table 1). For the isopropyl derivative the expected two sets of peaks correspond to the major and



SCHEME 3 Conformational sets for monocyclic 1,2,4,5-tetra-azacyclohexanes (see ref. 2)

minor conformers and from peak areas, $K_{eq} \cong 4$ ($\Delta G^0 = 0.7 \pm 0.1$ kcal mol^{-1}).

The ^{13}C spectra support and extend the above conclusions. The ring carbons absorb at 80.1—83.4 p.p.m., α-C at 40.0—53.8, and the β-C at 15.5—23.4 p.p.m. Again the isopropyl compound discloses the two sets: in each of them the Me groups of the isopropyl are distinct because of prochirality, indicating slow *N*-inversion on the n.m.r. time scale. The earlier work on the tetra-azacyclohexanes [2] showed the α-carbon atom chemical shifts to be larger in Set I (type Y) than in Set III (Z ⇌ W ⇌ Z') (Table 2, Scheme 3). For the isopropyl derivative (3) we can therefore assign the major and minor conformers as Z ⇌ W ⇌ Z' and Y respectively (Scheme 1). The ^{13}C shifts for (1) and (2) are consistent with the compounds existing in the set analogous to Set III, Scheme 3.

In summary, there is clear evidence that the methyl and the predominant isopropyl conformers exist in the Z ⇌ W ⇌ Z' forms, and from ^1H n.m.r. similarly for the ethyl conformer. The minor isopropyl conformer is in the Y form. Support for this comes from the geminal H–H coupling constant of N–CH_2–O (Table 1). (1), (2), and the predominant isomer of (3) all display coupling constants in the range 12.0—12.9 Hz, evidently that displayed by Z ⇌ W ⇌ Z', whereas the minor form of (3) shows J_{gem} 5.4 Hz, corresponding apparently to type Y. This difference was not however observed in the related 1,2,4,5-tetra-azacyclohexanes; [2] the geminal coupling constants for type Y and Z ⇌ W ⇌ Z' were

TABLE 1

^1H 60 MHz and ^{13}C 25.05 MHz n.m.r. spectra of monocyclic dioxadiazacyclohexanes (1)—(3)

Compound No.	R		^1H N.m.r. spectra (at 253 K) [a,b]: N–CH_2–O (AB quartet) *ax*	*eq*	*J* (Hz)	α-*H*	*J* (Hz)	β-*H*	*J* (Hz)	^{13}C N.m.r. spectra (at 233 K) [a,c]: N–*C*–O	α-*C*	β-*C*
(1)	Me		4.33	5.77	12.0	2.8 (s)				83.2	40.0	
(2)	Et		4.32	5.66	12.4	3.2; 2.7 [d]		1.10 (t)	6.9	83.4	46.3	15.5
(3)	Pr^i	M	4.69	5.56	12.9	3.45 (spt.)	6.1	1.1 (d)	6.1	80.5	48.6	22.5
								1.0 (d)				21.2
		m	4.23	4.48	5.4	2.72 (spt.)	6.1	Under major set		80.1	53.8	23.4
												22.0

[a] Chemical shifts in p.p.m. ref. to Me_4Si. [b] In $CDCl_3$. [c] In CF_2Cl_2. [d] Part of ABX_3 system which goes to an AB quartet when decoupled from methyl group. M = major set. m = minor set.

TABLE 2

^{13}C Chemical shifts of α-carbon atoms at temperatures below coalescence

R		Set I [a]	Set III	Set II	
Me			40.0		40.0
			40.8		
Et			49.2	47.1	46.3
			49.6		
Pr^i	major		46.1		48.6
		52.7	47.4		
	minor				53.8

[a] See Scheme 3.

TABLE 3

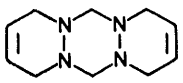
^1H and ^{13}C N.m.r. spectra of tricyclic dioxadiazacyclohexane (4) [a,b]

		N–CH_2–N					N–CH_2–O				
	Temp. (K)	Pattern	δ		J (Hz)	Relative intensity	Pattern	δ		J (Hz)	Relative intensity
^1H 100 MHz	298	AB quartet	4.06	5.33	15.0	1	singlet	4.94			2
^1H 300 MHz	298	AB quartet	4.06	5.33	13.9	1	AB quartet	4.90	4.99	12.8	2
^1H 300 MHz	200	AB quartet	4.11	5.31	14.0	2	AB quartet	5.03	5.15	12.8	2
							AB quartet	4.80	5.03	12.5	1
							AB quartet	4.76	4.98	12.3	1
^{13}C 25 MHz	298		60.5					92.6			
	223		60.5					91.6,[c] 92.7, 93.3			

[a] Chemical shifts in p.p.m. ref. to Me_4Si. [b] In $CDCl_3$. [c] Larger than other two peaks.

each found for the tetra-isopropyl compound to be 12.5 Hz.

N.m.r. Spectra of Tricyclic Dioxadiazacyclohexane (4) (*Table* 3).—The low-temperature n.m.r. spectra—both ^1H and ^{13}C—are unexpectedly simple in that only one set of signals originates from the central ring CH_2 groups at temperatures where ring inversion is 'slow', while the outer ring atoms give rise to three. We believe that this is due to accidental coincidence after having considered and discarded many other possible hypotheses. The conformers possible for (4) are shown in Scheme 2. The 300 MHz ^1H room temperature spectrum shows AB quartets, one for NCH_2N and another for NCH_2O (Figure 1a). The latter appears to be a singlet when run at 60 MHz: Δ_{AB} is therefore small but appreciable. This behaviour shows that, at 293 K, ring-reversal of the central tetra-azacyclohexane ring is not occurring although *N*-inversion and ring-reversal of the terminal rings are fast. The 303 K ^{13}C n.m.r. spectrum [Figure 2(a)] is consistent: it shows just two singlets for N–C–N



(5)

and N–C–O. By contrast the analogous tricyclic tetrahydrobis(pyridazinotetrazine) (5) undergoes rapid ring-reversal also for the central ring at room temperature: [2] however, the four extra oxygen ring atoms of (4) are expected to raise the energy of this process.

In the ^1H spectrum at low temperatures the AB pattern for the terminal ring CH_2-groups undergoes coalescence and then resharpening at 200 K to a complex pattern [Figure 1(b)]. This is assigned as three over-

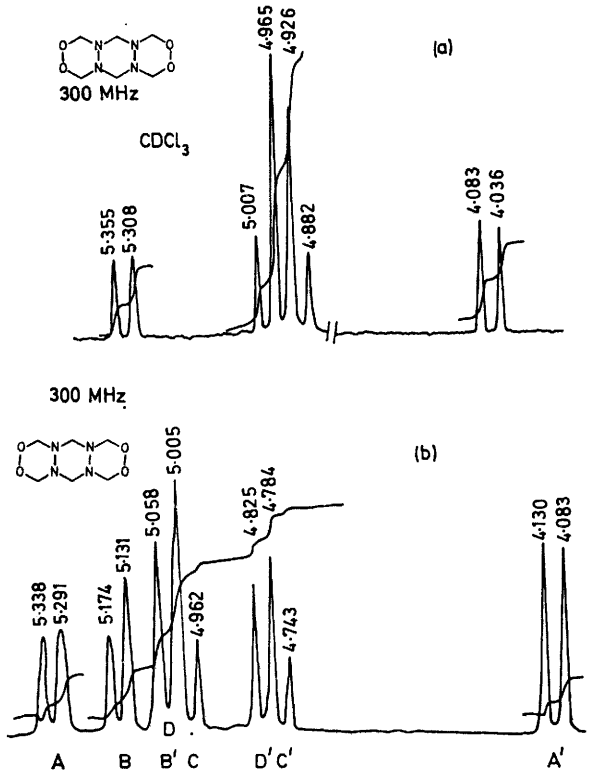


FIGURE 1 ^1H 300 MHz n.m.r. spectrum (in $CDCl_3$) of tricyclic dioxadiazacyclohexane (4) (a), 298K; (b), at 200 K

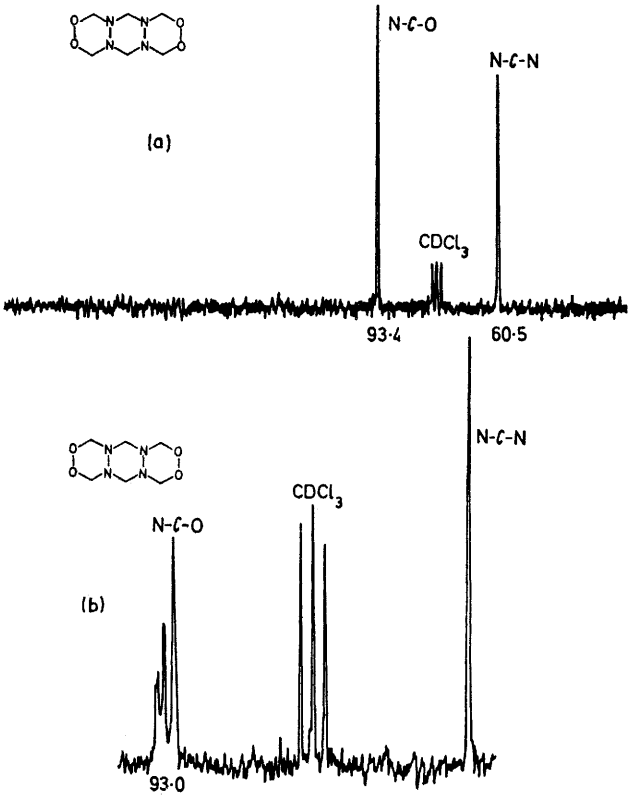


FIGURE 2 ^{13}C n.m.r. spectrum (in $CDCl_3$) of tricyclic dioxadiazacyclohexane (4) (a), at 298 K; (b), at 223 K

lapping AB quartets in integral ratio 2 : 1 : 1. If all inversion processes are halted, then we would expect that conformers (4Y), (4X), and (4Z) should give rise to 1, 2, and 4 AB quartets respectively. There are thus two possible interpretations: (a) equal parts of conformers (4Y) and (4X), or (b) solely conformer (4Z) in which there is accidental coincidence between two of the quartets.

The low temperature ^{13}C n.m.r. spectrum is capable of the same two alternative interpretations. The N–C–N remains an unresolved singlet but N–C–O splits into three peaks, one of which is larger than the other two. This behaviour is explicable in terms of the same two hypotheses (a) and (b). We have shown earlier that for the analogous tetrahydrobis(pyridazinotetrazine) (5), ^{13}C shifts for N–*C*–C vicinal-*gauche* to lone pairs are substantially to lower field (50—52.4 p.p.m.) than those for N–*C*–C vicinal-*trans* (40—40.8 p.p.m.). If explanation (a) were correct, the larger peaks deriving from conformer (4Y) in which the N–C–O is vicinal-*gauche* to the *N*-lone pair might be expected at lowest field. In fact the largest peak is at highest field: however, this evidence for hypothesis (b) is not strong because of the small range of chemical shift found for the CH_2 groups of (4). Evidently the heterocyclic oxygen atoms interfere seriously with the chemical shift patterns. Nevertheless we prefer hypothesis (b) and believe that the predominant conformer for (4) is the mono-axial triequatorial form (4Z).

EXPERIMENTAL

^{13}C N.m.r. spectra of compounds (1)—(3) were obtained in a JEOL FX-100 pulsed FT spectrometer operating at 25.05 MHz. Data lengths of 8 192 with sweep widths of 5 KHz were employed. The standard low-temperature unit was used, calibrated by reference to a copper–Constantan thermocouple; 10-mm n.m.r. tubes containing 2-ml CF_2Cl_2 solutions of the compounds and 0.5 ml of $(CD_3)_2CO$ for heteronuclear lock referenced to Me_4Si were employed.

60 MHz ^1H N.m.r. data on compounds (1)—(3) were measured on a JEOL C-60HL spectrometer with a standard low-temperature unit. 300 MHz ^1H N.m.r. data on compound (4) were obtained from the Institute of Polymer Science, University of Akron.

Preparation of Compounds.—The 1,2-dioxa-4,5-diazacyclohexanes (1)—(3) were synthesised as oils from the corresponding *NN'*-dialkylhydrazine hydrochloride, formaldehyde, and hydrogen peroxide:[4] they were characterised by their n.m.r. spectra.

The tricyclic compound (4) was prepared[3] from hydrazine sulphate, formaldehyde, and hydrogen peroxide and recrystallised from benzene (Found: C, 35.2; H, 5.8; N, 27.3. Calc. for $C_6H_{12}N_4O_4$: C, 35.3; H, 5.9; N, 27.5%). No m.p. was recorded as the compound exploded at 120 °C.

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