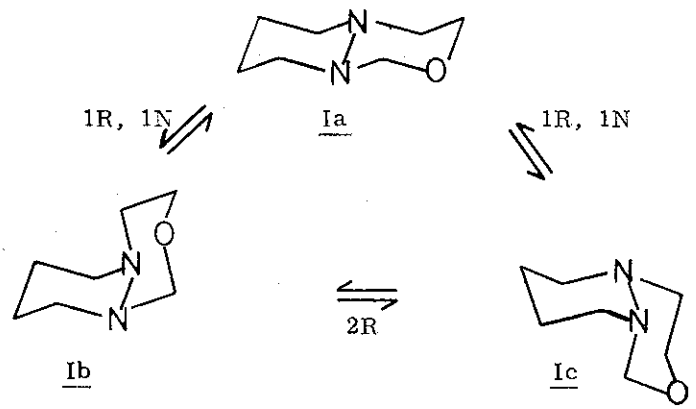
THE CONFORMATIONAL ANALYSIS OF SATURATED HETEROCYCLES. PART LXXXIII[1]. CONFORMATIONAL PROPERTIES OF 2-OXA-9,10-DIAZADECALIN

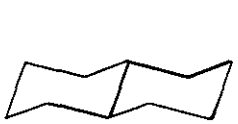
Victor J. Baker, Alan R. Katritzky*, and Fernando M. S. Brito Palma

School of Chemical Sciences, University of East Anglia, Norwich, England

Proton nmr spectroscopy shows that the newly synthesised bicycle I exists 70% in the trans conformation Ia and 30% in the cis conformation Ib.

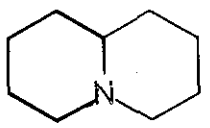
trans-Decalin (II) is more stable by ca. 2.7 kcal mol^{-1} than the cis-isomer (III).[2] In 9-azadecalins, the corresponding cis and trans forms are conformers interconvertible by nitrogen and ring inversion. The trans conformer remains predominant for 9-aza- (IV),[3] 9,10-diaza- (V),[4] and 2-oxa-10-azadecalin (VI).[5,6] However, the introduction of the second heteroatoms in the sequences IV → V and IV → VI should independently favour the cis conformer: cf. the differences between monocyclic piperidines and hexahydropyridazines[7] and between piperidines and 1,3-oxazanes.[8] It was therefore of interest to study the combined effects of two additional heteroatoms in 2-oxa-9,10-diazadecalin (I). We prepared the novel heterocycle I from hexahydropyridazine.[9]



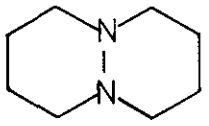


II

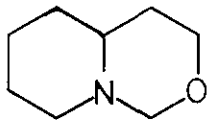
III



IV



V



VI

Conformational analysis

Three possible conformations may be assumed by compound I, one trans (Ia), and two cis (Ib, c) (Scheme). Interconversion between Ia and Ib and between Ia and Ic requires both ring and nitrogen inversion and between Ib and Ic requires two ring inversions. For these processes barriers of ca. 12-13 kcal mol^{-1} are expected.[10]

As regards the equilibrium, whereas conformer Ic should be high in energy for both steric and electronic reasons, Ia and Ib display an interesting balance of steric and electronic factors. For Ia destabilizing anti 1, 2, and syn 1, 3 lone pair interactions occur, while in Ib steric syn axial spacial interactions intervene.

^{1}H N. m. r. spectra

100 MHz ^{1}H nmr spectra were recorded on a Varian HA 100 over a temperature range +85 to -85 °C. For temperatures above 36 °C the solvent used was DMSO with hexamethyldisiloxane as internal reference; below 36 °C deuteroacetone was used with Me_4Si as reference. Spectral data are summarised in Tables 1 and 2.

Table 1: ^{1}H 100 MHz nmr spectrum of I at 355K, in DMSO[a)]

	$N-CH_2-O$	$N-CH_2CH_2-O$	$N-CH_2CH_2-O$	$N-CH_2(CH_2)_2CH_2-N$	$N-CH_2(CH_2)_2CH_2-N$
δ	3. 95s	3. 60t	2. 55t	2. 45m	1. 46m
		(J = 4. 7 Hz)	(J = 4. 7 Hz)		

a) Chemical shifts in p. p. m. downfield from hexamethyldisiloxane; s = singlet; t = triplet; m = multiplet.

Table 2: ^{1}H 100MHz nmr spectrum of I at 208K, in $(CD_3)_2CO$ a)

	ν (Hz) N-CH_2-O	$\Delta\nu_{AB}$ (Hz) N-CH_2-O	J_{AB} (Hz) N-CH_2-O	Peak weight	$\Delta G^{\neq}$ (kcal mol^{-1})
M:	424.3, 362.5	61.8	7.9	0.0491	14.6 (m→M)
m:	448.0, 421.3	26.8	10.0	0.0141	15.0 (M→m)

a) Chemical shifts in Hz downfield from TMS; M = major form; m = minor form.

At 85 °C interconversion of all conformers is rapid as shown by the NCH_2O singlet (δ 3.95) and the NCH_2CH_2O pair of triplets δ 2.55 and δ 3.60 (J 4.7 Hz) (Table 1). On lowering the temperature, changes are observed with eventual coalescence at 28 °C. At -65 °C the NCH_2O signal appears as two overlapping AB quartets of differing size (Table 2). The upfield half of the minor quartet and both halves of the major overlap with other signals, so to obtain accurate $\Delta\nu$ values decoupling experiments were performed. These confirmed the assignments.

Values were thus obtained for coalescence temperature (T_c), chemical shift difference ($\Delta\nu$) and coupling constant (J_{gem}) from both the minor and the major AB quartets. Substitution of the former set in the Eyring equation[11] led to the energy of activation: $\Delta G^{\neq}$ major → minor of 15.0 kcal mol^{-1}. Substitution of the values from the major AB quartet gave $\Delta G^{\neq}$ minor → major 14.6 kcal mol^{-1}.

The difference between the two figures represents ΔG^{o}, the Gibbs free energy, and this is 0.4 kcal mol^{-1}, which compares quite well with a direct determination based on peak sizes: this gave a value of 0.5 kcal mol^{-1}, which is equivalent to 70% of the major conformer at 28 °C.

Assignment of the major conformer to the trans form Ia may be made by reference to the coupling constants. Theoretical studies of J_{gem} values[5] predict -8.0 Hz for the trans form (Ia) and -10.0 Hz for the cis form (Ib). This compares with measured values of, for the major form 7.9 Hz and for the minor 10.0 Hz.

Conclusions

Two conformers are in equilibrium, about 70% trans (Ia) and 30% cis (Ib). This compares with about 5% of the cis form found in compound VI. Evidently the additional 1,2 syn diaxial lone pair interaction has substantially advanced the relative stability of the cis form. This demonstrates the importance of electronic effects on the conformation of such cyclic systems.

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9 Ethylene oxide (3. 6 g, 0. 08 mol) in methanol (20 ml) was added at 0 °C to hexahydropyridazine (7 g, 0. 08 mol) in methanol (50 ml). Stirring was continued for 30 min at 0 °C and a further 1 h at 25 °C. Evaporation of the solvent (40 °C, 15 mmHg) and distillation of the residue gave 1-(2-hydroxyethyl)hexahydropyridazine (3. 7 g, 35%) bp 86 °C 15 mmHg: the compound was characterised by the n. m. r. spectrum and was homogeneous by glc.

1-(2-Hydroxyethyl)hexahydropyridazine (2 g, 15 mmol) and paraformaldehyde (0 9 g, 30 mmol) were stirred under reflux in benzene (50 ml, 2 h), water being removed by Dean Stark apparatus. Subsequent evaporation of the solvent (50 °C, 15 mmHg) and distillation of the residue gave a mixture, bp 48-52 °C 15 mm. On preparative glc (Carbowax 20M at 180 °C, 18 lb in^{-2} nitrogen), the initial eluent proved to be 2-oxa-9,10-diazadecalin: the compound was characterised by the n. m. r. spectrumwas homogeneous by glc and showed the molecular ion peak m/e 142. 1107 (Calc. for $C_7H_{14}N_2O$ m.e 142. 1103).

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