The Conformational Analysis of Saturated Heterocycles. Part 100.[1] 1-Oxa-3-azacyclohexanes

By **Alan R. Katritzky,*† Victor J. Baker,** and **Fernando M. S. Brito-Palma,** School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ

Conformational equilibria and barriers to ring and nitrogen inversion are determined by ^1H and ^{13}C n.m.r. for 13 1-oxa-3-azacyclohexanes and correlated with recent work on the conformational analysis of saturated heterocycles.

THE effect of introducing heteroatoms into the cyclohexane ring has been much studied and considerable experimental data on 1-oxa-3-azacyclohexanes already exist. Early dipole moment work on 3-cyclohexyl-5-nitro-5-alkyl derivatives [2] supported existence in the chair form; more recently,[3] quantitative ring geometries are available from a computer program for strain energy minimisation. Dipole moments [3] gave $\Delta G°$ values, which are available also from studies of model compounds and J_{gem} values.[4] An NOE study [5] yielded only qualitative results owing to multiple relaxation possibilities. Variable temperature n.m.r. has been applied to the system by Lehn *et al.*,[6] who obtained a value for the ring inversion barrier in the 3-methyl derivative deuteriated at the 6-position, and by our own group,[7,8] who investigated the nitrogen inversion barrier. The value originally given [7] for 3-methyl-1-oxa-3-azacyclohexane is now thought too low. Results of some of the above work are included in Table 1.

TABLE 1

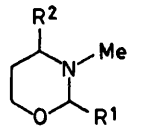
Dynmic n.m.r. data for ring inversion, nitrogen inversion, and equilibria of 1-oxa-3-azacyclohexanes

	$\Delta G_c^{\ddagger}$ [a] (R-inv.)				$\Delta G_c^{\ddagger}$ [a] (N-inv.)			
Compound	set B→TS		set A→TS	$\Delta G°$ [a,b] (set A ⇌ set B)	eq→ts		ax→ts	$\Delta G°$ [c] N-R_{eq} ⇌ N-R_{ax} within set A
(1)		10.0 [d-f]			7.45		7.55	−0.10
(2)				>2.0	7.63		7.58	+0.05
(3)	9.5		10.0	+1.3	7.45		7.55	−0.10
(4)				>2.0	7.79		8.55	−0.76
(5)		9.9 [e,]			6.44		6.94	−0.5
(6)				>2.0		6.5[f]		(N-R_{ax} pref.)
(7)	9.21		9.88	+0.67		6.6[f]		(N-R_{ax} pref.)
(8)				>2.0	6.4		7.0	−0.61
(9)	8.6		9.7	+1.1	8.0		8.7	−0.79
(10)		9.5 [e,f]				6.2 [h]		
		9.6 [f,g]						
(11)				>2.0				
(12)	8.68		9.11	+0.42				
(13)		9.1 [e,f]						

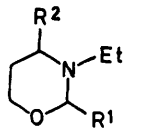
[a] In kcal mol^{-1}. [b] Positive values in favour of set A. [c] Positive values in favour of *N*-alkyl equatorial conformer. [d] Data from ref. 6. [e] From ^1H n.m.r. determinations; all others from ^{13}C n.m.r. [f] Average value. [g] From ^{13}C determinations using the diastereotopicity of the isopropyl methyl group. [h] Estimated.

The techniques applied to all the compounds (1)—(13) investigated are discussed in detail only for 3-methyl-1-oxa-3-azacyclohexane (1).

3-Methyl-1-oxa-3-azacyclohexane (1).—The proton-noise decoupled ^{13}C n.m.r. spectrum at 300 K consists of five sharp lines (Figure a) which persist on lowering the temperature to *ca.* 170 K when all the signals collapse. This is ascribed to the slowing of nitrogen inversion; the ring inversion barrier is undetectable by ^{13}C dynamic n.m.r. since the carbon atoms are rendered equivalent by the continuing rapid nitrogen inversion at that temperature. On further cooling, at 143 K clearly resolved sets of signals are observed (Figure b) for each of two conformations. The N-CH_3 and C-5 chemical shifts of the preferred conformer are displayed upfield relative to the other form: invoking the *γ-gauche* effect [9] this indicates that the major form has the *N*-methyl group



(1) $R^1 = R^2 = H$
(2) R^1 = Me, R^2 = H
(3) R^1 = H, R^2 = Me
(4) $R^1 = R^2$ = Me



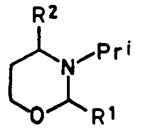
(5) $R^1 = R^2 = H$
(6) R^1 = Me, R^2 = H
(7) R^1 = H, R^2 = Me
(8) R^1 = Et, R^2 = H
(9) R^1 = Pr^i, R^2 = H

axial with $\Delta G°_{138}$ (*eq* ⇌ *ax*) −0.16 kcal mol^{-1}. Previous studies by ^1H n.m.r.[7,8] and dipole moments [10] came to the opposite conclusion; the reasons for believing that a change in assignment is needed are discussed below.

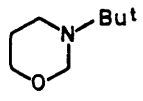
The Eyring equation [11] gave $\Delta G_c^{\ddagger}$ for nitrogen in-

† *New permanent address:* Department of Chemistry, University of Florida, Gainesville, Florida, U.S.A.

version as 7.5 ± 0.2 kcal mol^{-1}, significantly different from that previously reported from ^{1}H dynamic n.m.r. studies.[7,8] However reinvestigation of the proton work



(10) $R^1 = R^2 = H$
(11) $R^1 = Me, R^2 = H$
(12) $R^1 = H, R^2 = Me$



(13)

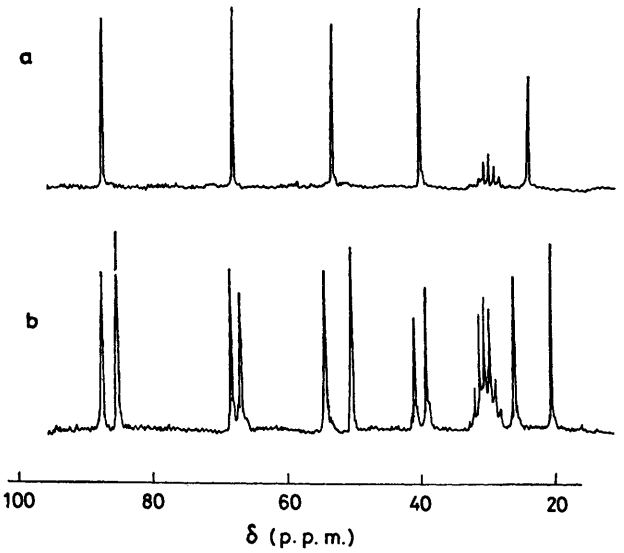
(Table 2) gave $\Delta G_c^{\ddagger}$ 7.6 kcal mol^{-1}: the earlier result probably suffered from inadequate correction for temperature gradients in the probe.

EXPERIMENTAL

Ethyl β-(Substituted-amino)propionates.—These were prepared from ethyl acrylate and the corresponding alkylamine,[10] characterised by ^{1}H n.m.r. spectra, and were homogeneous by g.l.c. (Carbowax 20M at 160 °C, N_2 pressure 18 lb in^{-2}) giving ethyl β-methylaminopropionate (52%), b.p. 68—69 °C at 15 mmHg (lit.,[10] 71 °C at 18 mmHg); ethyl β-ethylaminopropionate (75%), b.p. 78 °C at 15 mmHg (lit.,[10] 80 °C at 17 mmHg); ethyl β-isopropylaminopropionate (89%), b.p. 81 °C at 15 mmHg (lit.,[10] 84 °C at 16 mmHg); and ethyl β-t-butylaminopropionate (80%), b.p. 87 °C at 15 mmHg (lit.,[10] 92 °C at 18 mmHg).

Methyl β-(Substituted-amino)butanoates.—These were prepared from methyl crotonate and the corresponding alkylamine, characterised by ^{1}H n.m.r. spectra, and shown to be homogeneous by g.l.c. (Carbowax 20M at 170 °C, N_2 pressure 18 lb in^{-2}) giving methyl β-methylaminobutanoate (49%), b.p. 158—160 °C at 760 mmHg; methyl β-ethylaminobutanoate (40%), b.p. 64—66 °C at 18 mmHg; and methyl β-isopropylaminobutanoate (33%), b.p. 74—76 °C at 18 mmHg.

γ-(Substituted-amino)propanols.—These were obtained from the corresponding ethyl β-methylaminopropionate by $LiAlH_4$ reduction in dry $[CH_2]_4O$ [10] and characterised by ^{1}H n.m.r. spectra [d] giving γ-methylaminopropanol (56%), b.p. 104—108 °C at 30 mmHg (lit.,[10] 86 °C at 18 mmHg); γ-ethylaminopropanol (61%), b.p. 86—88 °C at 15 mmHg (lit.,[10] 90 °C at 18 mmHg); γ-isopropylaminopropanol (88%), b.p. 86 °C at 15 mmHg (lit.,[10] 94 °C at 18 mmHg); and γ-t-butylaminopropanol (87%), m.p. 66—67 °C (lit.,[10] 66—68 °C).



^{13}C Dynamic n.m.r. spectra of 3-methyl-1-oxa-3-azacyclohexane (1) at a, 300 K; b, 143 K

γ-(Substituted-amino)butanols.—These were similarly prepared by $LiAlH_4$ reduction in dry $[CH_2]_4O$ of the corresponding β-(substituted-amino)butanols and characterised by their ^{1}H n.m.r. spectra giving γ-methylaminobutanol (70%), b.p. 80—82 °C at 20 mmHg; γ-ethylaminobutanol (51%), b.p. 84—86 °C at 20 mmHg; and γ-isopropylaminobutanol (36%), b.p. 84—86 °C at 20 mmHg.

3-Alkyl-1-oxa-3-azacyclohexanes.—The γ-(substituted-amino)propanol and paraformaldehyde were refluxed in benzene (4 h) with removal of water by a Dean–Stark apparatus.[10] The products were characterised by ^{1}H n.m.r.

TABLE 2

100 MHz ^{1}H N.m.r. data for *N*-alkyl 1-oxa-3-azacyclohexanes

Compound	*N*-Substituent	Temp. (°C)	Chemical shifts [a] and coupling constants [b]: N-C*H*-X	X-C*H*-C	N-C*H*-C	C-C*H*-C	N-C*H*(-CH)	N-CH(-C*H*)
(1)	Me [c]	0	4.01 (2 H, s)	3.65 (2 H, t)	2.70 (2 H, t)	1.62 (2 H, m)	2.29 (3 H, s)	
		−140 [d] *a*					(2.48 (2) 2.00 (s)	
(5)	Et [c]	−36 [e]	4.15 (2 H, s)	3.70 (2 H, t, *J* 5 Hz)	2.83 (2 H, t, *J* 5 Hz)	1.68 (2 H, m)	2.63 (2 H, q, *J* 7 Hz)	1.04 (3 H, t, *J* 7 Hz)
		−110 [f]	4.23; 3.96 (*J* 9.7 Hz)					
(10)	Pr^i [c]	−10	4.25 (2 H, s)	3.69 (2 H, t, *J* 5 Hz)	2.95 (2 H, t, *J* 5 Hz)	1.57 (2 H, m)	2.95 (1 H, sept., *J* 6 Hz)	1.05 (6 H, d, *J* 6 Hz)
		−119 [e]	4.47; 3.99 (*J* 8.5 Hz)					
(13)	Bu^t	−40	4.24 (2 H, s)	3.63 (2 H, t, *J* 5 Hz)	2.85 (2 H, t, *J* 5 Hz)	1.60 (2 H, m)		1.08 (9 H, s)
		−134 [g]	4.62; 3.71 (*J* 8.7 Hz)					

[a] In p.p.m. downfield from Me_4Si. [b] In Hz. [c] Solvent CF_2Cl_2. [d] t_c −115 °C (for *N*-inversion). [e] t_c −76 °C. [f] t_c −70 °C. [g] t_c −80 °C.

spectra and were homogeneous by g.l.c. (Carbowax 20M at 180 °C, N_2 pressure 18 lb in^{-2}) giving 3-methyl-1-oxa-3-azacyclohexane (1) (62%), b.p. 124 °C at 760 mmHg (lit.,[10] 125 °C at 760 mmHg); 3-ethyl-1-oxa-3-azacyclohexane (5) (61%), b.p. 144 °C at 760 mmHg (lit.,[10] 144 °C at 760 mmHg); 3-isopropyl-1-oxa-3-azacyclohexane (10) (79%), b.p. 162—164 °C at 760 mmHg (lit.,[10] 55 °C at 12 mmHg); and 3-t-butyl-1-oxa-3-azacyclohexane (13) (63%), b.p. 72 °C at 15 mmHg (lit.,[10] 70 °C at 12 mmHg).

3-Alkyl-4-methyl-1-oxa-3-azacyclohexanes.—The γ-(substituted-amino)butanol and paraformaldehyde were refluxed in benzene (4 h) with removal of water by a Dean–Stark apparatus. The products were characterised by ^1H n.m.r. and were homogeneous by g.l.c. (propylene glycol at 150 °C, N_2 pressure 18 lb in^{-2}) giving 3,4-dimethyl-1-oxa-3-azacyclohexane (3) (65%), b.p. 128—130 °C at 760 mmHg (lit.,[12] 40—45 °C at 20 mmHg) (Found: C, 62.3; H, 11.5; N, 12.2. Calc. for $C_6H_{13}NO$: C, 62.6; H, 11.3; N, 12.2%); *3-ethyl-4-methyl-1-oxa-3-azacyclohexane* (7) (70%), b.p. 158—160 °C at 760 mmHg (Found: C, 64.8; H, 11.7; N, 10.7. $C_7H_{15}NO$ requires C, 65.1; H, 11.6; N, 10.9%); and *3-isopropyl-4-methyl-1-oxa-3-azacyclohexane* (12) (76%), b.p. 54 °C at 20 mmHg (Found: N, 9.3. $C_8H_{17}NO$ requires N, 9.8%).

3-Alkyl-2-methyl-1-oxa-3-azacyclohexanes.—Freshly distilled acetaldehyde was added to the γ-(substituted-amino)-propanol in ether solution (0 °C). After 2 h stirring with K_2CO_3 (N_2 atmosphere; 25 °C), fractional distillation gave the product. 2,3-Dimethyl-1-oxa-3-azacyclohexane (2) (67%) had b.p. 144 °C at 760 mmHg (lit.,[5] 97 °C at 700 mmHg); *3-ethyl-2-methyl-1-oxa-3-azacyclohexane* (6) (89%) b.p. 44—46 °C at 23 mmHg (Found: C, 65.2; H, 11.8; N, 10.8. $C_7H_{15}NO$ requires C, 65.1; H, 11.6; N, 10.9%); *3-isopropyl-2-methyl-1-oxa-3-azacyclohexane* (11) (55%), b.p. 64—66 °C at 23 mmHg (Found: N, 9.7. $C_8H_{17}NO$ requires N, 9.8%).

2-Alkyl-3-ethyl-1-oxa-3-azacyclohexanes.—An equimolar amount of the appropriate aldehyde was added dropwise to γ-(ethylamino)propanol in ether solution (0 °C). After 4 h stirring with K_2CO_3 (N_2 atmosphere; 25 °C), fractional distillation gave the products which were characterised by ^1H and ^{13}C n.m.r. and were homogeneous by g.l.c. *2,3-Diethyl-1-oxa-3-azacyclohexane* (8) (46%) had b.p. 28 °C at 0.5 mmHg, *m/e* 143 (P^+), 128 ($P^+ - 15$), and 114 ($P^+ - 29$) and *3-ethyl-2-isopropyl-1-oxa-3-azacyclohexane* (9) (42%) b.p. 29 °C at 0.5 mmHg, *m/e* 157 (P^+), 142 ($P^+ - 15$), 128 ($P^+ - 29$), and 114 ($P^+ - 43$).

Physical Measurements.—^{13}C N.m.r. spectra were obtained using a Jeol FX-100 pulsed Fourier transform spectrometer operating at 25.05 MHz. Data lengths of 8 192 with sweep widths of 5 KHz in general were employed. For broadening phenomena, the sweep width was chosen so that the minimum appropriate spectral range was pulsed to improve the number of data points. The standard JEOL low temperature unit, calibrated by reference to a copper–constantan thermocouple, utilised 10 mm n.m.r. tubes with 500 mg of the compound in *ca.* 2 ml of CF_2Cl_2 and 0.5 ml of $(CD_3)_2CO$ for heteronuclear lock referenced to Me_4Si.

100 MHz ^1H N.m.r. spectra were recorded using a Varian Associates HA-100 instrument with a modified low temperature accessory. Temperatures above 180 K were measured by the methanol shift method, and below this from a platinum resistance thermometer checked periodically against a copper–constantan thermocouple mounted in an n.m.r. tube and inserted in the probe.

Mass spectra were run on a Perkin-Elmer–Hitachi instrument RMU-6E.

RESULTS AND DISCUSSION

Chemical Shifts and Assignments.—The higher temperature (above nitrogen inversion barrier) ^{13}C n.m.r. spectra (Table 3) were mostly assigned unequivocally by simple chemical shift arguments. For example in 3-methyl-1-oxa-3-azacyclohexane (1) the C-2 atom between the two electronegative atoms appears to lowest field (δ 86.7 p.p.m.) and the C-5 atom which is adjacent to neither at highest field (δ 23.9 p.p.m.). The two remaining methylene groups are both as expected at lower field than the *N*-methyl group (δ 40.3 p.p.m.) and that adjacent to the more electronegative atom (oxygen) less shielded (δ 68.2 p.p.m.) than the other (δ 58.3 p.p.m.). In the off-resonance decoupled spectrum, the methyl group peak at δ 40.2 p.p.m. splits into a quartet; the other signals become triplets.

Similar arguments can be applied to the 2,3-dimethyl and 3,4-dimethyl compounds (2) and (3); the *N*-methyl group appears to lower field than the *C*-methyl; however the two *C*-methyl groups of the 2,3,4-trimethyl compound (4) cannot be unequivocally assigned. In 3-ethyl-1-oxa-3-azacyclohexane (5) the CH_3CH_2 group is found at δ 13.3 p.p.m.; comparison of compound (5) with the 3-ethyl-4-methyl analogue (7) (which may be unequivocally assigned) suggests that the peak at δ 45.3 p.p.m. is CH_3CH_2 and that at 49.6 p.p.m. is the C-4 signal. A similar argument for the 3-ethyl-2-methyl compound (6) assigns the peak at δ 42.0 p.p.m. to the ethyl methylene carbon atom. In 3-ethyl-4-methyl-1-oxa-3-azacyclohexane (7) the C-4 atom follows from its methine nature, and the CH_3CH_2 resonance occurs at δ 41.2 p.p.m. In the 2,3-diethyl compound (8) the chemical shifts of the carbon atoms of the *N*-ethyl group are similar to those found in (7); the C-4 shift at δ 49.5 p.p.m. agrees well with its analogue in (5) and (6), and the 5-methylene (δ 22.6 p.p.m.) is distinguished from the *C*-ethyl methylene (δ 26.9 p.p.m.) by analogy with the 5-methylene in (1), (5), and (6). The remaining peak at δ 10.0 p.p.m. is assigned to the *C*-ethyl methyl group.

For the isopropyl compounds, in 3-ethyl-2-isopropyl-1-oxa-3-azacyclohexane (9) the chemical shifts are in agreement with analogous previous assignments; the isopropyl methine appears at δ 30.2 p.p.m. and the isopropyl methyls separately at δ 18.9 and 19.1 p.p.m. due to their diastereotopic nature attached to a prochiral centre. In compounds (9), (11), and (12) the isopropyl methyl groups remain diastereotopic at all temperatures because the adjacent *C*-substituents render the molecules chiral even if fast *N*-inversion occurs. However, in (10) the enantiomeric forms are in rapid interconversion and chirality is lost until ring inversion is slowed. It is thus possible to compute the ring inversion barrier for (10) (Table 1). In the 3-isopropyl (10) and the 3-isopropyl-2-methyl compound (11) C-4 (δ 47.0 p.p.m.) and isopropyl methine (δ 49.0 p.p.m.) are respectively a triplet and doublet in off-resonance experiments.

Assignment of the isopropyl methine (δ 49.0 p.p.m.) and C-4 atom (δ 51.0 p.p.m.) in the 3-isopropyl-4-methyl compound (12) was done by comparison with the isopropyl shift in (10) and the C-4 atom in (7). As expected in the 3-t-butyl compound (13) the methyl groups are at relatively high field (δ 27.3 p.p.m.).

Chemical Shifts at Low Temperatures.—On lowering the temperature most of the compounds show significant spectral changes (Table 3) as ring and nitrogen inversions are slowed and additional peaks appear for the individual conformers. Of great significance so far as the assignment of chemical shifts is concerned is the *γ-gauche* effect:[9] steric perturbation of a C–H bond which leads to a displacement of charge towards carbon, causing *increased shielding* of the carbon atom and corresponding *deshielding* of the attached hydrogen atom. This results in an upfield ^{13}C shift both for the α-carbon of an axial substituent and the corresponding γ-ring carbon atom relative to those shifts in the equatorial conformer.

In those compounds (7) and (12) in which the slowing of ring inversion results in two sets of peaks in each case the predominant peaks appear to lower field than their counterparts in the other set indicating that, as expected, the conformers with equatorial *C*-substituents predominate. In compounds (3) and (9) for which broadening occurs although the minor set is not observed it is clear from the shifts that the *C*-alkyl group is equatorial.

At still lower temperatures changes corresponding to slowing of nitrogen inversion are found for all the compounds except (12) and (13). In compounds (1)—(7) distinct sets of peaks are seen for the different conformers and by reference to the α-substituent carbon atom and the C-5 atom it is possible to assign each set to the *N*-axial and *N*-equatorial conformer. With one ex-

TABLE 3

^{13}C N.m.r. shifts for 1-oxa-3-azacyclohexanes

Compound	Temp. (°C)	Conformation of *N*-atom substituent and set	Ring atoms				*N*-Substituent		*C*-Substituent	
			C-2	C-4	C-5	C-6	α-C	β-C	α-C	β-C
(1)	+20	*e* ⇌ *a*	87.6	53.3	23.9	68.2	40.2			
	−142	*e*(m)	87.4	54.0	25.7	66.8	40.7			
		a(M)	85.1	50.1	20.0	68.1	38.8			
(2)	+2	A *e* ⇌ *a*	91.2	55.1	24.1	68.2	37.4		20.3	
	−131	A *e*(M)	92.4	55.1	26.3	67.2	41.1		19.4	
		A *a*(m)	87.8	53.2	19.7	68.1	32.2		20.4	
(3)	0	set A ⇌ set B	87.6	56.4	30.9	68.0	35.1		20.2	
	−90	set A(M)	87.5	56.0	33.5	68.0	34.5		20.2	
	−135	A *e*(m)	87.4	58.3	33.9	67.8	36.8		20.1	
		A *a*(M)	86.8	53.4	26.6	67.8	32.2		20.1	
(4)	+8	A *e* ⇌ *a*	91.3	57.5	30.1	68.1	29.0		20.4; 20.8	
	−130	A *e*(m)	92.0	58.0	34.4	67.2	35.6		20.2; 19.6	
		A *a*(M)	89.4	55.8	25.9	67.7	24.6		20.2; 19.6	
(5)	−100	*e* ⇌ *a*	84.3	49.6	22.3	68.2	45.3	13.3		
	−140	*e*(m)	86.7	51.4	25.6		47.9			
		a(M)	82.9	48.4	20.6	68.1	44.1	13.5		
(6)	0	A *e* ⇌ *a*	90.1	49.9	23.3	68.1	42.0	13.4	20.2	
	−127	A *a*(M)	89.2	47.3	19.8	67.9	36.2	13.1	19.8	
(7)	+20	*set A* ⇌ *set B*	83.1	54.7	30.5	67.3	41.2	14.1	19.9	
	−110	*set B*(m)	77.3	49.9	25.0	63.9	47.0	14.1	17.7	
		set A(M)	82.4	55.1	29.6	68.1	37.1	13.8	20.2	
	−145	A *e*(m)	84.6				42.6			
		A *a*(M)	81.2	54.8	28.0	67.9	35.1	13.4	20.1	
(8)	+10	A *e* ⇌ *a*	95.1	49.5	22.6	68.3	40.8	13.9	26.9	10.0
	−141	A *a*(M)	94.1	46.7	19.3	68.6	36.0	13.5	23.5	10.8
(9)	+6	*set A* ⇌ *set B*	99.0	48.9	22.0	68.4	40.4	13.5	30.2	18.9, 19.1
	−95	*set A*(M)	99.0	47.7	20.0	68.9	37.4	13.3	30.5	18.9, —
	−130	A *a*(M)	98.9	47.1	19.2	68.9	36.3	13.6	30.6	18.8, 20.7
(10)	−70	*e* ⇌ *a*	83.1	47.0	23.9	68.3	49.0	20.7		
	−140	*e* ⇌ *a*	82.2	46.3	22.5	68.1	47.4	20.3, 12.3		
(11)	−28	A *e* ⇌ *a*	89.5	47.9	27.0	67.9	42.5	20.1, 22.2	14.4	
	−141	A *e* ⇌ *a*	89.7	48.0	26.4	66.8	42.0	20.1, 21.6	13.0	
(12)	0	*set A* ⇌ *set B*	78.8	51.0	32.2	66.1	49.0	22.9, 19.3	19.5	
	−110	*set A*(M)	79.6	53.3	35.1	68.1	45.8	21.6, 14.4	19.7	
		set B(m)	76.4	46.5	26.5	62.9	50.9	23.3	18.2	
(13)	−80	*e*	82.0	45.0	27.0	68.0	53.4	27.3		

ception the larger signals are to higher field demonstrating that the axial *N*-alkyl conformer predominates. In 2,3-dimethyl-1-oxa-3-azacyclohexane (2) the reverse is true: *N*-equatorial predominates. In compounds (8) and (9) the minor form is not observable but the chemical shifts suggest that the major form again has axial *N*-alkyl. In (10) and (11) the individual forms are not observable.

The introduction of adjacent 2- or 4-equatorial *C*-methyl groups has a shielding effect on an axial N-CH_3 substituent: [13] (1) at δ 38.8; (2) and (3) both with one *C*-methyl at 32.2; (4) with two *C*-methyls at 24.6 p.p.m. In the *N*-methyl equatorial series the effect is seen only for the 4-methyl *cf.* (1) and (2) at δ 40.7 and 41.1 with (3) and (4) at 36.8 and 35.6 p.p.m.

The chemical shifts correlate well within a series of conformers and can be used as confirmatory evidence of assignment (see Table 4). Chemical shift differences between corresponding ring carbon atoms of two compounds of the series are computed. Comparisons are then made for a series of compounds, keeping one of the pair constant. The results enable the assignment of conformers of a compound once the assignment of another in the same series is known. For example, assignment of the major conformer of (7) to (7*ae*) is suggested by a correlation of the low temperature shifts of (7) with those of (3) and (4), which also have an equatorial 4-methyl substituent.

TABLE 4

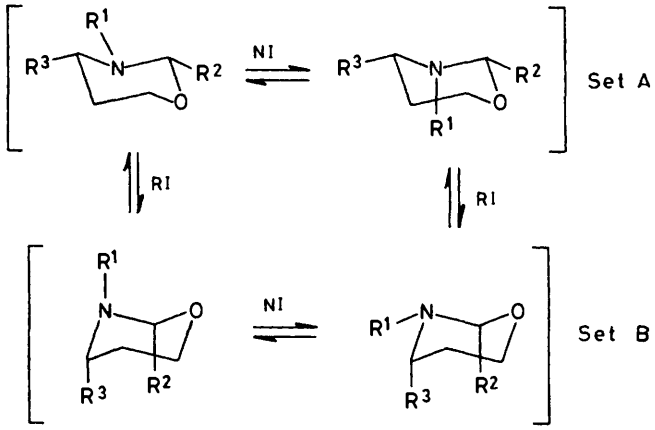
Chemical shift correlations

		δ[C-4(7)] − δ[C-4(X)] [a]		δ[C-5(7)] − δ[C-5(X)]	
	Compound (X)	*a*	*e*	*a*	*e*
(a)	(3)	+1.4	−3.5	+1.4	−5.9
	(4)	−1.0	−3.2	+2.1	−6.4
		δ[C-4(8)] − δ[C-4(X)]		δ[C-5(8)] − δ[C-5(X)]	
		a	*e*	*a*	*e*
(b)	(5)	−1.7	−4.7	−1.3	−6.3
	(6)	−0.6		−0.5	
		δ[C-4(9)] − δ[C-4(X)]		δ[C-5(9)] − δ[C-5(X)]	
		a	*e*	*a*	*e*
(c)	(5)	−1.3	−4.3	−1.4	−6.4
	(6)	−0.2		−0.6	
	(8)	+0.4		−0.1	

[a] *i.e.* δC-4 [compound (7)] (*N*-axial conformer) − δC-4 [compound (X)] (*N*-axial or equatorial conformer).

Coalescence and Broadening Phenomena.—In compounds (1), (5), (10), and (13) substituted only at nitrogen the slowing of ring inversion cannot be detected by ^{13}C n.m.r. as the two forms thus produced (set A and set B) are rendered equivalent by the continuing fast nitrogen inversion (Scheme). In compounds (2), (4), (6), (8), and (11) no spectral changes corresponding to the slowing of ring inversion are seen as the compounds are too heavily biased towards set A (with *C*-alkyl equatorial), showing incidentally that only the *cis*-configurational isomer of the trimethyl compound (4) is present. The *trans*-form with the *C*-methyl groups axial–equatorial should disclose significant amounts of both *ae* and *ea* forms on lowering the temperature.

In compounds (7) and (12) at low temperatures peaks corresponding to sets A and B can each be distinguished. Kinetic parameters were determined from the Eyring equation (Table 5). In compounds (3) and (9) there is clear broadening of the signals corresponding to the slowing of ring inversion and although at lower temperatures the signals of the minor set are too small to be observed, kinetic parameters may nevertheless be obtained (Table 6). In both compounds the C-6 atom



SCHEME

is most broadened, being *γ-gauche* to the 4-CH_3 and 2-$CH(CH_3)_2$, respectively, in set B. In compound (9) the CH_3CH_2 peak is itself significantly broadened. Surprisingly in compound (3) the 4-CH_3 is not broadened; in set B (*C*-methyl axial) the *N*-methyl group is presumably predominantly equatorial, and there is deshielding brought about by the adjacent *trans* lone pair compensating for the *γ-gauche* shielding effect.

In the foregoing it has been implicitly assumed that the ring inversion barrier is higher than that of nitrogen inversion, as seems to apply generally to multiheteroatom six-membered rings provided heteroatoms are not adjacent.[14] Nitrogen inversion barriers are clearly observable in compounds (1)—(7): distinct peaks are observable at low temperatures and the Eyring equation [11] may be applied (Table 5). In compounds (8) and (9) broadening of the C-5 and substituent α-carbon atom are observed (again a consequence of the *γ-gauche* effect) and kinetic parameters may be computed from the broadening data (Table 6). In compounds (10) and (11) although there are some slight signs of broadening at the lowest attainable temperature, no reliable conclusions could be drawn. In compounds (12) and (13) no nitrogen inversion coalescence phenomena were observed.

^1H N.m.r. Investigations.—In order to obtain as complete a picture as possible of the 1-oxa-3-azacyclohexanes, a ^1H investigation was undertaken of those compounds substituted only on nitrogen and not therefore capable of yielding ring inversion data from ^{13}C n.m.r. The *N*-methyl compound (1) has previously been investigated [7,8] both as regards the nitrogen (but see earlier) and ring

inversion barriers.[6] Results are shown in Table 2 and ring inversion barriers in Table 1. In all cases the NCH_2O protons collapse and reappear as an AB quartet, the lower field half of which is appreciably broadened compared with the upfield half. This is due to W type coupling with equatorial protons at the C-4 and -6 positions and the downfield half of the quartet is therefore ascribed to the equatorial proton.

Kinetic Parameters.—Ring and nitrogen inversion barriers should be quoted as ' half-barriers ', defined as minor form ⟶ transition state or major form ⟶ transition state.[15] Failure to quote half-barriers has in the past led to confusion. The half-barriers are available directly from the Anet method and from a simple equation applied to the Eyring equation derived barriers.[15] Ring inversion barriers decrease with increasing size of substituent in both the *C*-unsubstituted series (1), (5), (10), and (13), and the 4-methyl substituted series (3), (7), and (12) (Table 1): the ground state becomes increasingly planar with larger substituents. The effect of adding a 4-methyl substituent can be seen by comparing (1) and (3), (5) and (7), and (10) and (12): in each case the ring inversion barrier is smaller, as the substituent flattens the ring and raises the ground state energy.

Nitrogen inversion barriers also decrease with increasing size of substituent: compare again (1), (5), (10), and (13), and further (3), (7), and (12), and again (2), (6), and (11). From the same compounds it follows that the introduction of 2- and 4-methyl groups has little effect on the nitrogen inversion barrier: compare (1)—(3), further (5)—(7), and again (10—(12). There is thus only a very small ' passing ' [16] interaction in the inversion process. However, such ' passing ' interactions become much more significant in the nitrogen inversion barrier for the 2,3,4-trimethyl compound (4) (7.8 kcal mol^{-1} for the eq ⟶ ts barrier), owing to the crowded transition state. The series (5), (6), (8), and (9) contains a constant *N*-ethyl substituent and respectively H, Me, Et, and Pr^i at the 2-position: $\Delta G_c^{\ddagger}$ (*N*-inversion) is smilar for (5), (6), and (8) (6.4—6.6 kcal mol^{-1}), but is significantly higher for the isopropyl compound (9) (8.0 kcal mol^{-1}). Studies of cyclic hydrazines [13,17] and 1-oxa-3-aza- and 1,3-diaza-cyclohexanes [8] showed that electronic effects were the main cause of the difference between ' passing ' and ' non-passing ' *N*-inversion barriers for methyl and ethyl groups; but for isopropyl groups steric interactions were also important.[18]

TABLE 5

^{13}C Coalescence data for 1-oxa-3-azacyclohexanes [a]

Compound no.	$\Delta G°$	Process	t_c C-2	t_c C-4	t_c C-5	t_c C-6	t_c N-C	$\Delta\nu$ C-2	$\Delta\nu$ C-4	$\Delta\nu$ C-5	$\Delta\nu$ C-6	$\Delta\nu$ N-C	$\Delta G^{\ddagger}$ C-2	$\Delta G^{\ddagger}$ C-4	$\Delta G^{\ddagger}$ C-5	$\Delta G^{\ddagger}$ C-6	$\Delta G^{\ddagger}$ N-C
(1)	−0.10 ± 0.05	*N*-Inv	−116	−120	−113	−119	−110	2.3	3.9	5.7	1.3	1.9	7.5	7.4	7.5	7.4	7.5
(2)	+0.05 ± 0.05	*N*-Inv	−108	−114	−108	−118	−106	4.6	1.9	6.6	0.9	8.9	7.6	7.6	7.5	7.7	7.5
(3)	−0.10 ± 0.05	*N*-Inv		−109	−105		−107	0.6	4.9	7.3	0.0	4.6		7.6	7.6		7.7
(4)	−0.76 ± 0.05	*N*-Inv	−104	−104	−95	−114	−95	2.6	2.2	8.5	0.5	11.0	8.0	8.1	8.1	8.0	8.0
(5)	−0.5 ± 0.1	*N*-Inv	−128	−128	−128	−128	−128	3.8	3.0	5.0	*b*	3.8	6.6	6.6	6.6		6.6
(6)		*N*-Inv			−132			*b*	*b*	5.0 [c]	*b*	*b*			6.5		
(7)	+0.67 ± 0.05	R-Inv	−73	−73	−75	−75	−67	4.9	5.2	4.6	4.2	10.1	9.3	9.3	9.3	9.3	9.2
		N-Inv	−131				−126	3.4	*b*	*b*	*b*	7.5	6.6				6.6
(10)		R-Inv					−80					26.3					9.6 [d]
(12)	+0.42 ± 0.05	R-Inv	−85	−80	−75	−82	−82	3.2	6.8	8.8	5.2	5.1	8.8	8.9	9.0	8.8	8.9

[a] t_c Values in °C; $\Delta\nu$ in p.p.m., and ΔG in kcal mol^{-1}. [b] Not observed. [c] By analogy with data from (1), (2), and (5). [d] From coalescence of diastereotopic N–C–*C*.

TABLE 6

Broadening data for 1-oxa-3-azacyclohexanes

Compound no.	Signal	Process	t_c/°C	$\Delta w_{\frac{1}{2}}$ Hz [a]	$\Delta\nu$/Hz	$\Delta G_c^{\ddagger}$ [b]/ kcal mol^{-1}	$\Delta G_c°$ [c]/ kcal mol^{-1}
(3)	C-6	R-inv.	−65	4.9	125 [d]	9.5	1.3
(8)	C-5	*N*-inv.	−133	13.2	125 [e]	6.4	−0.6
(9)	C-6	R-inv.	−80	7.3	125 [d]	8.6	+1.1
	N-CH_2-CH_3	*N*-inv.	−192	10.0	100 [e]	8.0	−0.7

[a] Corrected for natural width. [b] From minor to transition state. [c] Positive values in favour of set A or *N*-alkyl equatorial conformer. [d] Estimated from (7), (12), and methylcyclohexane (F. A. L. Anet, C. H. Bradley, and G. W. Buchanan, *J. Amer. Chem. Soc.*, 1971, **93**, 258). [e] Estimated from (5).

Equilibrium Parameters.—Two equilibrium constants are calculated for some compounds. The first is for the process set A ⇌ set B (Scheme) and the second, within set A on the slowing of nitrogen inversion, is for *ee* ⇌ *ae* (the *C*-substituent remaining equatorial). Set A is found to be preferred throughout (*i.e.* $\Delta G°_{\text{set A} \rightleftharpoons \text{set B}} > 0$), but set B becomes relatively less disfavoured with bulkier *N*-substituents: the *C*-substituent equatorial position becomes somewhat less favoured owing to interaction with the adjacent *N*-substituent. Compare $\Delta G°_{\text{set A} \rightleftharpoons \text{set B}}$ for (3), (7), and (12).

1,3-*syn*-Axial interactions might be expected to be less in cyclohexane because of the longer C–C than C–N or C–O bonds. Methylcyclohexane, $\Delta G°$ 1.7 kcal mol^{-1},[19]

is more strongly biased toward equatorial than any of the 1-oxa-3-azacyclohexanes (3), (7), and (12) due to repulsion between adjacent equatorial alkyl groups. In the 2-alkyl-3-ethyl series $\Delta G°$ is only measurable in the isopropyl compound (9). Comparing (2) and (3), (6) and (7), and (11) and (12), it is seen that 2-methyl has a greater equatorial preference than 4-methyl: in the former case, the equatorial substituent can relieve interactions by bending towards the adjacent oxygen atom.

For the *N*-inversion equilibrium (within set A) all values of $\Delta G°_{eq \longrightarrow ax}$ are negative (*axial* predominating) except for the 2,3-dimethyl compound (2). As mentioned above, the result for the 3-methyl compound (1) is at variance with previous dipole moment [10] and ^1H n.m.r. results.[7,8] The ^1H and ^{13}C arithmetical values are similar (+0.16, compared with −0.10 kcal mol^{-1}) and thus it is the assignment which is in question. In the ^1H n.m.r. work [7,8] the assignment of the signals was made on the basis of comparative low temperature n.m.r. studies of a series of 2-alkyl-3-methyl-1-oxa-3-azacyclohexanes and it is now thought that this assignment was wrong. The *γ-gauche* effect in the ^{13}C spectrum puts the axial *N*-methyl peak to higher field and has been found to be a consistently reliable criterion. This assignment has also been found to be consistent with other work from this laboratory.[20] We now believe that quantitative dipole moment based conclusions of conformational equilibria should be treated with caution.* The 3-ethyl compound (5) adopts more readily the axial conformation than the 3-methyl (1); this again disagrees with the dipole moment results [10] but agrees with results found for 1,4-dioxa-2-azacyclohexanes.[21] From (1) and (2), an equatorial *C*-substituent at the 2-position has the effect of *increasing* the equatorial tendency at the 3-position, as was also observed for 1,4-dioxa-2-azacyclohexanes.[21]

The highest axial preference is found for the *cis*-2,3,4-trimethyl compound (4). This disfavoured nature of three equatorial methyl groups has been noted elsewhere,[13,22] The increasing interaction between adjacent alkyl groups can be observed in the 3-ethyl series (5), (6), (8), and (9), the 2-substituents being respectively H, Me, Et, and Pr^i.

* A critical survey of all the dipole moments results is presently in progress.

This series of 1-oxa-3-azacyclohexanes displays in general the conformational properties expected from previous work. The study emphasises the advantages of ^{13}C n.m.r. over ^1H in conformational work.

We thank Drs. R. C. Patel and I. J. Ferguson for discussion, Mr. G. Baysal for help with some experimental work, the University of Lisbon for leave (to F. B-P.), and I.N.I.C. (Portugal) for financial support (to F. B-P.).

[0/457 *Received*, 25*th March*, 1980]

REFERENCES

[1] Part 99, A. R. Katritzky, V. J. Baker, M. Camalli, R. Spagna, and A. Vaciago, preceding paper.
[2] D. Gürne and T. Urbanski, *J. Chem. Soc.*, 1959, 1912.
[3] I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332.
[4] F. G. Riddell and J. M. Lehn, *J. Chem. Soc.* (*B*), 1968, 1224.
[5] H. Booth and R. U. Lemieux, *Canad. J. Chem.*, 1971, **49**, 777.
[6] J.-M. Lehn, P. Linscheid, and F. G. Riddell, *Bull. Soc. chim. France*, 1968, 1172.
[7] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Chem. Comm.*, 1975, 255.
[8] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Perkin II*, 1977, 818.
[9] N. K. Wilson and J. B. Stothers, *Topics Stereochem.*, 1974, **8**, 4.
[10] R. A. Y. Jones, A. R. Katritzky, and D. L. Trepanier, *J. Chem. Soc.* (*B*), 1971, 1300.
[11] S. Glasstone, K. J. Laidler, and H. Eyring, ' The Theory of Rate Processes ', McGraw-Hill, New York, 1941, p. 195.
[12] C. Mannich and K. Roth, *Arch. Pharm.*, 1936, **274**, 527 (*Chem. Abs.*, 1937, **31**, 2216).
[13] S. F. Nelsen and G. R. Weisman, *J. Amer. Chem. Soc.*, 1976, **98**, 3281.
[14] R. K. Harris and R. A. Spragg, *J. Chem. Soc.* (*B*), 1968, 684; J. E. Anderson, *J. Amer. Chem. Soc.*, 1969, **91**, 6374.
[15] A. R. Katritzky R. C. Patel, and F. G. Riddell, *J.C.S. Chem. Comm.*, 1979, **674**; a review of this work is in preparation.
[16] R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, *J.C.S. Perkin II*, 1974, 406.
[17] S. F. Nelsen and G. R. Weisman, *J. Amer. Chem. Soc.*, 1976, **98**, 1842.
[18] V. J. Baker, A. R. Katritzky, J.-P. Majoral, S. F. Nelsen, and P. J. Hintz, *J.C.S. Chem. Comm.*, 1974, 823.
[19] H. Booth and J. R. Everett, *J.C.S. Chem. Comm.*, 1976, 278.
[20] A. R. Katritzky and R. C. Patel, *J.C.S. Perkin II*, 1979, 993.
[21] F. G. Riddell, M. H. Berry, and E. S. Turner, *Tetrahedron*, 1978, **34**, 1415.
[22] A. R. Katritzky, V. J. Baker, I. J. Ferguson, and R. C. Patel, *J.C.S. Perkin II*, 1979, 143.