The Conformational Analysis of Saturated Heterocycles. Part 101.[1] 1,3-Diazacyclohexanes and 1-Thia-3-azacyclohexanes

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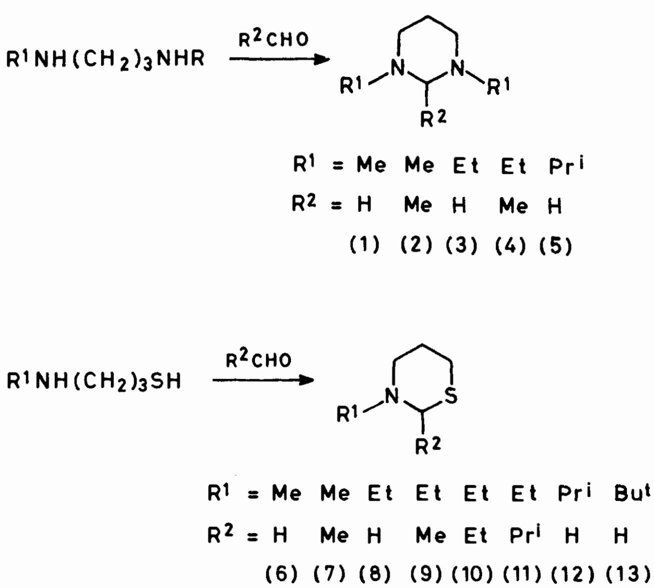
Conformational equilibria and barriers to ring and nitrogen inversion, determined by ^{1}H and ^{13}C n.m.r. for the title compounds, are correlated with other recent work on ring-1,3-diheteroatom-substituted cyclohexanes.

STUDY of the three further (*cf.* ref. 2) 1,3-diazacyclohexanes and eight 1-thia-3-azacyclohexanes (Scheme 1) with results for 1-oxa-3-azacyclohexanes[3] now enables general conclusions regarding the conformational effects of 1,3-dihetero-substitution within a cyclohexane ring.

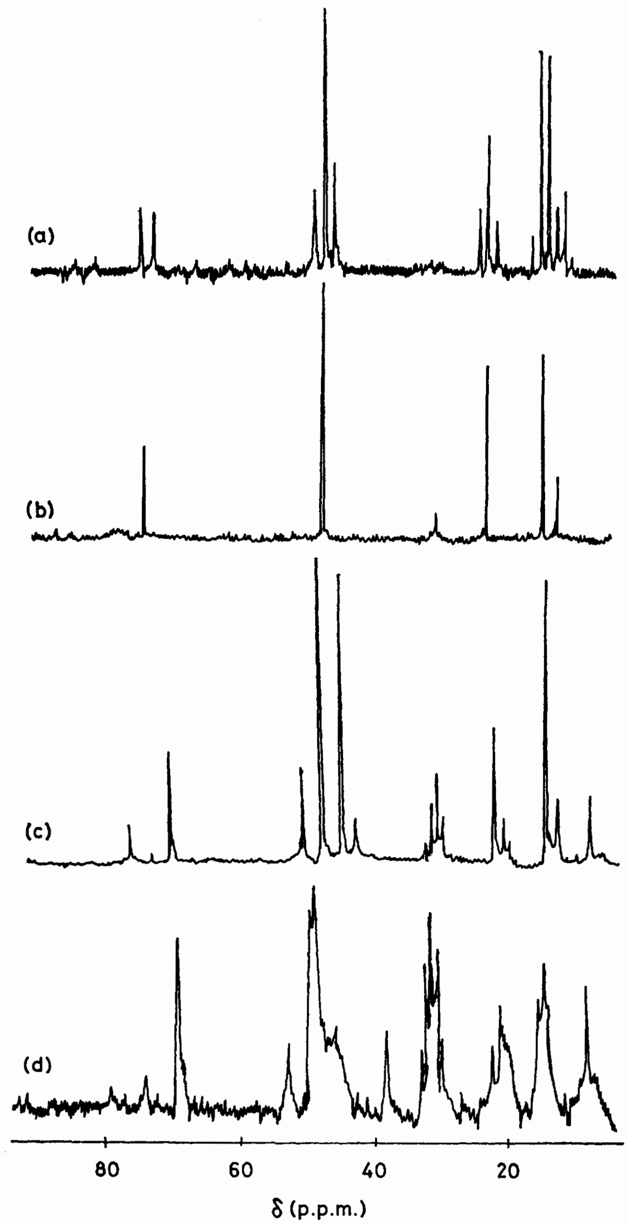
Considerable previous work exists for these compounds. Precise ring geometries are unknown, but approximations have been calculated utilising a computer strain energy minimisation program for 1,3-diaza-[4] and 1-thia-3-aza-cyclohexane.[5] The chair conformation for the latter is markedly puckered in the vicinity of the sulphur atom and flattened at nitrogen to accommodate the long C–S bond and small C–S–C bond angle, a conclusion supported by i.r. and n.m.r. data.[6]



SCHEME 1 Preparation of compounds

Ring inversion, the higher energy barrier process in these compounds,[3] has been studied by ^{1}H n.m.r. for 1,3-dimethyl- and 1,3-diethyl-diazacyclohexane ($\Delta G_c^‡$ 11.3 and 10.9 kcal mol^{-1}, respectively)[7] and for 3-ethyl-, 3-isopropyl-, and 3-t-butyl-1-thia-3-azacyclohexane (ΔG_c^+ 9.8, 9.2, and 9.4 kcal mol^{-1}, respectively),[8] and by ^{13}C n.m.r. for 1,2,3-trimethyl-1,3-diazacyclohexane.[2]

Nitrogen inversion barriers for 1,3-diaza- and 1-thia-3-aza-cyclohexanes have previously been reported only for 1,3-dimethyl- and 1,2,3-trimethyl-1,3-diazacyclohexane: these are, respectively, $\leqslant$ 6.7 and $\leqslant$ 8.0 kcal mol^{-1} from



^{13}C N.m.r. spectra of 1,3-diethyl-2-methyl-1,3-diazacyclohexane: (a) off-resonance decoupled, 285 K; (b) proton noise decoupled, 285 K; (*c*) 181 K (slow ring inversion); (d) 134 K (slow ring and nitrogen inversion)

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^{1}H,[9] and 7.2 and 7.3 kcal mol^{-1} from ^{13}C n.m.r.[2] Attempts to observe nitrogen inversion in 3-alkyl-1-thia-3-azacyclohexanes by low temperature ^{1}H n.m.r. were unsuccessful.[8]

Early attempts to quantify the equilibrium in 1,3-diazacyclohexanes relied on the chemical shift (Δae) criterion,[10-12] now known to be of doubtful validity,[13] or geminal coupling constants [12] which can also give misleading results.[14] Dipole moment studies of 1,3-diazacyclohexanes [15] and 1-thia-3-azacyclohexanes [8] are also quantitatively unreliable.[3] The ^{1}H and ^{13}C n.m.r. studies mentioned [2,9] gave equilibrium constants: $\Delta G°_{173}$ +0.65 kcal mol^{-1} (^{13}C n.m.r.) for 1,3-dimethyl-1,3-diazacyclohexane and $\Delta G°_{298}$ −0.85 (^{1}H) and $\Delta G°_{173}$ −0.8 kcal mol^{-1} (^{13}C) for 1,2,3-trimethyl-1,3-diazacyclohexane (positive values indicate equilibria which favour *N*-alkyl diequatorial).

We now extend the use of ^{13}C, and to a lesser extent ^{1}H n.m.r., to measure accessible kinetic and equilibrium parameters of a wider variety of compounds of this type. The 1,3-diaza- and 1-thia-3-aza- were prepared as in Scheme 1: some have previously been reported, and the others were made by an adaptation of the literature method.[8] As an example of the methodology, 1,3-diethyl-2-methyl-1,3-diazacyclohexane (4) is discussed in detail; other results are shown in Tables 1 and 3 (1,3-diazacyclohexanes) and Tables 2 and 4 (1-thia-3-azacyclohexanes). ^{1}H Data are collected in Table 5.

TABLE 1

^{13}C N.m.r. chemical shift data [a] for 1,3-diazacyclohexanes

Compound	Temp. (K)	Conformer	Chemical shifts [b] C-2	C-4,6	C-5	*N*-Substituent α-C	β-C	C(2)-CH_3
(1) [c]	278	*ee* ⇌ *ae*	80.4	55.0	24.1	43.2		
	123	*ee*	80.0	54.2	25.1	43.6		
		ae	77.1	56.2 [d], 50.4 [e]	19.4	43.6 [d], 40.6 [e]		
(2) [c]	283	set A ⇌ set B	80.0	55.9	22.5	37.7		17.8
	143	set A: *aee*	78.1	57.7 [d], 54.3 [e]	20.4	42.7 [d], 33.3 [e]		19.3
(3)	183	*ee* ⇌ *ae*	76.2	52.9 [f]	23.8	49.6 [f]	12.8	
	125	*ee* (major)	77.0	53.2 [f]	25.0	50.4 [f]	12.5	
		ae (minor)	72.6	*g*	19.9	45.3	*g*	
(4)	285	set A ⇌ set B	73.7	46.8	22.1	46.8	13.6 [f]	11.2 [f]
	181	set A (minor)	76.6	50.6	20.2	42.5	12.0 [f]	19.3 [f]
		set B (major)	70.3	44.5	21.4	47.8	13.5 [f]	6.9 [f]
	134	set A *eee* (minor)	78.7			51.6		
		set A *aee* (major)	73.1			37.1		
(5)	263	*ea* ⇌ *ae*	70.4	49.2	24.5	52.4	19.7	
	166	*ea* ⇌ *ae*	68.6	48.6	23.7	52.0	19.1	

[a] Solvent CF_2Cl_2–[$^2H_6$]acetone. [b] In p.p.m. downfield from Me_4Si. [c] Ref. 2. [d] Adjacent to N-Me equatorial. [e] Adjacent to N-Me axial. [f] May be interchanged. [g] Not observed.

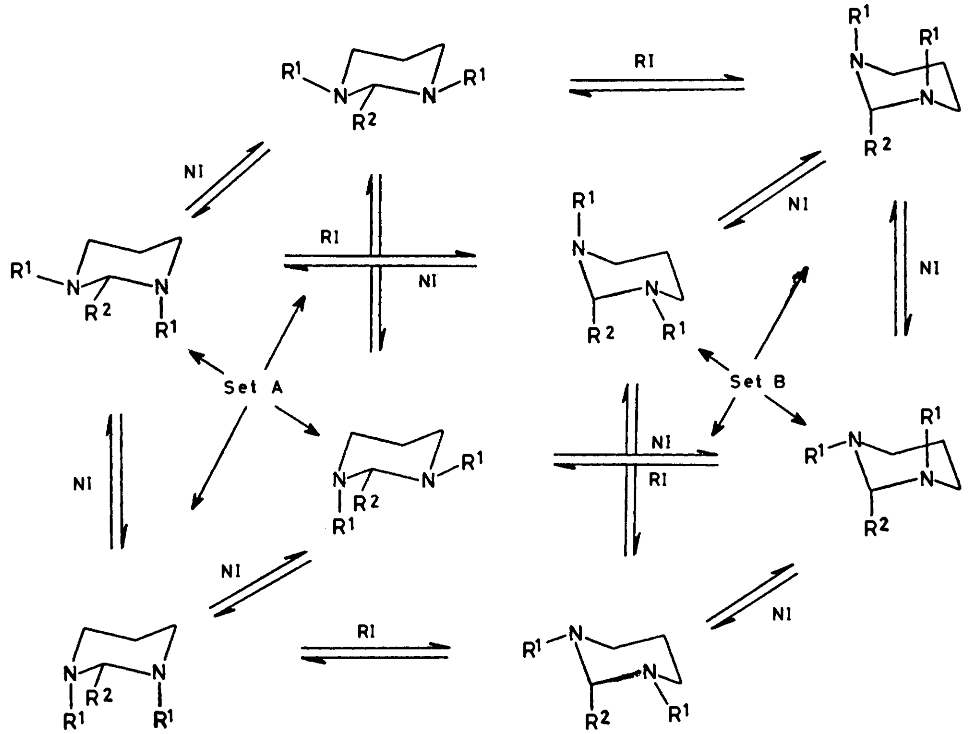
TABLE 2

^{13}C N.m.r. chemical shift data [a] for 1-thia-3-azacyclohexanes

Compound	Temp. (K)	Conformer	Chemical shifts [b] C-2	C-4	C-5	C-6	*N*-substituent α-C	β-C	*C*-substituent α-C	β-C
(6)	283	*e* ⇌ *a*	58.8 [c]	55.2 [c]	21.8	29.5	41.1			
	135	*e* (minor)	*d*	57.0	28.0	*d*	47.3			
		a (major)	58.1	53.2	18.4	29.5	38.6			
(7)	183	*e* ⇌ *a*	64.9	56.9	17.7	30.3	32.5		21.1	
	133	*a* (major)	64.9	56.9	17.4	30.3	32.5		21.3	
(8)	285	*e* ⇌ *a*	56.2 [c]	53.3 [c]	21.5	29.6	46.1	13.2		
	127	*a* (major)	54.4	52.9	18.9	29.4	43.5	13.1		
(9)	273	set A ⇌ set B	64.4	50.6	18.3	29.1	40.2	14.3	21.4	
	173	set A (major)	65.2	50.7	16.9	30.1	36.8	13.8	21.1	
		set B (minor)	58.9	44.5	18.3	21.7	46.9	*d*	*d*	
	138	set A (major)	65.0	50.0	16.4	29.9	36.3	13.3	21.0	
(10)	285	set A ⇌ set B	70.9	49.6	18.6	28.4	41.1	13.9	28.4	11.9
	173	set A (major)	72.0	50.2	17.3	30.1	36.5	13.3	28.2	11.9
		set B (minor)	65.7	45.2	18.2	24.0	46.7	13.8	27.5	12.6
	133	set A (major)	71.7	49.7	17.0	28.0	36.0	13.0	30.1	12.0
(11)	285	set A ⇌ set B	76.2	48.9	18.4	27.9	31.2	13.6	42.3	20.6, 22.0
	178	set A (major)	78.2	50.2	16.9	30.2	32.0	12.9	36.5	20.3, 21.7
		set B (minor)	71.1	46.1	18.3	24.4	30.7	14.0	46.9	20.7, 22.5
(12)	273	*e* ⇌ *a*	54.7 [c]	50.4 [c]	23.2	29.7	49.6	20.7		
	143	*e* ⇌ *a*	54.5	49.5	19.9	29.3	46.1	20.8, 21.2		
(13)	280	*e* ⇌ *a*	55.7	48.3	29.1 [c]	29.3 [c]	51.4	27.3		
	143	*e* ⇌ *a*	55.7	47.7	28.6	28.6	50.6	26.3		

[a] Solvent CF_2Cl_2–[$^2H_6$]acetone. [b] In p.p.m. downfield from Me_4Si. [c] May be interchanged. [d] Not distinguished.

1,3-Diethyl-2-methyl-1,3-diazacyclohexane (4).—The ^{13}C spectra (Figure) vary with temperature: at 285 K peaks indicative of fast ring and nitrogen inversion are shown (a coincidence occurs at δ 46.8 p.p.m.) and assignment is helped by the off-resonance decoupled spectrum (a). Cooling results in spectral changes in two different temperature ranges: first slowing of the lowest energy ring inversion (Scheme 2) splits the signals into two unequal sets (181 K). The ring inversion barrier follows from the Eyring equation (Table 3). Set B (Scheme 2) with axial *C*-alkyl is the major form as it displays 2-CH_3 and C-4 and -6 to higher field than in the minor, by virtue of the *γ-gauche* effect,[3] and $\Delta G°$ is obtained by integration at 181 K. At still lower temperatures the set A signals (*C*-alkyl equatorial) undergo a second coalescence and at 134 K further signals are distinguishable: this is ascribed to the slowing of nitrogen inversion enabling observation of the separate conformers within set A; again inversion barrier and equilibrium data are computed (Table 3). There are indications that the set



SCHEME 2

TABLE 3

Kinetic and equilibrium parameters [a] for 1,3-diazacyclohexanes

Compound	Carbon atom examined	Ring inversion T_c/K	$\Delta G_c^{\ddagger}$ [b] (set A → ts)	$\Delta G_c^{\ddagger}$ [b] (set B → ts)	$\Delta G_c°$ [c] (set A → set B)
(2) [f]	C-2	233	11.0	10.0	+1.0
(4)	C-2	208	9.4	9.8	−0.4
(5)	–C–*C*	193 [i]	10.3 [i]		
		220 [j]	10.4 [j]		

Compound	Carbon atom examined	Nitrogen inversion T_c/K	Δν/Hz	$\Delta\omega_{\frac{1}{2}}$/Hz [d]	$\Delta G_c^{\ddagger}$ [e] (eqeq → ts)	$\Delta G_c^{\ddagger}$ [e] (axeq → ts)	$\Delta G_c°$ [c] (N-R eqeq → N-R axeq)
(1)	C-2	153	73		7.6	6.9	+0.7
(2)	C-2	163	73 [g]	5	7.2	8.1	−0.9
(3)	C-2	140 [h]	110 [h]		6.9	6.3	*ca.* +0.6
(4)	C-2	145	140		6.7 [h]	7.1 [h]	*ca.* −0.4 [h]

[a] From ^{13}C n.m.r. data except where specified. [b] ±0.3 kcal mol^{-1}. [c] ±0.1 kcal mol^{-1}. [d] Corrected for natural line width [e] ±0.5 kcal mol^{-1}. [f] Ref. 2. [g] By analogy with corresponding atom in (1). [h] Within set A. [i] From diastereotopicity of isopropyl methyl groups. [j] From ^{1}H n.m.r. data; coalescence of NCH_2N.

B signals also begin to coalesce at the lowest attainable temperatures. The interpretation of results is discussed below.

EXPERIMENTAL

Diazacyclohexanes.—Equimolar amounts of 1,3-diethyl- and 1,3-di-isopropylpropane-1,3-diamine and paraformaldehyde were refluxed in benzene (4 h) with removal of water by a Dean–Stark apparatus. Distillation gave the products which were homogeneous by g.l.c. (propylene glycol, 160 °C, N_2 18 lb in^{-2}): 1,3-diethyl-1,3-diazacyclohexane (3), b.p. 66 °C at 20 mmHg (75%) (lit.,[7] 60—64 °C at 17 mmHg); 1,3-di-isopropyl-1,3-diazacyclohexane (5), b.p. 78—80 °C at 20 mmHg (68%) (lit.,[15] 44 °C at 0.04 mmHg).

1,3-Diethyl-1,3-diazacyclohexane (4) was prepared by stirring for 4 h equimolar amounts of 1,3-diethylpropane-1,3-diamine and freshly distilled acetaldehyde in ether, under N_2, in the presence of K_2CO_3. Distillation gave the product (43%), b.p. 82 °C at 25 mmHg (lit.,[7] 60—64 °C at 17 mmHg).

1-Thia-3-azacyclohexanes.—Compounds (6), (8), (12), and (13) were prepared by literature methods.[8]

2,3-Dimethyl-1-thia-3-azacyclohexane (7) was obtained from 3-methyl aminopropane-1-thiol[8] and acetaldehyde (molar ratio 1 : 2) in MeOH at room temperature in the dark for 12 h. After evaporation of the solvent and drying, distillation gave the product (47%), b.p. 74—75 °C at 20 mmHg.

2-Methyl-, 2-ethyl, and 2-isopropyl-3-ethyl-1-thia-3-azacyclohexanes (9)—(11) were prepared from 3-ethylaminopropane-1-thiol[8] and the appropriate aldehyde under the same conditions as above. Distillation gave (9) (38%), b.p. 74—75 °C at 10 mmHg, (10) (61%), b.p. 86—87 °C at 10 mmHg, and (11), (21%), b.p. 98 °C at 12 mmHg.

TABLE 4

Kinetic and equilibrium parameters for 1-thia-3-azacyclohexanes

Compound	Carbon atom examined	Ring inversion				
		T_c/K	Δν/Hz	$\Delta G_c^{\ddagger}$ [a] (set A ⟶ ts)	ΔG_c [a] (set B ⟶ ts)	ΔG_c° [b] (set A ⇌ set B)
(6)						
(7)						
(8)						
(9)	C-2	203	158	10.1	9.3	+0.8
(10)	C-2	207	158	10.0	9.5	+0.5
(11)	C-2	213	178	9.8	10.2	+0.4
(12)	–C–*C*	173	9	8.9 [f]		
(13)						

Carbon atom examined	Nitrogen inversion within set A					
	T_c/K	Δν/Hz	$\Delta\omega_{1/2}$/Hz [c]	$\Delta G_c^{\ddagger}$ [d] (eq ⟶ ts)	$\Delta G_c^{\ddagger}$ [d] (ax ⟶ ts)	ΔG_c° [b] (N-R eq ⇌ N-R ax)
{ C-4	153	95		6.9	7.6	−0.7
{ N-CH_3	158	218	23	6.9	7.6	−0.7
						< −2.0
C-5	141	240 [e]		6.0	6.8	−0.8
						< −2.0
						< −2.0
						< −2.0
						> 2.0

[a] ±0.3 kcal mol^{-1}. [b] ±0.1 kcal mol^{-1}. [c] Corrected for natural line width. [d] ±0.5 kcal mol^{-1}. [e] By analogy with Δν for the C-5 in (6). [f] From diastereotopicity of isopropyl methyl group.

TABLE 5

^{1}H 100 MHz n.m.r. data [a]

Compound	Temp. (K)	Chemical shifts [b]							
		2-H	4-H	5-H	6-H	N-C*H*-CH_3	N-CH-C*H*$_3$	C(2)-CH	C(2)-CC*H*$_3$
Diazacyclohexane									
(5)	273	3.32 (s)	2.56 (t)	1.55 (m)	2.56 (t)	2.75 (sept)	1.00 (d)		
	168	3.77, 2.91 (ABq)							
Thiazacyclohexanes									
(9)	309	4.29 (q)	*c*	1.47 (m)	*c*	*c*	1.02 (t)	1.37 (d)	
	166	4.45 (q)					1.03 (t)	1.27 (d)	
(10)	309	3.95 (t)	*d*	*e*	*d*	*d*	1.03 (t)	*e*	0.96 (t)
	166	4.02 (t)							
(11)	309	3.49 (d)	*f*	1.49 (m)	*f*	*f*	1.03 (t)	2.13 (m)	1.03 (d), 0.97 (d)
	166								

[a] Solvent CF_2Cl_2. [b] In p.p.m. downfield from Me_4Si. [c] Overlapping region δ 2.67—3.34. [d] Overlapping region δ 2.55—3.35 (m). [e] Overlapping region δ 1.15—2.05 (m). [f] Overlapping region δ 2.46—3.34.

Physical Measurements.—100 MHz ^{1}H N.m.r. spectra were recorded on a Varian HA-100 spectrometer in 5 mm tubes. Temperatures were measured by methanol shift (⩾ 180 K) or a platinum resistance thermometer (< 180 K) and checked with a copper–constantan thermocouple in the probe. ^{13}C N.m.r. spectra were recorded on Varian XL

100 and JEOL FX-100 instruments, the former in 12 mm and the latter in 10 mm tubes. The deuterium lock utilised $CDCl_3$ or $(CD_3)_2CO$; Me_4Si was the internal reference. Instrument temperature recordings were verified with a copper–constantan thermocouple in the probe. The standard Varian and JEOL low temperature units were used.

RESULTS AND DISCUSSION

^{13}C Chemical shifts for the 1,3-diazacyclohexanes are compared with data for (1) and (2) [2] in Table 1. For the higher temperature spectra, most assignments are unequivocally from relative chemical shifts and off-resonance decoupling. Thus the C-2 atom (adjacent to two nitrogen atoms) appears at δ 70.4—76.2 p.p.m. while the C-5 atom is at considerably higher field, δ 22.1—24.5 p.p.m. In the di-isopropyl compound (5), the C-4 and -6 atoms at δ 49.2 p.p.m. appear as triplets in the off-resonance decoupled spectrum in contrast to the isopropyl methines which in the off-resonance decoupled spectrum show as a doublet at δ 52.4 p.p.m. The isopropyl methyls are at δ 19.7 p.p.m. Assignments for 1,3-diazacyclohexanes (3) and (4) are less certain. In (4) the ethyl methylene carbons and C-4 and -6 atoms are coincident at δ 46.8 p.p.m.; the 2-methyl and the ethyl methyl carbon probably occur at δ 11.2 and 13.6 p.p.m., respectively. In (3) the ethyl methyl carbon is at δ 12.8 p.p.m., but specific assignment of the δ 49.6 and 52.9 p.p.m. peaks to the ethyl methylene and C-4 and -6 atoms cannot be made.

The ^{13}C shifts for the 1-thia-3-azacyclohexanes are shown in Table 2. In the compounds without a 2-substituent, C-2 appears at δ 51.1—58.8 p.p.m.; a 2-substituent displaces the peak to lower field, down to δ 76.2 p.p.m. in (11). The C-5 atom usually absorbs at δ 17.7—23.2 p.p.m., but for the 3-t-butyl compound (13) it is at an unexpectedly low field and cannot be assigned unequivocally with respect to the C-6 atom (δ 29.1 and 29.3 p.p.m.). The C-6 atom is at higher field (δ 27.9—30.3 p.p.m.) than the C-4 atom at δ 48.3—56.9 p.p.m., reflecting the smaller effect of sulphur as compared with nitrogen (and also oxygen [3]).

The chemical shifts of the *N*-substituents are as expected except for the 3-methyl shifts for (6) (δ 41.1 p.p.m.) and (7) (δ 32.5 p.p.m.) are rather different. The ethyl substituents of (8)—(11) display methylenes at δ 41.1—46.1 p.p.m. and methyls at δ 13.2—14.3 p.p.m. The isopropyl (12) and t-butyl (13) shifts are broadly as expected, the quaternary carbon in the latter being at lower field (δ 55.7 p.p.m.), than the tertiary atom in the former (δ 49.6 p.p.m.). The chemical shifts of the 2-alkyl groups in (9)—(11) are unexceptional with the α-carbon shifts to higher field than those of the equivalent *N*-substituents.

On lowering the temperature, substanial changes in all the ^{13}C spectra [except for (7) and (13)] correspond to the slowing of ring [(5), (9)—(12)], or nitrogen inversion [(3), (6), and (8)], or both [(4)]. The signals initially broaden or collapse and then well resolved peaks reappear. If ring inversion is the process slowed, peaks corresponding to both sets A and B (Scheme 2) can be found, but not if the equilibrium is highly biased. If nitrogen inversion is slowed, again peaks due to two individual conformers within the sets may appear. Kinetic and equilibrium parameters (Tables 3 and 4) were obtained, from either the Eyring equation [16] or the Anet broadening method.[17] The ring inversion barriers in the *N*-isopropyl compounds (5) and (12) are also available from the temperature-dependent behaviour of the isopropyl group, the methyls of which become diastereotopic when ring inversion is slowed. The results (Tables 3 and 4) agree well with those from proton spectra (Table 3 and ref. 8).

Assignments of the individual set(s) of low temperature peaks to set A and/or B, or to specific conformers utilises the *γ-gauche* effect: the upfield shift of *γ-gauche* carbon atoms; this is discussed in the previous paper [3] for the 1-oxa-3-azacyclohexanes. On slowing of ring inversion set B predominates for the diazacyclohexane (4) and set A for the thiazacyclohexanes (9)—(11). On slowing nitrogen inversion within set A, the *N*-alkyl axial form predominates for all the thiazacyclohexanes except the t-butyl compound (13); among the diazacyclohexanes the *N*-axial-*N'*-equatorial form predominates for (4) but the *NN'*-diequatorial form for (3). Individual conformers within set B unfortunately cannot be studied: they are present in amounts too small to be experimentally observable or, in the case of (4), have too low a coalescence temperature.

^1H N.m.r. chemical shifts for the diazacyclohexane (5) and thiazacyclohexanes (9)—(11) are shown in Table 5: unfortunately considerable overlap precludes direct observation of the minor set in any of the thiazacyclohexanes, but the ring inversion barrier obtained for (5) (Table 3) is in good agreement with the ^{13}C result.

Weighted average inversion barriers computed from the Eyring equation, together with the $\Delta G°$ value give the individual ' half-barriers ' minor ⟶ ts and major ⟶ ts.[18] The minor ⟶ ts half-barrier is obtained directly from the Anet broadening technique. Discussion in terms of the individual half barriers is far superior to the use of weighed average barriers.[18]

Ring Inversion Barriers.—Barrier magnitudes decrease in the order (5), 3-isopropyl-1-oxa-3-azacyclohexane,[3] (12) [$\Delta G°$ ts ⟶ major: 10.3, 9.6 (average value), and 8.9 kcal mol^{-1}], as expected the same order as for torsional barriers.[19] Also as expected, in both 1,3-diaza- and 1-thia-3-aza-cyclohexanes ring barriers decrease with increasing size of substituent: compare (1),[7] (3),[7] and (5) with 11.3, 10.9, and 10.3 kcal mol^{-1}, also (8) [8] and (12) with 9.8 and 8.9 kcal mol^{-1}.

In the 1-oxa-3-azacyclohexane series,[3] the introduction of 2- or 4-substituents reduces the ring-inversion barrier and this trend is also observed in the 1,3-diaza- and 1-thia-3-aza-cyclohexane series for the introduction of 2-methyl groups: compare (3) [7] and (4) (10.9 and 9.4 or 9.8 kcal mol^{-1}), and (8) [8] and (9) (9.8 and 9.3 or 10.1 kcal mol^{-1}). However, introduction of 2-ethyl or 2-isopropyl groups appears to raise the barrier [*cf.* (10) and (11)].

Nitrogen Inversion Barriers.—As for the 1-oxa-3-

azacyclohexanes,[3] these decrease with increasing size of N-substituent for both series [*cf.* the barriers for (1) [2] and (3) and (6) and (8)]. Decrease in both ring and nitrogen inversion barriers with increasing size of N-substituent reflects increasing planarity at nitrogen. The variation in the half-barrier magnitudes (eq ⟶ ts and ax ⟶ ts) in the series 1-methyl-1-oxa-3-aza-, 1,3-dimethyl-1,3-diaza- (1) and 1-methyl-1-thia-3-aza-cyclohexane (6) is irregular because it depends on the interaction of electronic (anomeric) and steric (ring puckering) effects. This has been explained in detail elsewhere.[18] The corresponding ethyl-substituted compounds are found to follow a similar pattern.

Bending away of a 2-methyl group in the 1-oxa-3-azacyclohexane series relieves transition state strain and hence 2-alkyl substitution alters little the nitrogen inversion barrier. Such deformation is less easy for 1,3-diazacyclohexanes and 2-substitution significantly raises the ax ⟶ ts barriers [*cf.* (1) and (2) and also (3) and (4)]. The eq ⟶ ts barrier is not however significantly altered because the equatorial ground state is raised in energy due to the reluctance of three adjacent groups to be equatorial.[2] Insufficient data preclude comparisons with the thiazacyclohexanes.

Equilibrium Data.—All compounds studied, including the 1-oxa-3-azacyclohexanes,[3] show predominance of set A (C-alkyl equatorial) over set B with the single exception of 1,3-diethyl-2-methyl-1,3-diazacyclohexane (4): for the analogous 1,2,3-trimethyl compound (2) set A predominates and the replacement of 1,3-dimethyl by 1,3-diethyl causes a marked swing of 1.4 kcal mol^{-1} in $\Delta G_c°$, illustrating a large buttressing effect of N-ethyl groups vicinal to the C-methyl.

The increasing proportion of the minor set B in the 1-thia-3-azacyclohexane series [*cf.* (9)—(11)] on increasing the size of the C-alkyl substituent, is probably due to the long C–S bond. This flattens the ring at the nitrogen atom such that an equatorial alkyl group at the 2-position will partially eclipse an N-alkyl axial group. Torsional strain increases with the bulk of the 2-alkyl group and this results in a relative increase of set B.

If the equilibrium at nitrogen were governed entirely by the anomeric effect, the relative electronegativities of nitrogen, sulphur, and oxygen should result in increasing N-alkyl axial orientation in the series diazacyclohexane ⟶ thiazacyclohexane ⟶ oxazacyclohexane. The observed reverse in the position of the last two systems is again probably ascribable to distortion about the sulphur atom.

For the 1,3-diazacyclohexanes the equilibrium is biased to N_{axeq} in the presence of a 2-alkyl equatorial group, but to N_{eqeq} when there is no 2-alkyl substituent [*cf.* (1) and (2) and (3) and (4)], by simple steric crowding.

For both diazacyclohexanes and thiazacyclohexanes there is little difference in free energy between N-methyl and N-ethyl substituted compounds [*cf.* (1) and (3) and (6) and (8)]. Among the thiazacyclohexanes $\Delta G_c°$ values are available only for (6) and (8) from the dynamic n.m.r. technique. It is however possible to assign the observed conformer in other compounds of the series by examination of the C-5 chemical shift. Thus in (7) the C-5 chemical shift is seen to resemble the corresponding shifts of (6) and (8) in which N-alkyl axial (on the basis of the *γ-gauche* effect) is thought to be preferred (Table 2). The axial preference is expected, as introduction of the equatorial 2-methyl group will tend to increase the preference already observed in (6).

Although certain trends have been established within the compounds under discussion, however the experimental data result from the interaction of several factors. If one factor predominates, regular trends will be observed: however, if two or more factors are important then results may appear 'anomalous' and can be rationalised only by knowledge of the relative importance of all the factors involved.

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REFERENCES

[1] Part 100, see ref. 3.
[2] A. R. Katritzky, V. J. Baker, I. J. Ferguson, and R. C. Patel, *J.C.S. Perkin II*, 1979, 143.
[3] A. R. Katritzky, V. J. Baker, and F. M. S. Brito-Palma, preceding paper.
[4] 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.
[5] I. D. Blackburne, A. R. Katritzky, D. M. Read, P. J. Chivers, and T. A. Crabb, *J.C.S. Perkin II*, 1976, 418.
[6] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1970, **26**, 3941.
[7] F. G. Riddell, *J. Chem. Soc.* (*B*), 1967, 560.
[8] L. Angiolini, A. R. Katritzky, and D. M. Read, *Gazzetta*, 1976, **106**, 111.
[9] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Perkin II*, 1977, 818.
[10] F. R. Farmer and J. Hamer, *Tetrahedron*, 1968, **24**, 829.
[11] R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, 1968, **90**, 7174.
[12] F. G. Riddell and D. A. R. Williams, *Tetrahedron Letters*, 1971, 2073.
[13] L. Angiolini, R. P. Duke, R. A. Y. Jones, and A. R. Katritzky, *J.C.S. Perkin II*, 1972, 674.
[14] P. J. Halls, R. A. Y. Jones, A. R. Katritzky, M. Snarey, and D. L. Trepanier, *J. Chem. Soc.* (*B*), 1971, 1320.
[15] R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc.* (*B*), 1970, 131.
[16] S. Glasstone, K. J. Laidler, and M. Eyring, 'Theory of Rate Processes', McGraw-Hill, New York, 1941, p. 195.
[17] F. A. L. Anet and V. J. Basus, *J. Amer. Chem. Soc.*, 1973, **95**, 4424; F. A. L. Anet in 'Topics in Carbon-13 NMR Spectroscopy', ed. G. C. Levy, Wiley-Interscience, New York, 1974, vol. 1, p. 220; F. A. L. Anet, I. Yavari, I. J. Ferguson, A. R. Katritzky, M. Moreno-Manas, and M. J. T. Robinson, *J.C.S. Chem. Comm.*, 1976, 399.
[18] 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.
[19] J. B. Lambert and S. I. Featherman, *Chem. Rev.*, 1975, **75**, 611.