The Conformational Analysis of Saturated Heterocycles. Part 84.[1] Conformational Consequences of Internal β-Heteroatoms. Ring and Nitrogen Inversion in 3,5-Dimethyl-1-oxa-3,5-diaza-, 5-Methyl-1,3-dioxa-5-aza-, and 1,3,5-Trimethyl-, -Triethyl-, -Tri-isopropyl-, and -Tri-t-butyl-1,3,5-triaza-cyclohexanes

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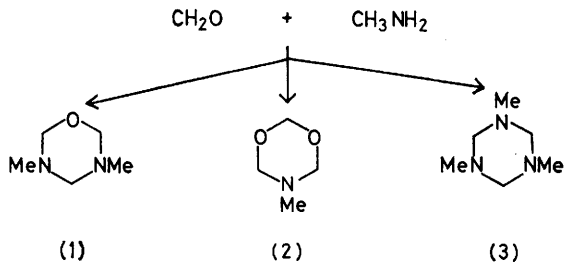
Variable temperature proton and carbon-13 dynamic n.m.r. spectroscopy has been used to study the inversion barriers and preferred conformations of 3,5-dimethyl-1-oxa-3,5-diaza-, 5-methyl-1,3-dioxa-5-aza-, and 1,3,5-trimethyl-1,3,5-triaza-cyclohexane. The conformational consequences of consecutively replacing O with NMe in passing from 1,3,5-trioxacyclohexane to 1,3,5-trimethyl-1,3,5-triazacyclohexane are discussed. The observed effects of increasing size of alkyl substituent on the 1,3,5-triazacyclohexane system are also discussed.

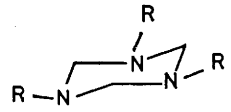
In recent years, while the conformational properties of 1,3,5-triazacyclohexane [2,3] and 1,3,5-trioxacyclohexane [4] have received attention, the other members of this series, 1-oxa-3,5-diaza- and 1,3-dioxa-5-aza-cyclohexane, have been little investigated. In an attempt to understand better the effect of β-heteroatoms on inversion processes and equilibria, and obtain an overall view of the conformational consequences of consecutively replacing O with NMe in passing from 1,3,5-trioxacyclohexane to 1,3,5-triazacyclohexane, we have now studied 3,5-dimethyl-1-oxa-3,5-diaza- (1) and 5-methyl-1,3-dioxa-5-aza-cyclohexane (2), by both proton and carbon-13 dynamic n.m.r. spectroscopy. For the sake of completeness, we also reinvestigated the conformational properties of 1,3,5-trimethyl-1,3,5-triazacyclohexane (3) by carbon-13 dynamic n.m.r. A further study involved a series of 1,3,5-trialkyl-1,3,5-triazacyclohexanes (3)—(6) with a view to discovering the effect of increasing size of alkyl group on conformational properties.

Preparation of Compounds (*Scheme* 1).—Attempts at a



SCHEME 1

specific synthesis of 3,5-dimethyl-1-oxa-3,5-diazacyclohexane (1) by reduction of the corresponding 4-oxo-compound with diborane or lithium aluminium hydride were unsuccessful. However, it is well known [5] that the reaction of methylamine with formalin, as well as yielding 1,3,5-trimethyl-1,3,5-triazacyclohexane (3), the major product, also gives a number of minor products including 3,5-dimethyl-1-oxa-3,5-diaza- (1) and 5-methyl-1,3-dioxa-5-aza-cyclohexane (2). Judicious choice of reactant ratios and reaction time leads to a mixture in which the 1-oxa-3,5-diaza- and 1,3-dioxa-5-aza-systems are the major products, although at room temperature these disproportionate to the 1,3,5-triaza-system. Distillation permits effective separation of the triaza- (3) and the dioxa-aza-derivative (2), but attempts to isolate the oxadiaza-compound (1) were unsuccessful owing to its instability: consequently the spectroscopic study was conducted on a mixed sample of the oxa-diaza- (1) and the dioxa-aza-analogue (2), as well as on pure samples of the triaza- (3) and the dioxa-aza-derivative (2).



(4) R = Et
(5) R = Pr^i
(6) R = Bu^t

The 1,3,5-triaza-compounds (4)—(6) were also prepared by condensation of the appropriate primary amine and formaldehyde, proportions and reaction time being chosen so as to maximise the yield in each case. The compounds were obtained in pure form by distillation.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a Varian HA-100 spectrometer. Temperatures (±2 °C) were measured with the standard methanol sample [6] above −90 °C; below this temperature a platinum resistance thermometer was used. Chemical shifts (±0.01 p.p.m.) were measured in CF_2Cl_2, with Me_4Si as internal standard. Natural abundance carbon-13 n.m.r. spectra were measured with a Varian XL-100 spectrometer, in pulsed FT mode using an ICL 1903T computer. The resonance frequency for the carbon-13 nuclei was 25.16 MHz; sealed 12 mm tubes were employed. The ^{2}H-heteronuclear lock and proton noise decoupling to ascertain chemical shifts were used. Gated decoupling was conducted using a pulse delay of 8 s with a 50 μs pulse width. Temperatures as low as 133 K could be attained using as solvent $(CD_3)_2CO$–CF_2Cl_2 (1 : 3). Temperatures are accurate to at least ±3 K.

[1] Part 83, V. J. Baker, A. R. Katritzky, and F. M. S. Brito-Palma, Heterocycles, 1977, **8**, 451.
[2] R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc.* (*B*), 1970, 135.
[3] C. H. Bushweller, M. Z. Lourandos, and J. A. Brunelle, *J. Amer. Chem. Soc.*, 1974, **96**, 1591.
[4] (*a*) J. E. Anderson, *Fortschr. Chem. Forsch.*, 1974, **45**, 139; (*b*) B. Pedersen and J. Schaug, *Acta Chem. Scand.*, 1968, **22**, 1705.
[5] W. J. Kauffman, *J. Heterocyclic Chem.*, 1975, **12**, 409; W. V. Farrar, *Rec. Chem. Progr.*, 1968, **29**, 85.
[6] A. L. Van Geet, *Analyt. Chem.*, 1970, **42**, 679.

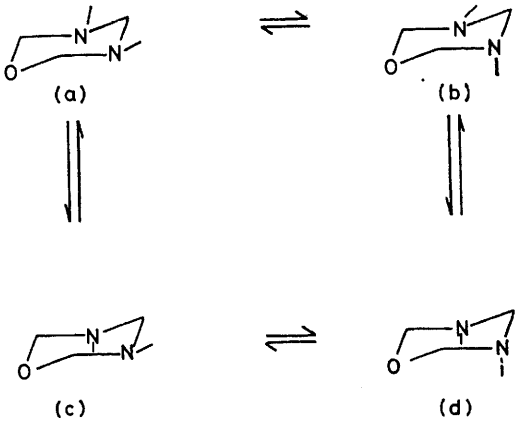
1,3,5-Trisubstituted 1,3,5-Triazacyclohexanes.—1,3,5-Trimethyl-1,3,5-triazacyclohexane (3) [7] (b.p. 50—52 °C at 15 mmHg; lit.,[7] b.p. 160—164 °C at 760 mmHg) and 1,3,5-triethyl-1,3,5-triazacyclohexane (4) [2] (b.p. 92—96 °C at 15 mmHg; lit.,[2] 69—70 °C at 2 mmHg) were prepared by standard methods. Similarly prepared were 1,3,5-tri-isopropyl-1,3,5-triazacyclohexane (5) (using isopropylamine), an oil (29%), b.p. 110—112 °C at 15 mmHg (lit.,[2] 81 °C at 1 mmHg); and 1,3,5-tri-t-butyl-1,3,5-triazacyclohexane (6) (using t-butylamine), a yellowish oil (22%), b.p. 120—126 °C at 15 mmHg (lit.,[2] 125—130 °C at 20 mmHg).

3,5-Dimethyl-1-oxa-3,5-diazacyclohexane (1).—This was prepared as for 5-methyl-1,3-dioxa-5-azacyclohexane. The oil obtained by extraction from the reaction mixture with dichloromethane was distilled at 45 °C at 20 mmHg to yield a mixture of the oxadiaza- and dioxa-aza-compounds, which was kept at −78 °C. Careful redistillation yielded an unstable oil, *3,5-dimethyl-1-oxa-3,5-diazacyclohexane*, b.p. 45 °C at 15 mmHg; δ(CF_2Cl_2) 2.33 (3 H, s), 3.43 (1 H, s), and 4.17 (2 H, s); *m/e* 116.

5-Methyl-1,3-dioxa-5-azacyclohexane (2).—Aqueous $MeNH_2$ (30%; 5 ml, 0.02 mol) was added to a rapidly stirred solution of HCHO (30%; 50 ml, 0.5 mol) below 5 °C. After 0.5 h the mixture was extracted with CH_2Cl_2 (4 × 30 ml). The extracts were dried, and the solvent removed to give a product mixture containing the triaza- (3), the oxadiaza- (1), and the dioxa-aza-compound (2). Careful double distillation afforded *5-methyl-1,3-dioxa-5-azacyclohexane*, b.p. 38 °C at 15 mmHg (Found: C, 45.9; H, 9.0; N, 13.2. $C_4H_9NO_2$ requires C, 46.0; H, 8.7; N, 13.6%); δ(CF_2Cl_2) 2.73 (3 H, s), 4.51 (4 H, s), and 5.02 (2 H, s); *m/e* 103.

DISCUSSION

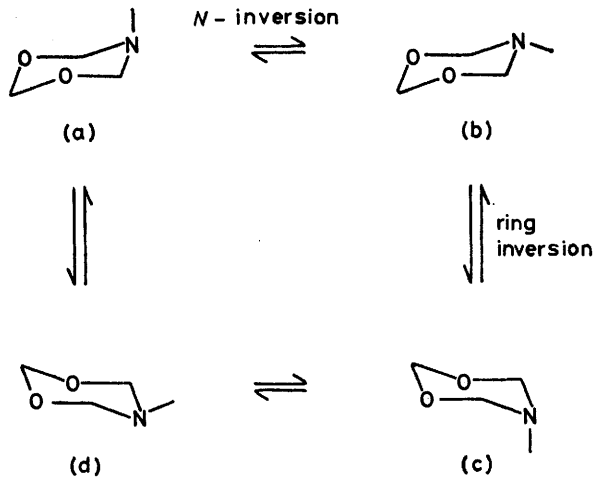
Expected Population Trends.—The 1-oxa-3,5-diaza-compound, which can exist in four possible conformers, two of which are degenerate (Scheme 2), might be



SCHEME 2

expected to reflect the conformational equilibrium of hexahydro-1,3-dimethylpyrimidine ($\Delta G_{25}°$ 0.54 kcal mol^{-1} in favour of the diequatorial conformer [8]). However, the inclusion of an additional β-heteroatom should mitigate against any appreciable population of the diequatorial form (a) and thus result effectively in the exclusive population of the equatorial axial form (1b, c) on the basis of the anomeric effect and reduced 1,3-*syn*-diaxial interactions.

The dioxa-aza-compound (2) (Scheme 3) should exhibit



SCHEME 3

effective population of one conformer with the *N*-methyl in an axial environment (2a, c), as the advantageous removal of 1,3-*syn*-diaxial interactions and the relief of adverse anomeric effects support population of the *N*-methyl axial conformer. A similar preference is observed with 1,3-dithia-5-azacyclohexanes.[9]

The conformational equilibrium of 1,3,5-trimethyl-1,3,5-triazacyclohexane has previously been investigated [3] by proton dynamic n.m.r. The results showed the monoaxial, diequatorial conformer effectively to be the only populated form.[3] Similar results were obtained for the other 1,3,5-triazacyclohexanes.

Inversion Processes.—The barrier to ring inversion would be expected to exhibit a consistent increase in magnitude in passing from 1,3,5-trioxa- to 1,3,5-triazacyclohexane, as the result, in part, of an increase in torsional strain in the transition state when O is replaced with NMe.

Recently two [10,11] alternative quantitative assessments of steric and electronic increments to *N*-inversion barriers in saturated six-membered heterocycles have been produced, which allow the prediction of unknown barriers. The treatments would predict a free activation energy for *N*-inversion of 7.2 kcal mol^{-1} [10] and 5.6 kcal mol^{-1} [11] respectively for 3,5-dimethyl-1-oxa-3,5-diazacyclohexane.

In the case of the 1,3,5-triaza-series, a decrease would be expected in the size of the ring inversion activation energy barrier with increasing size of alkyl substituent. This is due to the raising of the ground state energy with increasing substituent size, the ground state being more

[7] J. Graymore, *J. Chem. Soc.*, 1924, 2283.
[8] R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc.* (*B*), 1970, 131.
[9] L. Angiolini, R. P. Duke, R. A. Y. Jones, and A. R. Katritzky, *Chem. Comm.*, 1971, 1308.
[10] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Chem. Comm.*, 1975, 255.
[11] F. G. Riddell and H. Labaziewicz, *J.C.S. Chem. Comm.*, 1975, 766.

sensitive to the extra crowding than the transition state owing to 1,3-diaxial interactions in the former.

A similar decrease is expected in the case of nitrogen inversion barriers with increasing substituent size: as substituent size increases, there is an increasing tendency to planarity of the nitrogen atom and hence decrease in barrier size.

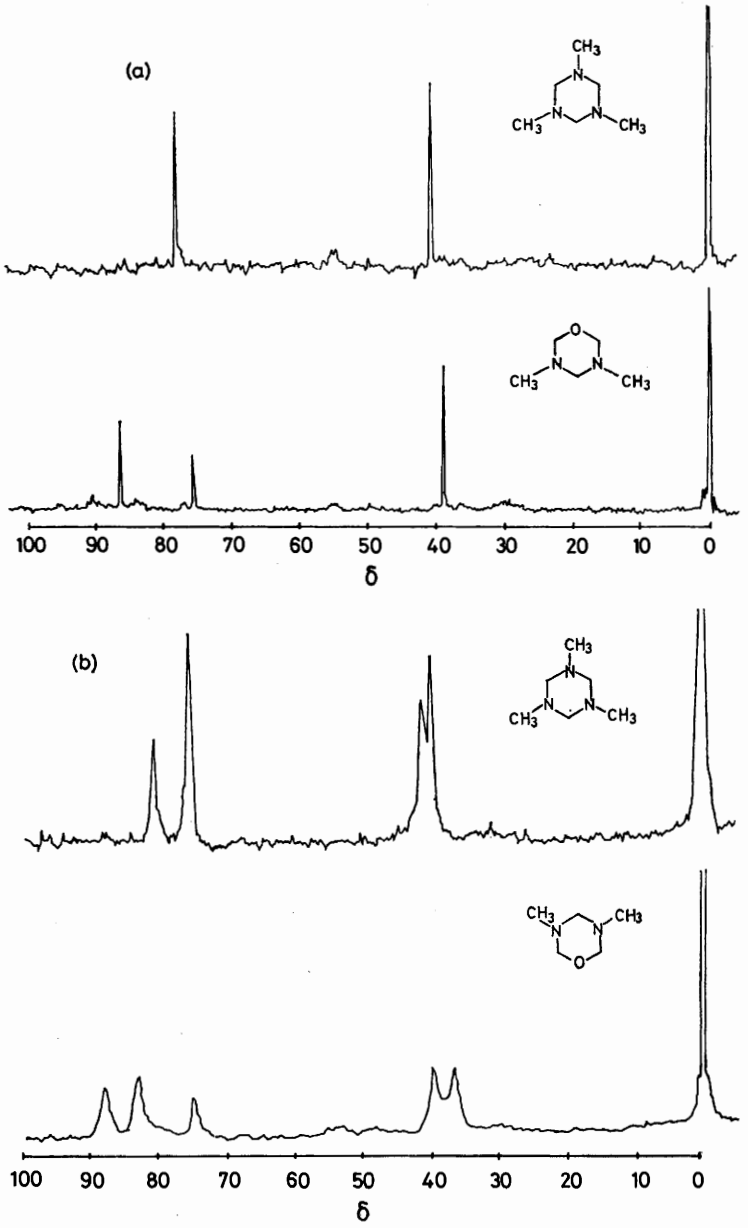


FIGURE 1 Pulsed ^{13}C Fourier transform n.m.r. spectra (25.16 MHz) with proton decoupling of 1,3,5-trimethyl-1,3,5-triaza-, 3,5-dimethyl-1-oxa-3,5-diaza-, and 5-methyl-1,3-dioxa-5-aza-cyclohexane at (a) +36 °C; (b) −150 °C

Results.—The proton n.m.r. spectrum of 3,5-dimethyl-1-oxa-3,5-diazacyclohexane at 34 °C exhibits a simple first-order three-line pattern (Table 1) consistent with rapid ring and *N*-inversion. On lowering the temperature, ring inversion is the first process to become slow (*ca.* −43 °C), the methylene singlets collapsing and separating into two AB quartets. The free activation energy for ring inversion was calculated to be 11.2 kcal mol^{-1} (Table 2). Further lowering of temperature appeared to slow *N*-inversion by −140 °C; however, the results were obscured by line broadening and only an approximate value of 6.8 ± 0.4 kcal mol^{-1} for the free activation energy to *N*-inversion was obtained.

A pulsed ^{13}C FT dynamic n.m.r. study under proton-decoupling conditions gave a simple three-line spectrum for the oxadiaza-compound (1) (Figure 1, Table 3). No changes were apparent in the temperature range 34 to −66 °C; however, at lower temperatures the ^{13}C signals of NCH_3 and OCH_2N collapse and then reappear as doublets of approximately equal intensity while the NCH_2N signal remains a singlet (Figure 1, Table 3).

The spectrum corresponds to that expected of conformer (1b, c) and the process slowed is the interconversion of conformer (1b) with its mirror image (1c). As can be seen from Figure 2 the axial,equatorial conformer (1b, c) can interconvert *via* either the diaxial (d) or the di-equatorial (a) intermediate. We believe that electronic interactions result in the transition state I being highest in energy and thus the route *via* the transition state II should be preferred. The process slowed is thus II *ae* ⇌ *aa* with $\Delta G_c^{\ddagger}$ 6.8 kcal mol^{-1} (Table 4). The ^{13}C temperature-dependent spectra of 5-methyl-1,3-dioxa-5-azacyclohexane exhibited no observable spectral changes over the temperature range +34 to −145 °C, indicative of only the *N*-methyl (axial) conformer being populated. An analogy can be drawn with the 1,3-dithia-5-azacyclohexanes.[9]

Riddell *et al.*[12] have studied the model compounds (7) and (8); comparison of n.m.r. data (Table 1) with those for (1) and (2) substantiates the axial,equatorial and axial conformer preference, respectively.

TABLE 1

^{1}H Chemical shifts (p.p.m. from Me_4Si) at 100 MHz for 3,5-dimethyl-1-oxa-3,5-diaza- and 5-methyl-1,3-dioxa-5-aza-cyclohexane and compounds (7) and (8) at various temperatures

Compound		T/K	N·CH$_3$	N·CH$_2$·N	N·CH$_2$·O	O·CH$_2$·O
(1)	*a*	307	2.33	3.43	4.17	
	b	204	2.33	3.58, 3.28 (ABq,[2] J_{HH} 10.0 Hz)	4.02, 4.32 (ABq,[2] J_{HH} 10.0 Hz)	
		124	2.51, 2.15	*c*	*c*	
(2)	*a*	307	2.73		4.51	5.03
	b	204	2.73		4.69, 4.29 (ABq,[2] J_{HH} 10.0 Hz)	5.03
(7)	*a*	307		0.52 ($\Delta\nu$),[d] (ABq,[2] J_{HH} 11.2 Hz)		
(8)	*a*	303			4.55, 4.66 (ABq,[2] J_{HH} 10.5 Hz)	

[a] In $CDCl_3$. [b] In CF_2Cl_2. [c] Complex [d] $\Delta\nu$ is the chemical shift difference between H_{ax} and H_{eq}.

TABLE 2

^{1}H N.m.r. coalescence data and activation energies for the triaza–trioxa-series

Ring inversion [a] (CF_2Cl_2)	Signal observed	$\Delta\nu$/Hz	J/Hz	T_c/K	$\Delta G_c^{\ddagger}$/kcal mol^{-1}
3,5-Dimethyl-1-oxa-3,5-diaza- (1)	NCH_2N	29.4	10.0	227	11.2
	NCH_2O	30.0	10.0	227	11.1
5-Methyl-1,3-dioxa-5-aza- (2)	NCH_2O	40.0	10.0	215	10.5
1,3,5-Trioxa-	NCH_2O				10.9 [c]
1,3,5-Trimethyl-1,3,5-triaza- (3)	NCH_2N	90.0	9.9	264	12.8 [b]
1,3,5-Triethyl-1,3,5-triaza- (4)		108		251	11.4
1,3,5-Tri-isopropyl-1,3,5-triaza- (5)		92		232	11.0
1,3,5-Tri-t-butyl-1,3,5-triaza- (6)		120		219	10.2

[a] From ^{1}H spectral data. [b] Ref. 3. [c] Ref. 4*b*; in ref. 4*a* this is given as 10.2 kcal mol^{-1}.

TABLE 3

Carbon-13 chemical shifts (p.p.m. from Me_4Si) [a] at 25.16 MHz and at various temperatures

Cyclohexane	T/K	N·*C*H$_3$	N·*C*H$_2$·N	O·*C*H$_2$·N	O·*C*H$_2$·O
3,5-Dimethyl-1-oxa-3,5-diaza-	307	39.26	76.26	86.89	
	128	41.00 37.51	76.14	89.54 84.21	
5-Methyl-1,3-dioxaza-5-aza-	307	39.02		85.22	95.65
	128	38.68		84.25	94.94
1,3,5-Trimethyl-1,3,5-triaza-	307	40.55	78.09		
	128	41.43 39.94	80.74 75.51		

[a] Solvent CF_2Cl_2–$(CD_3)_2CO$, 2 : 1.

TABLE 4

^{13}C N.m.r. coalescence data and activation energies for nitrogen inversion

Cyclohexane	Signal observed	$\Delta\nu$/Hz	T_c/K	$\Delta G_c^{\ddagger}$/kcal mol^{-1}
3,5-Dimethyl-1-oxa-3,5-diaza- (1)	N*C*H$_3$	37.7	143	6.89
	N*C*H$_2$O	130.8	148	6.78
1,3,5-Trimethyl-1,3,5-triaza- (3)	N*C*H$_3$	37.7	148	7.15
	N*C*H$_2$N	130.8	157	7.21
1,3,5-Triethyl-1,3,5-triaza- (4)	N*C*H$_2$N	112.2	143	6.80
1,3,5-Tri-isopropyl-1,3,5-triaza- (5)	N*C*H$_2$N	171.1	133	5.99

1,3,5-*Trialkyltriazacyclohexanes*.—The room temperature ^{1}H n.m.r. spectrum displayed a single peak for the ring methylene protons in the case of each triazane (3)—(6); characteristic signals were observed for each *N*-substituent. Reduction in temperature resulted

[12] F. G. Riddell and D. A. R. Williams, *Tetrahedron Letters*, 1971, 2072; F. G. Riddell and J. M. Lehn, *J. Chem. Soc.* (*B*), 1968, 1224.

initially in the formation of an AB quartet for the ring methylene protons in each case. At this stage the lack of change in the substituent group signals is thought to be due to the slowing of ring inversion while nitrogen

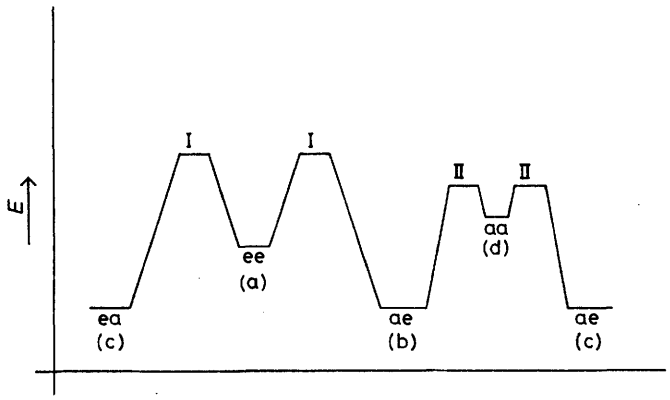


FIGURE 2 *N*-Inversion pathways for interconversion of the 3,5-dimethyl-1-oxa-3,5-diazacyclohexane conformers

inversion remained fast. On lowering the temperature further, unfortunately only the trimethyl compound (3) displayed further coalescence behaviour. Compounds

(7) X = NMe

(8) X = O

(4)—(6) showed further peak broadening at temperatures approaching −150 °C, but this was probably due to freezing out or relaxation effects rather than coalescence.

Ring inversion barriers calculated for each compound using the Eyring equation (Table 2) were in good agreement with the previously quoted results.[13] Increasing substituent size results in lowered barriers, as expected.

The ^{13}C n.m.r. studies on the series of 1,3,5-triazacyclohexanes, which for 1,3,5-trimethyl-1,3,5-triazacyclohexane confirmed the findings of Bushweller *et al.*,[3] are consistent with the above. At room temperature single peaks for the ring carbon atoms were observed, together with expected signals for the substituent group. ^{13}C N.m.r. spectroscopy does not reveal changes as ring inversion is slowed because the carbon atoms remain magnetically equivalent owing to nitrogen inversion. When nitrogen inversion is also slowed changes occur in the spectrum. The greater chemical shift differences in ^{13}C n.m.r. spectroscopy as compared with ^{1}H n.m.r. reveal nitrogen inversion coalescence phenomena for compounds (4) and (5) [as well as (3)]: at *ca.* −135 °C the N–*C*–N and N–C–*C* peaks each split into an unequal doublet and the N–*C*–C peak became noticeably broadened. As expected, the trimethyl compound (3) confirmed the ^{1}H n.m.r. results and the methyl and methylene carbon atom peaks both split into two unequal peaks. The barrier for the t-butyl compound (6) is evidently so low as to be inaccessible even to studies by ^{13}C n.m.r. The Eyring equation was applied (Table 4): as expected, increasing size of substituent results in marked lowering of the nitrogen inversion barrier.

Conclusion.—The results indicate that an *N*-methyl substituent in a saturated six-membered ring containing two β-heteroatoms will preferentially adopt an axial environment reflecting the overall effect of the non-bonded interactions. The conformational preference and *N*-inversion barrier deduced from the carbon-13 study for the triaza-compound (3) are in excellent agreement with those obtained previously [3] and show that approximation methods [14] for the determination of barriers are of value when suitably applied. Further, the results confirm the expected trend of a consistent increase in the magnitude of ring inversion in passing from 1,3,5-trioxa- to 1,3,5-trimethyl-1,3,5-triaza-cyclohexane. In particular the value for nitrogen inversion of 3,5-dimethyl-1-oxa-3,5-diazacyclohexane (1) is in fair agreement with our preliminary published account of *N*-inversion barriers in six-membered rings [10] and not with that proposed by Riddell.[11] Further discussion on this point awaits future work.* Specifically neither of the earlier treatments distinguishes between $N_{ax} \longrightarrow N_{eq}$ and $N_{eq} \longrightarrow N_{ax}$ inversion energies, quantities that can be considerably different for biased equilibria.

In the case of the 1,3,5-triaza-series, the expected trends of decreasing ring and nitrogen inversion barrier with increasing size of substituent are confirmed. The usefulness of the ^{13}C dynamic n.m.r. method is well illustrated by these studies: only one of the four compounds studied yields its *N*-inversion barrier to ^{1}H n.m.r. spectroscopy whereas the application of ^{13}C spectroscopy shows unequivocally the order for the entire series of compounds and yields quantitative information for all but one.

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* We have implicity assumed a transmission coefficient of 1 for the calculation of $\Delta G^{\ddagger}$. However, it could be less than this, down to a limit of 0.5 if the energy of the diaxial form is sufficiently below that of the transition state. Taking $f = 0.5$ gives $\Delta G^{\ddagger}$ 6.6 kcal mol^{-1}. Dr. Riddell informs us that a value of 6.6 for $\Delta G^{\ddagger}$ is close to a prediction based on a revision of his scheme of increments.

[13] H. S. Gutowsky and P. A. Temussi, *J. Amer. Chem. Soc.*, 1967, **89**, 4358.

[14] G. Binsch, *Topics Stereochem.*, 1968, **3**, 97.