The Conformational Analysis of Saturated Heterocycles. Part 90.[1] Syntheses and Conformational Analysis of 1,2,4-Trimethyl- and 1,2,3,4-Tetramethyl-1,2,4-triazacyclohexanes [2]

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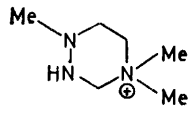
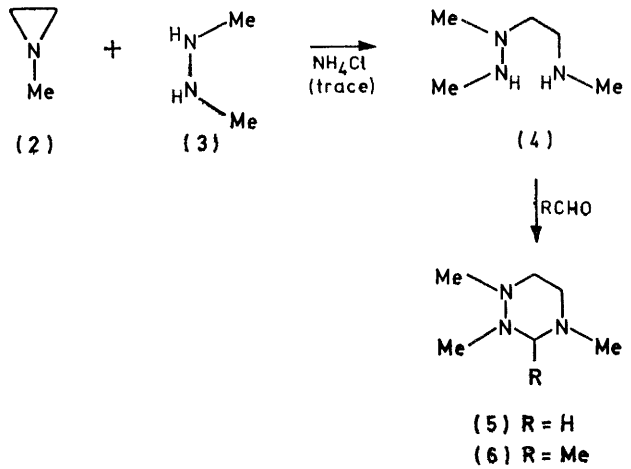
The first syntheses are described of saturated 1,2,4-triazacyclohexanes. The 1,2,4-trimethyl derivative exists predominantly in the *eae* conformation: at lower temperatures minor amounts of *eee*⇌*eea* (*ca.* 10%) and then *aee* (*ca.* 5%) are frozen out. Kinetic and thermodynamic parameters are obtained from variable-temperature ^{13}C n.m.r. spectra. 'Passing' ($\Delta G_c^{\ddagger}$ *ca.* 12 kcal mol^{-1}) and 'non-passing' ($\Delta G_c^{\ddagger}$ *ca.* 8 kcal mol^{-1}) nitrogen-inversion barriers are clearly differentiated.

CONSIDERABLE interest in the conformations of six-membered rings containing both 1,2- and 1,3-diaza-moieties led to the present study of the combined effects of both hydrazine and 1,3-diazacyclohexane fragments when incorporated in a six-membered ring. The resultant saturated 1,2,4-triazacyclohexane ring system was apparently hitherto unknown except for a brief report [3] on the quaternary salt (1) prepared in 7% yield.



(1)

Previous trials of possible routes to the 1,2,4-triazacyclohexane ring system [4] indicated that the best was *via* the ring-opening reaction of aziridine with hydrazine leading to the precursor β-aminoethylhydrazine (see Scheme 1) which could be further treated to obtain the 1,2,4-triazacyclohexane.



SCHEME 1

sym-Dimethylhydrazine (3) and *N*-methylaziridine (2) gave the resultant open chain β-aminoethylhydrazine (4) in good yield. Subsequent ring closure with paraformaldehyde and acetaldehyde afforded 1,2,4-trimethyl-1,2,4-triazacyclohexane (5) and 1,2,3,4-tetramethyl-1,2,4-triazacyclohexane (6). These reactions required pure freshly distilled reactants, inert atmosphere during reaction, and rapid work-up with subsequent dark storage in inert atmosphere. Without these precautions poor yields and rapid decay of the isolated product were invariably recorded.

EXPERIMENTAL

Physical Methods.—Proton n.m.r. spectra were recorded following the standard method.[5] ^{13}C N.m.r. spectra were recorded on a JEOL FX-100 (25.05 MHz) n.m.r. spectrometer incorporating a JEC-980B computer. Spectra were routinely run proton-noise-decoupled with spectral width of 3 000 Hz, thus setting a digital resolution of 0.4 Hz. For linewidth measurements, smaller spectral widths were employed (1 500 Hz) to increase digital resolution further (0.2 Hz).

Sample size was normally 500 mg in *ca.* 3—4 ml solution. A heteronuclear (^2H) lock was employed: $(CD_3)_2CO$ with Me_4Si added as internal reference. Temperatures were measured using the standard instrument dial, which was checked against an inserted copper–constantan thermocouple.

Preparation of Compounds.—The compounds were distilled under reduced pressure and transferred in an inert atmosphere into sealed ampoules. Even with these precautions, satisfactory chemical analyses could not be obtained and the results of such analysis of the same sample varied with time.[6] All the new compounds were satisfactorily characterised by ^{13}C and ^1H n.m.r. and by mass spectra.

1,2-*Dimethyl*-1-[2-(N-*methylamino*)*ethyl*]*hydrazine* (4).—Freshly distilled *sym*-dimethylhydrazine (4.5 g, 70 mmol) was heated with ammonium chloride (0.01 g) on a water-bath. Freshly distilled *N*-methylaziridine (2.5 g, 44 mmol) was added dropwise to the hydrazine and the mixture was stirred at 40 °C for 2 h. Excess of hydrazine was evaporated under nitrogen: the residue was distilled to give 1,2-*dimethyl*-1-[2-(N-*methylamino*)*ethyl*]*hydrazine* (2.1 g, 45%) as an oil, b.p. 54 °C at 20 mmHg, *m/e* 117 (P^+) and 92 ($P^+ - 15$).

1,2,4-*Trimethyl*-1,2,4-*triazacyclohexane* (5).—1,2-Dimethyl-1-[2-(*N*-methylamino)ethyl]hydrazine (1.0 g, 8.5 mmol), benzene (25 ml), and paraformaldehyde (*ca.* 0.3 g, 9 mmol) were heated at reflux in order to remove azeotropically water of reaction. Removal of benzene under reduced pressure yielded a yellow residue which was distilled to give the 1,2,4-*triazacyclohexane*, b.p. 49 °C at 20 mmHg (0.8 g, 74%), *m/e* 129 (P^+), 114 ($P^+ - 15$), 99 ($P^+ - 30$), and 84 ($P^+ - 45$).

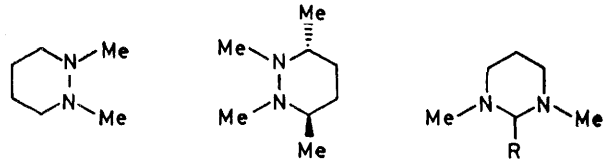
1,2,3,4-*Tetramethyl*-1,2,4-*triazacyclohexane* (6).—1,2-Dime-

thyl-1-[2-(*N*-methylamino)ethyl]hydrazine (1.0 g, 8.5 mmol) in sodium-dried ether (50 ml) was cooled to −10 °C under dry nitrogen. Freshly distilled acetaldehyde (1.0 g, 23 mmol) was added dropwise: the temperature rose to −7 °C. The reaction mixture was stirred for 1 h (−10 °C) and then saturated with dry K_2CO_3. Removal of K_2CO_3 and ether yielded a yellow residue which distilled to give a colourless oil, 1,2,3,4-*tetramethyl*-1,2,4-*triazacyclohexane*, b.p. 69 °C at 20 mmHg (*ca.* 1.0 g, 83%); *m/e* 143 (P^+), 128 ($P^+ - 15$), 113 ($P^+ - 30$), and 98 ($P^+ - 45$).

DISCUSSION

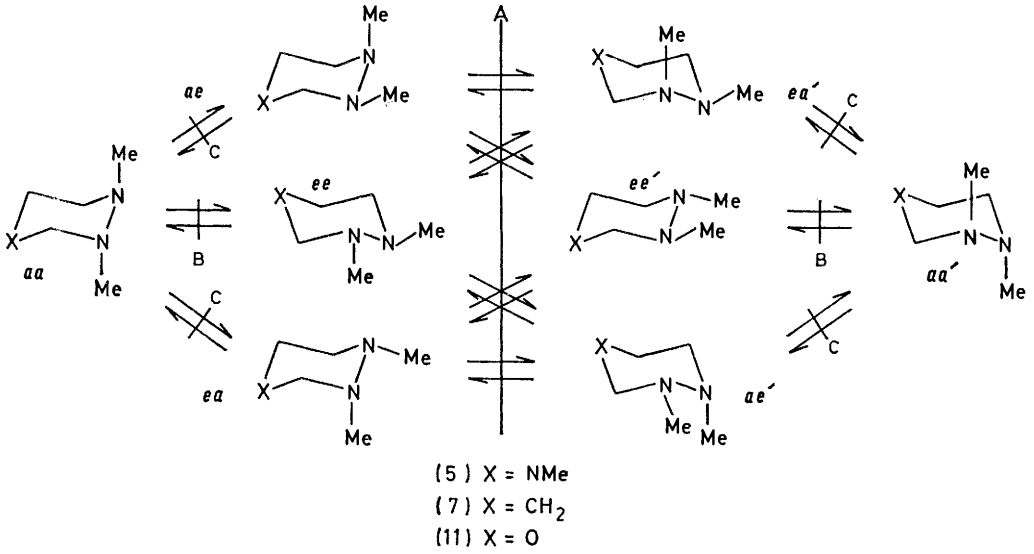
Background to Conformational Analysis.—The conformational analysis of the 1,2,4-triazacyclohexanes, (5) and (6), is best discussed with reference to 1,2-dimethyl- (7) and 1,2,3,6-tetramethyl-1,2-diazacyclohexane (8), and 1,3-dimethyl- (9) and 1,2,3-trimethyl-1,3-diazacyclohexane (10).

The $\Delta G_c^{\ddagger}$ of 7.85 kcal mol^{-1} for the low barrier for *trans*-1,2,3,6-tetramethyl-1,2-diazacyclohexane (8),[8] indicates that when an *N*-methyl group in a chair six-membered ring ' passes ' an adjacent equatorial *C*-methyl group, $\Delta G_c^{\ddagger}$ is raised by only *ca.* 0.3 kcal mol^{-1}



(7) (8) (9) R = H (10) R = Me

[*cf.* $\Delta G_c^{\ddagger}$ 7.56 kcal mol^{-1} for (7)]. Thus only a small part of the difference in $\Delta G_c^{\ddagger}$ for the two types of *N*-inversions in 1,2-dimethyl-1,2-diazacyclohexane (7) (7.6



(5) X = NMe
(7) X = CH_2
(11) X = O

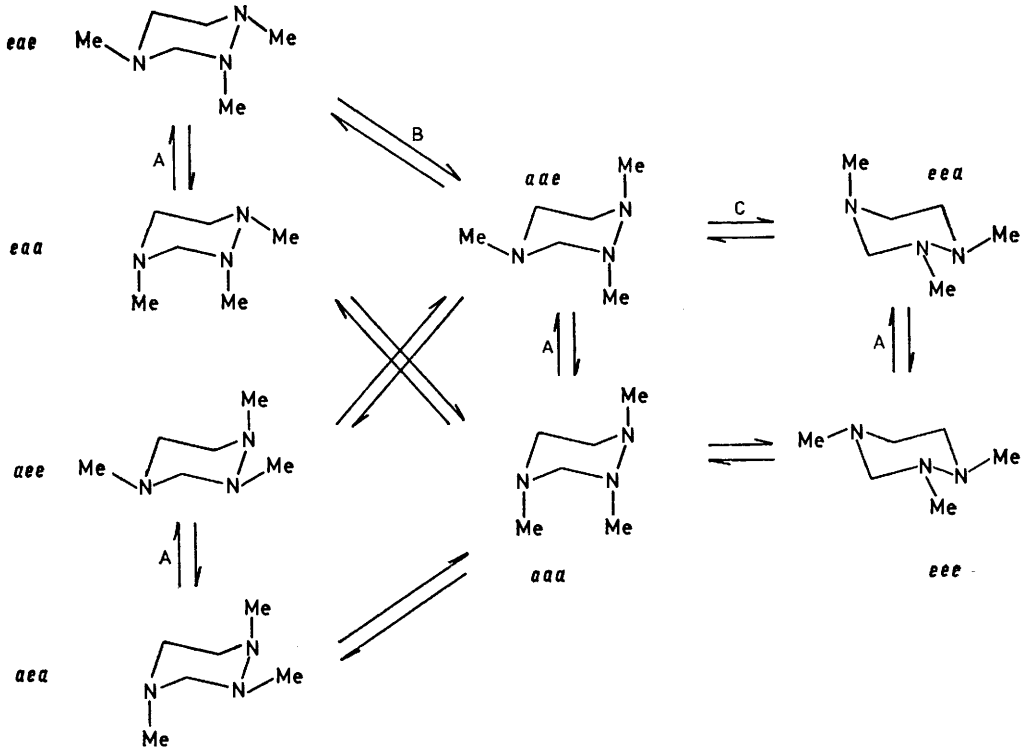
SCHEME 2 Conformational interconversions of six-membered compounds with 1,2-diaza-moieties: A, high-energy ($\Delta G_c^{\ddagger} \geqslant 12.0$ kcal mol^{-1}) ' passing ' inversions; B, intermediate ($10.0 \leqslant \Delta G^{\ddagger} \leqslant 11.4$) ' non-passing ' ring inversions; C, low ($\Delta G_c^{\ddagger}$ *ca.* 7.6 kcal mol^{-1}) non-passing *N*-inversions

1,2-Diazacyclohexanes show three types of barriers[7] (Scheme 2): (A) high (*ca.* 12 kcal mol^{-1} or more) relating to ring or *N*-inversions involving a crossing or ' passing ' of the two substituents, (B) intermediate (*ca.* 10—11 kcal mol^{-1}) for *ee*⇌*aa* ring inversion in saturated systems, and (C) low (*ca.* 8 kcal mol^{-1} or less) relating to nitrogen inversion without ' passing ' of substituents (*ae*⇌*aa*⇌*ea*). Nelsen and Weisman[8] used the postulate of three types of barriers in interpreting the variable-temperature ^{13}C n.m.r. spectrum of 1,2-dimethyl-1,2-diazacyclohexane (7): it showed the two lower barriers of 10.3 and 7.6 kcal mol^{-1}. The high barrier of 12 kcal mol^{-1} is observed by ^1H n.m.r.[9] but not by ^{13}C n.m.r.[8] because all the carbon sites are averaged until the intermediate barrier (*ae*⇌*aa*)⇌*ee* is ' slowed '. The conformational equilibrium for compound (7) was estimated to be 58% *ee* and 42% *ae* at 20 °C, on the basis of ^{13}C chemical shifts[8]: no evidence for the *aa* form was obtained.

and 12.0 kcal mol^{-1}) is accounted for by the steric effect. Clearly, the *p*–sp^3 lone pair–lone pair interaction,[10,11] which develops in the higher energy *N*-inversion [$\Delta G_c^{\ddagger}$ *ca.* 12.0 kcal mol^{-1}) and not in the lower-energy inversion $\Delta G_c^{\ddagger}$ 7.6 kcal mol^{-1}), is responsible for this large difference of *ca.* 4.5 kcal mol^{-1}.

For 1,3-dimethyl-1,3-diazacyclohexane (9) the di-equatorial conformation predominates by *ca.* 0.45 kcal mol^{-1} at 20 °C and the *N*-methyl inversion barrier is 7.0 kcal mol^{-1}.[5] Hence the *N*(4)-inversion should for 1,2,4-trimethyl-1,2,4-triazacyclohexane (5) be the ' fastest ' of all its conformational processes, assuming that the hydrazine unit exhibits similar conformational properties to those found for 1,2-dimethyl-1,2-diazacyclohexane (7).

The Conformational Equilibria for the 1,2,4-*Triazacyclohexane Ring System.*—1,2,4-Trimethyl-1,2,4-triazacyclohexane (5) possesses 16 chair conformers. These form two (mirror image) sets, and interconversion be-



SCHEME 3 Conformational interconversions in 1,2,4-trimethyl-1,2,4-triazacyclohexane

tween one set and the other can occur only *via* a high energy 'passing' *N*-inversion or 'passing' ring-reversal. Within each set (Scheme 3) interconversion between conformers takes place *via* low-energy ring (C) and *N*-inversions (A,B) which do not involve passing p–sp^3 lone pair–lone pair interaction.

Of the eight conformers of Scheme 3, *aaa*, *eaa*, *aea*, and *aae* possess two or more axial *N*-methyl groups and may be regarded as unstable intermediates. In addition to the results quoted above for 1,2-dimethyl-1,2-diazacyclohexane (7) and 1,3-dimethyl-1,3-diazacyclohexane (9), the predominant conformer of 3,4-dimethyl-1,3,4-

TABLE 1

Proton chemical shifts [a] and coupling data [b] of n.m.r. signals at high and low [c] temperature

Compound	Low temp. (°C)	N–CH_3		N–CH_2–X or N–CH–X		Other signals		Ref.
		At 34 °C	At low T	At 34 °C	At low T	At 34 °C	At low T	
(5) [d]	−68	2.51 [s, N(2)–CH_3] 2.46 [s, N(1)–CH_3] 2.16 [s, N(4)–CH_3]	2.44 (s) 2.36 (s) 2.02 (s)	3.42 (2 H, s)	3.43, 3.24 (bq, $^2J_{HH}$ 11.0 Hz)	2.74 (4 H, bm, N–CH_2)	2.61 (bt, $^2J_{HH}$ 12 Hz) 3.02 (dt, $^2J_{HH}$ 2, $^2J_{HH}$ 12 Hz) 2.25 (m [e])	
(6) [d]	*f*	2.52 [s, N(2)–CH_3] 2.49 [s, N(1)–CH_3] 2.09 [s, N(4)–CH_3]	*f*	3.45 (q, 1 H, $^3J_{HH}$ 6.3 Hz)		2.75 (4 H, m, N–CH_2) 1.21 (d, C–CH_3, $^3J_{HH}$ 6.1 Hz)		
(7) [g,h]	−70	2.33 (3 H, s)	2.24 (s)			2.59 (m)	2.38 (bq, δ_{HH} 30.0, J_{HH} 11.3 Hz)	9
(10) [h]	−140	2.07 (s)	2.25 (s, *ax*) 1.96 (s, *eq*)					13
(11) [h,i]	−120	2.51 [s, N(3)–CH_3] 2.46 [s, N(4)–CH_3]	2.40 (s, *ax*) 2.32 (s, *eq*)	4.45 (s, 2 H)	4.47, 4.13 (q, $^2J_{HH}$ 10.5 Hz)	2.68 [t, C(5)H_2] 3.83 [t, C(6)H_2]	2.99 [m, C(5)H_2] 3.71 [m, C(6)H_2]	12

[a] Chemical shifts of main lines or averages of groups of lines are in p.p.m. downfield from $SiMe_4$ measured at 100 MHz: s, singlet; d, doublet; q, quartet; m, multiplet; bt, broad triplet; bq, broad quartet; dt, double triplet. [b] All couplings are in Hz. [c] 'Low' temperature is suitably below any coalescence observed to give sharp lines. [d] Solvent $(CD_3)_2CO$. [e] Under *N*–CH_3 signals. [f] No satisfactory spectrum obtained at low temperatures. [g] Measured at 60 MHz. [h] Solvent CF_2Cl_2. [i] Room-temperature spectrum in $CDCl_3$–$CFCl_3$ (1 : 1).

oxadiazacyclohexane (11) [12] is $N(3)$-methyl axial, $N(4)$-methyl equatorial; thus the β-oxygen has the effect of increasing the proportion of the *ax-eq* form (*ea*). We expect therefore *eae* to predominate in the equilibrium for (5) together with (*eea*⇌*eee*) and (*aee*) as minor components.

Proton N.M.R. Studies of 1,2,4-*Trimethyl*-1,2,4-*triazacyclohexane* (5).—The ambient (*ca.* 34 °C) temperature proton n.m.r. spectrum of (5) consists of four singlets and a broad multiplet: assignments follow from integration and chemical shifts (Table 1): comparison (Table 1) with the ^{1}H n.m.r. data at *ca.* 34 °C for 3,4-dimethyl-1,3,4-oxadiazacyclohexane [12] [(11); δ 2.51 N(3)-CH_3 and δ 2.46 N(4)-CH_3] and 1,2,3-trimethyl-1,3-diazacyclohexane [13] [(10); δ 2.07, N-CH_3] allowed assignment of the three N-CH_3 singlets (δ 2.51, 2.46, and 2.16) to N(2)-, N(1)-, and N(4)-CH_3 protons respectively.

On lowering the temperature, the methylene signals originally at δ 3.40 and 2.74 broaden and coalesce into an AB quartet and complex triplets respectively. The low-field half of the AB quartet is broadened (see Figure 1), presumably due to long range W-type coupling [14] with the equatorial C(5)-hydrogen. A barrier of 12.0 ± 0.2 kcal mol^{-1} is estimated from the first coalescence of the N-CH_2-N ABq (Table 2). However, this coalescence

TABLE 2

^{1}H N.m.r. coalescence data [a] for 1,2,4-trimethyl-1,2,4-triazacyclohexane and 1,2,3,4-tetramethyl-1,2,4-triazacyclohexane

Compound	T (°C)	Signal observed	$\Delta\nu$ (Hz)	J (Hz)	$\Delta G_c^{\ddagger}$ (kcal mol^{-1})
(5)	−31	N–CH_2–N	19.2	11.0	12.0
(6)	−10< [b] <10	N–CH–N			12.4 [c]

[a] Employing the Eyring equation, H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228. [b] Signal broadens in this temperature region. [c] Obtained from ^{13}C d.n.m.r. (Table 6).

at −31 °C is not sharp because of the second dynamic phenomenon which is most clearly observed in the broadening and resharpening of the two N-methyl singlets at δ 2.51 and 2.16 over the temperature region −30 to −70 °C. {A signal at δ 2.96 (+15 °C), which moves downfield at lower temperatures, becoming well resolved by −68 °C at δ 3.68 (marked * in Figure 1), is assigned to N-H of the open chain compound [Scheme 1; (4)]}.

This highest barrier ($\Delta G_c^{\ddagger}$ = 12.0 ± 0.2 kcal mol^{-1}) is assigned to the lowest of all the ' passing ' N- and ring inversion processes possible for the trimethyltriazacyclohexane (5) [*cf.* $\Delta G_c^{\ddagger}$ = *ca.* 12.0 kcal mol^{-1} for 1,2-dimethyl-1,2-diazacyclohexane (7) [9] and 12.6 kcal mol^{-1} for 3,4-dimethyl-1,3,4-oxadiazacyclohexane (11) [12]. Any accurate assessment of the energy barrier responsible for the second coalescence [observed as broadening of the $N(2)$- and $N(4)$-methyl signals] by use of the Anet equations [15] requires the unknown magnitude of Δν, the chemical shift difference.

Comparison of the ^{1}H n.m.r. shifts at low temperature (Table 1) of 1,2,4-trimethyl-1,2,4-triazacyclohexane (5) with the chemical shifts for 1,2,3-trimethyl-1,3-diazacyclohexane (10) (which exist predominantly in the *eea* conformation [5,10,13]) suggests the predominance for (5) of the $N(2)$-methyl axial and $N(4)$-methyl equatorial

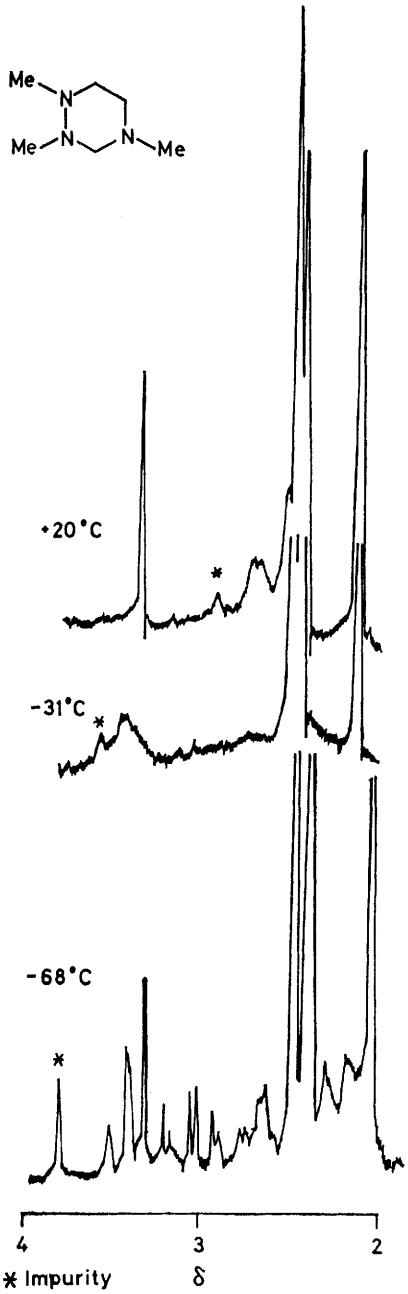


FIGURE 1 ^{1}H N.m.r. (100 MHz) spectra of 1,2,4-trimethyl-1,2,4-triazacyclohexane (5)

conformation (*eae*) [*cf.* N-CH_3 axial at δ 2.25 and equatorial at δ 1.96 for (10), and N(2)-CH_3 at δ 2.36 and N(4)-CH_3 at δ 2.02 for (5)]. This conclusion is further supported by comparison of the N(1)-CH$_3$ shift at low temperature for (5) (δ 2.44) with that for N(4)-CH$_3$ of 3,4-dimethyl-1-oxa-3,4-diazacyclohexane (11) (δ 2.40).

TABLE 3

^{13}C N.m.r. (25.05 MHz) data [a] for 1,2,4-trimethyl-1,2,4-triazacyclohexane

Temp. (°C)	N(1)–*C*	N(2)–*C*		*C*–3		N(4)–*C*	*C*–5	*C*–6
ca. 30 δ(p.p.m.)	42.5 [b]	32.9		77.1		43.0 [b]	54.4	46.4
−56	42.3	30.4		76.9		43.0	54.6	44.6
−113	42.5	28.2		78.0		42.8	55.2	44.3
Multiplicity [c]	q	q		t		q	t	t
Broadening data [d]	*e*					*ef*	*e*	*f*
t_c (°C)	−99 [g]	−13	−92	−19	−92		−99	−13
$\Delta\omega_{\frac{1}{2}}$ [h] (Hz)		22.1	32.1	10.7	20.5		9.8	26.1
$\Delta\nu$ [i] (p.p.m.)		12.8	11.7	5.0	10.0		15.2	15.2
Pop.[j] (%)		6.9	9.1	8.5	8.2		2.5	6.9
ΔG_c° [k] (kcal mol^{-1})		1.34	0.82	1.17	0.87		1.27	1.35
$\Delta G_c^{\ddagger}$ (kcal mol^{-1})		11.2	7.7	11.4	7.7		7.3	11.1

[a] Solvent: CF_2Cl_2–$(CD_3)_2CO$, 2 : 1. [b] Tentative assignment, may be interchanged. [c] Obtained from off-resonance decoupling. [d] Anet's equations.[15] [e] No broadening effect near −10 °C. [f] No broadening effect near −90 °C. [g] Overlap precludes accurate assessment of broadening parameters. [h] Corrected for natural line-width in absence of 'slow' exchange: natural line-width = 3.9 Hz. [i] Predicted from model compounds [(7), (9), and *N*-methylpiperidine]; see Tables 4 and 5. [j] Pop. of minor conformation(s): 1st phenomenon (*eea* + *eee*): 2nd phenomenon (*aee* + *aea*). [k] In favour of *eae*.

TABLE 4

^{13}C N.m.r. (25.05 MHz) data for piperidine and 1,2- and 1,3-diazacyclohexane

(a) Chemical shifts [a]

Ring	*N*-methyl orientation	N–CH_3 *eq*	N–CH_3 *ax*	N–CH_2 [b] *eq*	N–CH_2 [b] *ax*	γC–CH_2–C [b] *eq*	γC–CH_2–C [b] *ax*	N–CH_2–N
Piperidine [c]	1-*eq*	47.2		57.9		25.8		
	1-*ax*		*ca.* 37.2		56.1		19.4	
1,2-Diazacyclohexane [d]	1-*eq*, 2-*eq*	44.7		58.2		25.4		
	1-*ax*, 2-*eq*	43.5	26.5	43.0	54.2	25.4	15.6	
1,3-Diazacyclohexane [e]	1-*eq*, 3-*eq*	43.6		54.2		25.1		80.1
	1-*ax*, 3-*eq*	43.6	39.0	56.4	50.5	19.4		77.2

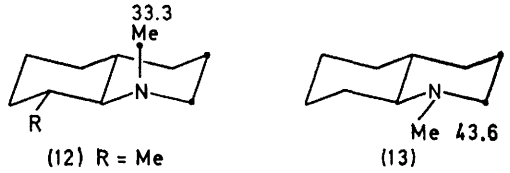
(b) Chemical shift effects [f] due to structural modification of the *N*-methylpiperidine ring

	N–CH_3 (*eq*)			N–CH_3 (*ax*)		
	N–CH_3	*C*–2	*C*–3	N–CH_3	*C*–2	*C*–3
Chemical shift [g]	47.2	57.9	25.8	37.2	56.1	19.4
α N–CH_3 *eq*	−2.5	+22.2	+32.4	−10.7	+21.1	+23.6
α N–CH_3 *ax*	−3.7	+19.3	+28.4			
β N–CH_3 *eq*	−3.6	+0.3	−0.7	+1.8	−1.9	0
β N–CH_3 *ax*	−3.6	−14.9	−6.4			

[a] In p.p.m. downfield from Me_4Si. [b] *eq*/*ax* refer to orientation of closest *N*-methyl group. [c] Ref. 16. [d] Ref. 8. [e] Ref. 5. [f] In p.p.m. relative to corresponding shifts in *N*-methylpiperidine. [g] Chemical shifts for *N*-methylpiperidine from ref. 16.

^{13}C *N.M.R. Studies of* 1,2,4-*Trimethyl*-1,2,4-*triazacyclohexane*.—The proton noise decoupled ^{13}C n.m.r. spectrum of (5) at 30 °C consists of the expected six lines (Table 3, Figure 2) of which the N-CH_2-N carbon is immediately assigned to the most downfield signal. On decreasing the temperature, two dynamic broadening phenomena (at *ca.* −15 and *ca.* −95 °C) are observed, indicating a biased equilibrium with successive 'freezing' out of two minor components, present in insufficient quantity to display signals of their own. The very low-temperature spectrum hence comprises just the signals of the major conformation.

Conformations *eae*, *eee*, *eea*, and *aee* have to be considered (*vide supra*, for reasons). We have tabulated the ^{13}C chemical shifts [Table 4(a)] of the individual conformers of 1,2-dimethyl-1,2-diazacyclohexane (7),[8] 1,3-dimethyl-1,3-diazacyclohexane (9),[5] and *N*-methylpiperidine.[16] * For the latter compound, shifts in the N-CH_3 axial conformer were derived from derivatives of *trans*-*N*-methyldecahydroquinoline [16] which constrain the *N*-methyl group axial or equatorial [(12) and (13)]: the chemical shift for N-CH_3 axial is thus *ca.* 10 p.p.m.



upfield to the shift of N-CH_3 equatorial carbon resonance in *N*-methylpiperidine.[16] Since ^{13}C chemical shifts accurately reflect specific molecular environments,[8] this allows the estimation of the shift effects caused by α *N*-methyl (axial and equatorial) and β *N*-methyl (axial and equatorial) groups when incorporated into the piperidine ring [Table 4(b)]. Weisman and Nelsen [17] used a similar scheme referenced to cyclohexanes to predict shifts in some bicyclic 1,2-diazacyclohexanes. It is emphasised that the empirical 'increments' in Table 4(b) may not be additive: nevertheless, we believe a summation of the relevant increments should predict the

* Since ^{13}C n.m.r. shifts of *N*-methylpiperidine with axial *N*-methyl are unknown, these were estimated from ^{13}C-n.m.r. shifts of *trans*-perhydroquinolines [16b] which constrained the *N*-methyl group axial or equatorial. The equatorial N–CH_3 shift was taken from ref. 16*a* and the axial N–CH_3 deduced using $\Delta\nu$ = 10 p.p.m. from *trans*-perhydroquinoline derivatives.[16b]

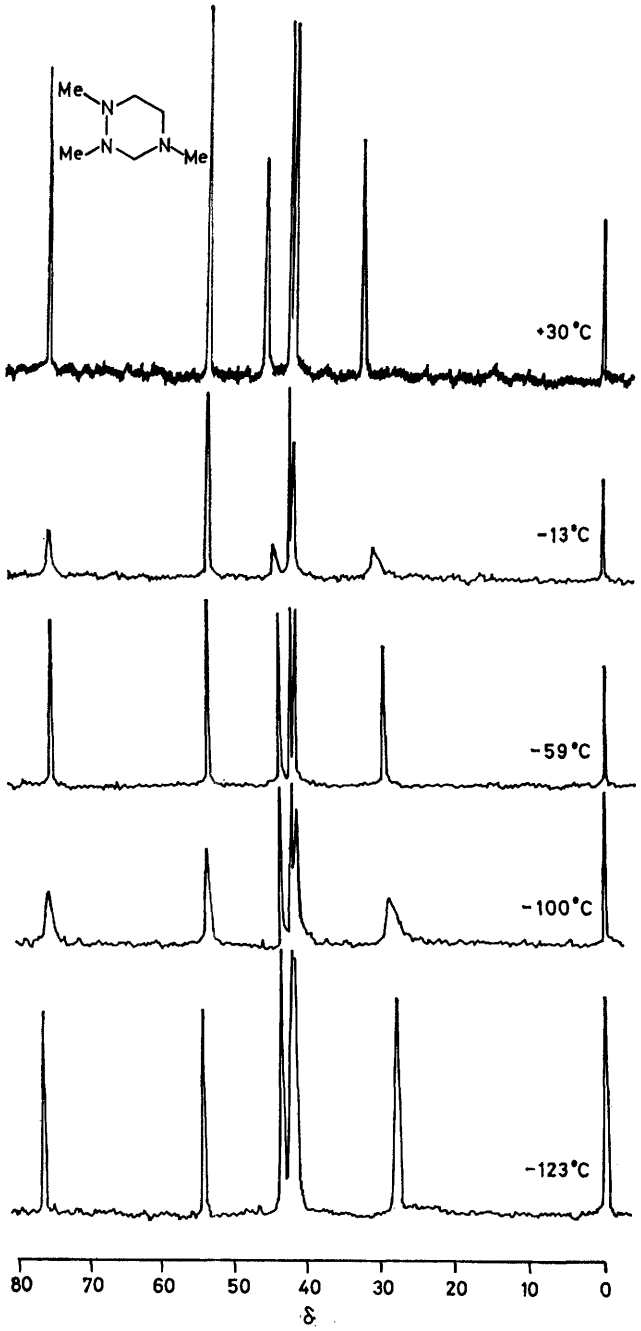


FIGURE 2 ^{13}C N.m.r. (25.05 MHz) variable temperature spectra of 1,2,4-trimethyl-1,2,4-triazacyclohexane (5)

relative order of the shifts of specific carbon atoms for different conformers.

Four sets of shifts were calculated for the *eae*, *eee*, *eea*, and *aee* forms of 1,2,4-trimethyl-1,2,4-triazacyclohexane (Table 5). Comparison with the set observed at low temperature points convincingly to *eae* as the predominant form. Furthermore, as the temperature is decreased, the signal for the *N*(2)-methyl shifts upfield, this is expected if *eae* is the major form and it is the minor forms (*eee*⇌*eea*) and *aee* which are successively ' frozen ' out. These conclusions are also in accord with

TABLE 5

^{13}C N.m.r. chemical shifts predicted from data in Table 4

Conformer	N(1)–*C*	N(2)–*C*	*C*–3	N(4)–*C*	*C*–5	*C*–6
eae	43.5	28.3	75.3	43.6	58.2	43.3
eee	44.7	41.1	80.4	43.6	58.2	58.5
eea	44.7	41.1	77.5	39.0	54.2	43.0
aee	26.5	39.9	65.2	43.6	43.0	52.3
aea	26.5	39.9	62.3	39.0	41.2	39.3
Found [a]	42.5	28.2	78.0	42.8	55.2	44.3

[a] Observed shifts at *ca.* −113 °C.

the proton n.m.r. study. All the ^{13}C signals for 1,2,4-trimethyl-1,2,4-triazacyclohexane can now be assigned (Table 3).

The first biased dynamic change takes place at *ca.* −15 °C. The N(2)-CH_3, *C*-3, and *C*-6 signals broaden and then sharpen at lower temperatures (Table 3, Figure 2) and the N(2)-CH_3 signals display a marked upfield shift. This change is consistent with conformer *eae* being major and ring ' non-passing ' inversion [*eae*⇌(*eee*⇌*eea*); Scheme 3, C] becoming ' slow ': *cf.* the first coalescence on ^{13}C n.m.r. for 1,2-dimethyl-1,2-diazacyclohexane [*ee* ⇌ (*ae*⇌*aa*⇌*ea*)].[8]

Since signals for the minor forms (*eea*⇌*eee*) are not observed at lower temperatures, Δν, the chemical shift differences for use in the Anet equations [15] were estimated by comparing predicted shifts of conformer *eae* with the corresponding shifts of minor form *eee* (Tables 3 and 5) *e.g.* Δν for N(2)-CH_3 was calculated to be |δ 28.3 (*eae*) − δ 41.1 (*eee*)| = 12.8 p.p.m. A barrier of 11.4 ± 0.2 kcal mol^{-1} was calculated, with a free-energy difference of 1.20 ± 0.1 kcal mol^{-1}, representing *ca.* 8—10% of *eee*⇌*eea* at *ca.* −15 °C. A second dynamic broadening is observed at *ca.* −95 °C in the line width of N(1)-CH_3, N(2)-CH_3, *C*-3, and *C*-5 carbon resonances. These signals sharpen up at lower temperature (Figure 2) accompanied again by a marked upfield shift for the N(2)-CH_3 signal (Table 3), as would be expected if *eae* is the major conformer and *aee*⇌*aea* are minor forms ' freezing ' out at these temperatures: *cf.* predicted shifts (Table 5) for N(2)–CH_3 carbon atom in *eae* (δ 28.3) and *aee*(*aea*) (δ 39.9) conformers. The chemical shift differences (Δν) were calculated from the predicted shifts of *eae* and *aee*(*aea*): application of Anet's equations [15] yields a value of 7.5 ± 0.2 kcal mol^{-1} (Table 3) for the ' non-passing ' *N*-inversion barrier: the free-energy difference ΔG_c° was found to be 1.0 ± 0.1 kcal mol^{-1} in favour of *eae*, with *ca.* 5% *aee* at −95 °C.

1,2,3,4-*Tetramethyl*-1,2,4-*triazacyclohexane* (6).—The proton n.m.r. of (6) at 34 °C (Table 1) consists of the expected three *N*-methyl singlets, the N–C*H*–N AB_3 quartet, the *C*-methyl doublet, and the methylene multiplets which were assigned by comparison with the trimethyl analogue (5). On lowering the temperature complex broadening of the N–C*H*–N quartet and of two of the *N*-methyl singlets is observed below *ca.* 10 °C. To analyse these biased dynamic phenomena quantitatively, the variable-temperature ^{13}C n.m.r. of (6) was studied.

At 38 °C, the proton-noise-decoupled ^{13}C n.m.r. spectrum of 1,2,3,4-tetramethyl-1,2,4-triazacyclohexane (6) consists of the expected averaged seven lines. Assignments follow from comparison with the ^{13}C proton-noise-decoupled spectrum of the trimethyl analogue (5) (Table 6). Reduction of temperature leads to a first dynamic process characterised by a dramatic broadening of N(2)–CH_3, *C*-3, C(3)-CH_3, and *C*-5 resonances in the range +27 to −10 °C. Long-term accumulation spectra at *ca.* −50 °C show signals of a minor conformation. This allowed determination of $\Delta\nu$, the chemical-shift difference, for use in the Anet equations. A barrier of 12.4 ± 0.3 kcal mol^{-1} was calculated (Table 6): calculation of ΔG_c° leads to a large range of values ($0.55 \leqslant \Delta G_c^\circ \leqslant 1.50$ kcal mol^{-1}). It is clear that as the original authors indicated for ' minor ' populations in the 10—20% range the Anet equation [15] $\{P \cong (\Delta\omega_{\frac{1}{2}})/\Delta\nu\}$* to deduce ΔG_c° no longer holds and, furthermore, this problem is accentuated by the greater error in assessing the line widths at half height at coalescence ($\Delta\omega_{\frac{1}{2}}$).

The first dynamic process is assigned to the slowing of the *C*-methyl axial–equatorial equilibrium. Chair conformations with three or more adjacent equatorial substituents are not favoured; *cf.* 1,2,3-trimethyl-1,3-diazacyclohexane [5] (10) preferentially adopts the *eea* conformation (Scheme 4) and the *eae* form (*ca.* 10%) is populated to a comparable extent to the *eee* form (6%) with three equatorial methyl groups. This aversion excludes all the conformers possible for (6) except *eaee*, *eeae*, and *aeea* (Scheme 4). Comparison of the very low temperature ^{13}C n.m.r. shifts of (6) *ca.* −136 °C where one conformation is assumed to predominate with the analogous shifts of (5 *eae*) indicates that *eaee* is the major conformer for (6) [compare *C*-6 shifts for (5 *eae*) (δ 44.3) and (6 *eaee*) (δ 45.2)]. Therefore the first broadening observed at *ca.* 15 °C represents the ' freezing ' out of (6 *eeae*) from the equilibrating mixture *eaee*⇌*aeea* and thus ' slowing ' of passing ring inversion.

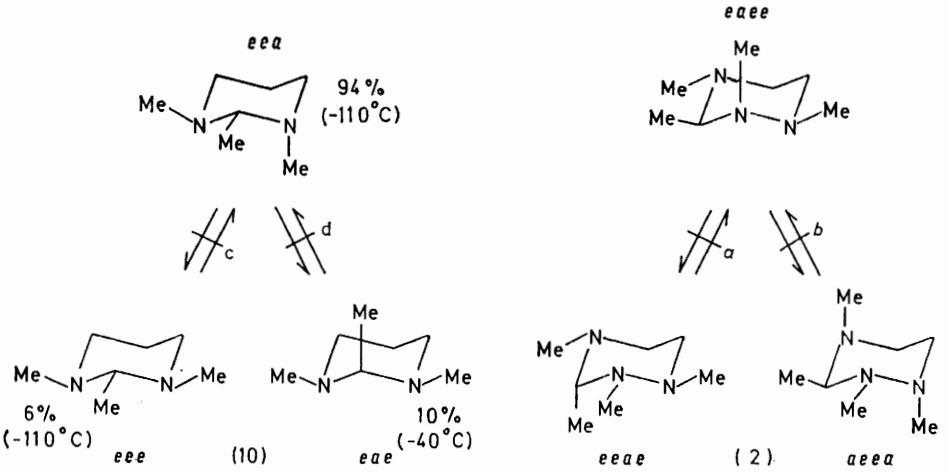
Equilibration between *eaee* and *aeea* requires only

TABLE 6

Variable-temperature ^{13}C n.m.r. data for 1,2,3,4-tetramethyl-1,2,4-triazacyclohexane

Temp. (°C)		N(1)–*C*	N(2)–*C*	*C*–3	C(3)–*C*	N(4)–*C*	*C*–5	*C*–6
38 [a]	Chemical shift (δ)	41.9 [b]	25.0	78.8	17.6	42.6 [b]	55.2	45.9
	Multiplicity [c]	q	q	d	q	q	t	t
−51 [d]	Chemical shift	41.9	23.2	79.1	18.9	42.5	56.2	45.6
			(30.4) [e]	(77.6) [e]	(8.9)		(48.0) [e]	
−118		41.8	22.0	79.5	18.9	42.5	56.2	45.2
First broadening phenomenon								
	t_c (°C)	*f*	2	−5	11	−12	7	−12
	$\Delta\omega_{\frac{1}{2}}$ (Hz) [g]		23	1.9	*ca.* 70	1.0	41	1.0
	$\Delta\nu$ (p.p.m.)		7.2	1.5	10.0		3.2	
	Minor pop. (%)		13	5	*ca.* 28		*ca.* 20	
	ΔG_c° (kcal mol^{-1})		1.1	1.6	0.5		0.8	
	$\Delta G_c^\ddagger$ (kcal mol^{-1})		12.2	12.7	12.4		12.3	
Second broadening phenomenon								
	t_c (°C)		−92	−104	−112	−112	−104	
	$\Delta\omega_{\frac{1}{2}}$ (Hz) [g]		12	8	1.8	2	7	

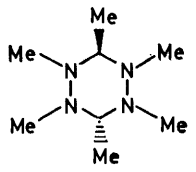
[a] Solvent: $CDCl_3$–$(CD_3)_2CO$. [b] Assignment may be interchanged. [c] Obtained from off resonance spectra. [d] Solvent: CF_2Cl_2–$(CD_3)_2CO$. [e] Minor signals. [f] Remains sharp. [g] Corrected for natural line-width (4 Hz).



SCHEME 4 Predominant conformational interconversions in (2) and (10): (a) 1st broadening (ring inversion), (b) 2nd broadening (non-passing *N*-inversion), (c) *N*-inversion, and (d) ring inversion

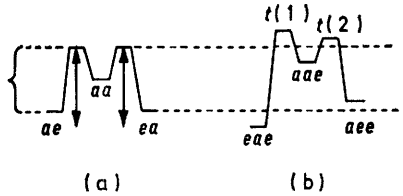
* *P* is the fractional population of minor form, $\Delta\omega_{\frac{1}{2}}$ is the broadening (Hz) of line width at half height (corrected for natural line-width), and $\Delta\nu$ is the chemical shift difference for particular carbon resonance (in Hz).[15] The Anet equation gives k_c for least stable→transition state: to obtain most stable→transition state ΔG^0 has to be added.

non-passing N-inversion processes; hence the second dynamic process observed at lower temperature (−90 °C) represents the freezing out of the second minor component (6 *aeea*), leaving the signals of the major form (6 *eaee*). The barrier of between 7.3 and 7.9 kcal mol^{-1} may be assigned for this process, in good agreement with non-passing N-inversion barriers in *trans*-1,2,3,6-tetramethyl-1,2-diazacyclohexane [8b] [(8); $\Delta G_c^{\ddagger}$ 7.85 kcal mol^{-1}] and *trans*-1,2,3,4,5,6-hexamethyl-1,2,4,5-tetra-azacyclohexane [18] [(14); $\Delta G_c^{\ddagger}$ 7.7 kcal mol^{-1}].



(14)

Conclusions.—The inclusion of a β-N-methyl group into the 4-position of a 1,2-diazacyclohexane ring leads to the predominance of the *eq*-N(1)-methyl, *ax*-N(2)-methyl form. The relatively large proportion of 42%



SCHEME 5 (a) Low-energy non-passing interconversion route in 1,2-dimethyl-1,2-diazacyclohexane (7); (b) low-energy non-passing interconversion route in 1,2,4-trimethyl-1,2,4-triazacyclohexane (5)

axial-equatorial (*ae*) [8] form for 1,2-dimethyl-1,2-diazacyclohexane (7) at 35 °C was explained by Weisman and Nelsen [17] to be due to increased alkyl–alkyl interaction in the diequatorial form, induced by the shorter N–N bond. In 1,2,4-trimethyl-1,2,4-triazacyclohexane (5), the β hetero-atom reduces 1,3-*syn*-axial interactions as well as increasing the proportion of *ax*-2-methyl by the anomeric effect. The presence of an adjacent C-methyl group in the tetramethyl analogue (6) further increases the tendency for N(2)-methyl to be axial: failing this, the C-methyl group itself adopts an axial position to avoid three or more adjacent equatorial groups.

The lowest energy process ($\Delta G_c^{\ddagger}$ *ca.* 7.5 kcal mol^{-1}) could be the non-passing inversion of either the N(1) or N(2) methyl groups. 1,2-Dimethyl-1,2-diazacyclohexane (7) displays [8] $\Delta G_c^{\ddagger} = 7.6$ kcal mol^{-1} for the *ae*⇌*ea* ' non-passing ' N-inversion which proceeds *via* the intermediate *aa*. Hence the measured barrier in this case represents the equatorial to transition state (*eq* to *ts*) activation energy (Scheme 5a). 1,2,4-Trimethyl-1,2,4-triazacyclohexane (5), however, is a much more complex case because N-inversion at N-1, N-2, and N-3 atomic centres will not be equivalent. Assuming that N(4)-inversion is the ' fastest ' (*cf.* $\Delta G_c^{\ddagger}$ 7.0 kcal mol^{-1} for 1,3-dimethyl-1,3-diazacyclohexane [5]), Scheme 5b has to be considered with regard to inversion at N-1 and N-2. Two points become clear; (i) comparison of *ae* with *eae* suggests that *eae* should have a lower ground state energy than *ae* because in *eae* the *syn*-axial C-H/N(2)-methyl interactions (*cf. ae*) are alleviated by the N-4 lone pair. Hence the N-1 *eq* to *ts* inversion in *eae* should be >7.6 kcal mol^{-1}: (ii) on the other hand *aee* should have a higher ground-state energy than *ae* because of the *syn*-axial lone pair–lone pair interaction responsible for the generalised anomeric effect; [19] thus N-2 *eq* to *ts* should be <7.6 kcal mol^{-1}.

The problem is further complicated by the probable inequality of transition states t(1) and t(2).

The actual barrier obtained is $\Delta G_c^{\ddagger}$ 7.7 kcal mol^{-1} (minor to major) with ΔG_c° 1.0 kcal mol^{-1} in favour of *eae*. 1,2,4-Trimethyl-1,2,4-triazacyclohexane (5) shows clearly that N-inversion barriers in complex systems with many heteroatoms, which influence ground states as well as transition states, cannot be predicted by the simple ' incremental ' schemes previously suggested.[10,20,*] However, the ring ' non-passing ' barrier ($\Delta G_c^{\ddagger} = 10.2$ kcal mol^{-1}) for (3) is enhanced, as expected, to 11.4 kcal mol^{-1} in (5) and *ca.* 12.4 kcal mol^{-1} in (6) with the inclusion of a β-N-methyl group in (5) and β-N-methyl and α-C-methyl groups in (6).

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[8/663 *Received*, 10*th April*, 1978]

* *Note added at proof:* Development of the treatment of nitrogen-inversions in terms of ' half-barriers ' made in ref. 6 has since allowed a rationalisation of α- and β-heteroatom effects which incorporates significant elements of both the incremental schemes previously suggested, and allows assessment of the heteroatom effects with regard to both ground and transition states (A. R. Katritzky, R. C. Patel, and F. G. Riddell, in preparation).

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