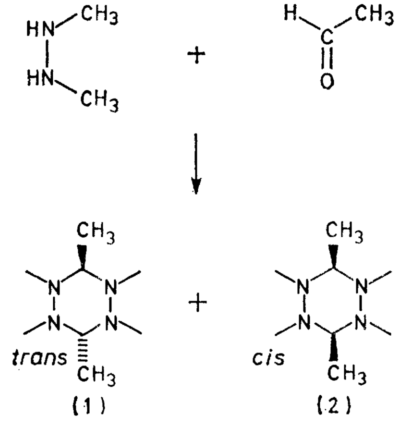
The Conformational Analysis of Saturated Heterocycles. Part 89.[1] Conformational Analysis of *trans*-1,2,3,4,5,6-Hexamethyl-1,2,4,5-tetra-azacyclohexane [1]

By **Alan R. Katritzky,*** **Ian J. Ferguson,** and **Ranjan C. Patel,** School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ

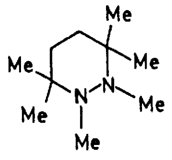
Variable-temperature ^{13}C n.m.r. shows the title compound to be the *trans*-isomer which adopts a symmetric conformation with the *C*-methyl groups diequatorial and the *N*-methyl groups symmetrically diaxial diequatorial (*aeae*). The *N*-inversion barrier ($\triangle G_c^{\ddagger}$ 7.7 kcal mol^{-1}) provides strong evidence for the three conformational sets previously postulated for 1,2,4,5-tetra-azacyclohexanes.

CONTINUING interest in the 1,2,4,5-tetra-azacyclohexane ring system prompted us to extend previous investigations [2] to the highly substituted *trans*-1,2,3,4,5,6-hexamethyl-1,2,4,5-tetra-azacyclohexane (1).

sym-Dimethylhydrazine reacts with acetaldehyde to give a mixture of *cis*- and *trans*-1,2,3,4,5,6-hexamethyl-1,2,4,5-tetra-azacyclohexanes.[3] One isomer is crystalline and can be separated from the mother liquor. The authors did not discuss the configuration of the *C*-methyl groups in this solid; however, the low-temperature ^{13}C n.m.r. of solutions of the crystalline solid shows dynamic splitting of the *N*-methyl signal ($\Delta G_c^{\ddagger}$ 7.7 kcal mol^{-1}) and no splitting of the C-methyl signal (*vide infra*). If it were the *cis*-compound (2), a high ring-inversion barrier ($\Delta G_c^{\ddagger}$ *ca.* 12 kcal mol^{-1}; *cf.* ring inversion barrier $\Delta G_c^{\ddagger}$ 11.7 kcal mol^{-1} for *cis*-1,2,3,6-tetramethyl-1,2-diazacyclohexane) [4] would be expected to result in splitting of the *C*-methyl signals. On this basis, the crystalline solid was assigned to the *trans*-isomer (1); the *cis*-isomer (2) is a liquid at ambient temperature. *trans*-Hexamethyltetra-azacyclohexane (1) is also expected to be more ordered and hence more likely to be crystalline than the *cis*-isomer (2) because the *C*-methyl groups can adopt identical sites. Non-chair conformations for the *trans*-hexamethyltetra-azacyclohexane in solution were discounted on similar grounds to the argument by Nelsen and Weisman [5] that, for 1,2,3,3,6,6-hexamethyl-1,2-diazacyclohexane (3), twist–boat conformations relieve less of the strain associated with *gauche* interactions inherent in the chair form than distortions in the chair form.



SCHEME 1



(3)

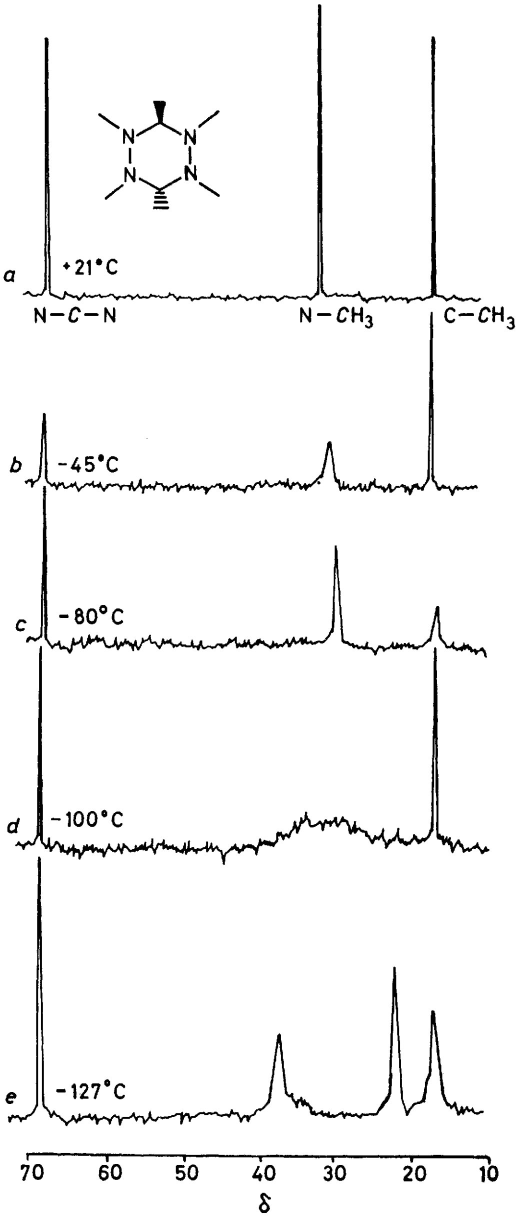
The proton n.m.r. spectrum of (1) consists of the C–*H* quartet (δ 4.45 and 4.25, ^3J 6.0 Hz), N–CH_3 singlet (δ 2.43), and C–CH_3 doublet (δ 1.06, ^3J 6.0 Hz) signals in appropriate ratios. No change is observed down to *ca.* —100 °C; below this, broadening due to sample ' freezing ' precluded further analysis. The room-temperature proton-noise-decoupled ^{13}C n.m.r. spectrum consists of three lines assigned on relative chemical shift grounds and from the undecoupled spectrum as N–*C*–N, N–*C*H$_3$ and C–*C*H$_3$ respectively (Table). At —45 °C conformational broadening of the signals is apparent, most marked for the N–*C*H$_3$ signal (Table, Figure). The signals sharpen up by —70 °C but in the temperature region —90 to —110 °C, the N–*C*H$_3$ signal undergoes a second dynamic coalescence and splits into a doublet. At still lower temperatures sample freezing occurs. The Eyring equation [6] gives a barrier of 7.7 ± 0.2 kcal mol^{-1} for the dynamic splitting of the N–*C*H$_3$ signal at *ca.* —100 °C. Calculation of precise energies from the

Carbon-13 d.n.m.r. data (25.05 MHz) of *trans*-1,2,3,4,5,6-hexamethyl-1,2,4,5-tetra-azacyclohexane

Temp. (°C)		N–*C*–N	N–*C*H$_3$	C–*C*H$_3$
21	Chemical shift [a] (δ)	65.7	31.3	17.3
		(d, $^1J_{CH}$ 146.1)	(q, $^1J_{CH}$ 136.6)	(q, $^1J_{CH}$ 123.3)
—80 [b]		68.7	31.0	18.2
—127 [b]		69.0	37.9 *eq* 22.4 *ax*	17.4
First broadening data				
	t_c (°C)	—53	—45	—68
	$\Delta\omega_{\frac{1}{2}}$ (Hz) [c]	6.5	12.0	*ca.* 2
Coalescence data [d]				
	t_c (°C)		—97	
	$\Delta\nu$ (p.p.m.)		15.5	
	$\Delta G_c^{\ddagger}$ (kcal mol^{-1})		7.7 ± 0.2	

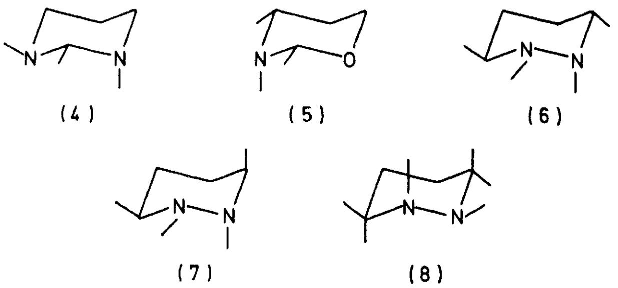
[a] Solvent: $(CD_3)_2CO$; p.p.m. downfield from Me_4Si; all coupling data in Hz. [b] Solvent: CF_2Cl_2–CD_3OD. [c] Corrected for natural line-width (2 Hz). [d] Eyring equation, ref. 6.

Anet-type broadening phenomenon[7] observed at *ca.* −45 °C requires estimation of Δν, the chemical shift difference: this is difficult because shifts of the carbon environments in the different conformations of tetra-azacyclohexanes are not all known. However, the temperature range of the broadening suggests 9 to 10 kcal mol^{-1} for the barrier (minor→major) and *ca.* 2 to 5% for the population of the minor form (assuming Δν = 10 p.p.m.).



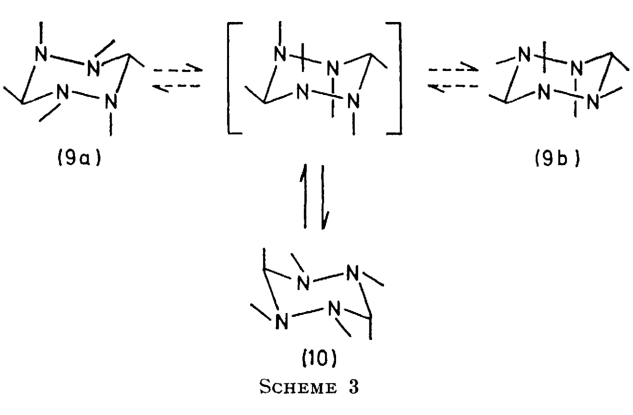
Carbon-13 n.m.r. spectra of *trans*-1,2,3,4,5,6-hexamethyl-1,2,4,5-tetra-azacyclohexane at various temperatures (a) in $(CD_3)_2CO$; (b—e) in CF_2Cl_2–CD_3OD

Six-membered chair conformers with three or more adjacent equatorial methyl groups, are destabilized with respect to conformations avoiding this arrangement: (4) for 1,2,3-trimethyl-1,3-diazacyclohexane,[8] (5) for 2,3,4-trimethyl-1-oxa-3-azacyclohexane,[9] (6) for *trans*-1,2,3,6-tetramethyl-1,2-diazacyclohexane,[4] and (7) for *cis*-1,2,3,6-tetramethyl-1,2-diazacyclohexane.[4] The preferred conformation (8) of 1,2,3,3,6,6-hexamethyl-1,2-diazacyclohexane (3) also avoids placing three or more adjacent groups equatorial, in spite of the 1,3-*syn* axial methyl-methyl interactions in (8).[5] Although twelve non-degenerate forms are possible for *trans*-hexamethyltetra-azacyclohexane, which are divided by high barriers involving ' passing ' electronic interactions into conformational sets as postulated for 1,2,4,5-tetra-azacyclohexanes,[2] only two, (9) and (10), remain if those with three adjacent equatorial methyl groups are eliminated. Interconversion between (9a) and its mirror image (9b) is accomplished *via* low-energy ' non-passing ' *N*-inversions comparable to the inversions in Set II of 1,2,4,5-tetramethyl-1,2,4,5-tetra-azacyclohexane[2] and in *trans*-1,2,3,6-tetramethyl-1,2-diazacyclohexane (6),[4] but interconversion between (9) and (10) requires ' non-passing ' ring inversion. The observed dynamic ^{13}C n.m.r. effects are consistent with (9) as the major conformation and probably (10) as the minor form: the first coalescence represents ' freezing ' out of (10) while the (9a) $\rightleftharpoons$ (9b) interconversion remains ' fast '. The second coalescence at *ca.* −100 °C ' slows ' the (9a) to (9b) *N*-inversion, thus confirming that ' non-passing ' interconversions within the three conformational sets proposed for 1,2,4,5-tetra-azacyclohexane[2] possess $\Delta G_c^{\ddagger}$ values of *ca.* 7.6 kcal mol^{-1}.



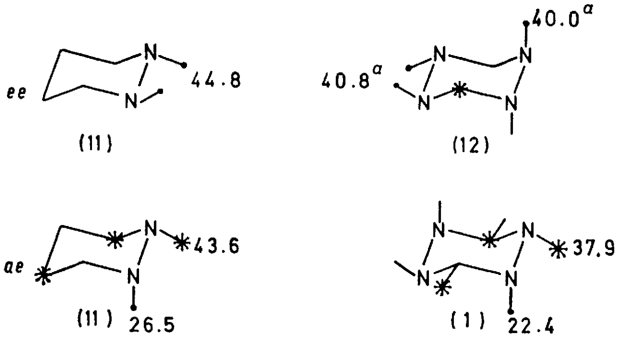
SCHEME 2

A consideration of the ^{13}C chemical shifts of (8) at low temperature confirms that (9a)/(b) must be the major conformer. Nelsen's ^{13}C n.m.r. study[4] of 1,2-dimethyl-1,2-diazacyclohexane has shown the marked *γ-gauche* upfield shift effect[10] experienced at the axial N-CH_3



SCHEME 3

carbon atom [*cf.* δ 26.5 in (11*ae*) conformer for axial *N*-methyl carbon atom, and δ 44.8 in (11*ee*) for equatorial *N*-methyl carbon atom] resulting from steric C–H polarizations marked *. Removal of an adjacent equatorial *N*-methyl group reduces the upfield shift as found in 1,2,4,5-tetramethyl-1,2,4,5-tetra-azacyclohexane which adopts the unsymmetric diequatorial/diaxial conformer (12) [2]: compare δ 40.0 and 26.5 for the axial *N*-methyl carbon atom in (12) and (11*ae*) respectively. Thus, the axial $N{-}CH_3$ resonance in (9a)/(b) should be shifted further upfield because the axial carbon atom experiences 4 *γ-gauche* upfield shift effects (3 C–H and 1 N-lone pair steric polarizations). Indeed the *N*-methyl signal of (1) at low temperatures splits into two signals (δ 22.4 and 37.9), the upfield part of which is consistent with an axial $N{-}CH_3$ carbon atom which is subject to 3 C–H *γ-gauche* interactions. The observed chemical shifts thus exclude all conformations other than (9a)/(b).



SCHEME 4 *a* May be interchanged

EXPERIMENTAL

Natural abundance C-13 n.m.r. spectra were obtained on a JEOL FX-100 n.m.r. spectrometer operating at 25.05 MHz, using 10 mm JEOL n.m.r. tubes containing *ca.* 500 mg of solute in 3 ml of solvent. Proton decoupled spectra used standard settings; off-resonance spectra required the ^1H irradiating power low and offset 50.8 kHz. Pulse delay of 6 s was used for n.O.e. suppressed spectra. Dial temperatures were accurate to ±1 °C by comparison with a copper–constantan thermocouple mounted in an n.m.r. tube.

trans-1,2,3,4,5,6-*Hexamethyl*-1,2,4,5-*tetra-azacyclohexane*.—Freshly distilled acetaldehyde (1.6 g, 0.38 mol) was added dropwise to freshly distilled *sym*-dimethylhydrazine (2 g, 0.35 mol) in sodium dry ether (50 ml) under dry nitrogen at −5 to −10 °C. After 2 h, the tetra-azacyclohexane separated and was recrystallised from n-pentane as prisms, m.p. 32 °C (lit.,[3] m.p. 30.5—31 °C) (2.5 g, 87%) [Found (after drying over P_2O_5 at 15 mmHg for 10 h and handling under dry N_2 gas): C, 55.2; H, 11.7; N, 32.3. Calc. for $C_8H_{20}N_4$: C, 55.8; H, 11.6; N, 32.6%]; *m/e* 172 (P^+) and 112 ($P^+ - 60$).

[8/662 *Received*, 10*th April*, 1978]

REFERENCES

[1] Part 88, A. R. Katritzky and R. Patel, *Heterocycles*, 1978, 263.

[2] V. J. Baker, A. R. Katritzky, J.-P. Majoral, A. R. Martin, and J. M. Sullivan, *J. Amer. Chem. Soc.*, 1976, **98**, 5748.

[3] W. Skorianetz and E. sz. Kováts, *Helv. Chim. Acta*, 1970, **53**, 251.

[4] S. F. Nelsen and G. R. Weisman, *J. Amer. Chem. Soc.*, 1976, **98**, 3281.

[5] G. R. Weisman and S. F. Nelsen, *J. Amer. Chem. Soc.*, 1976, **98**, 7007.

[6] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.

[7] F. A. L. Anet, I. Yavari, I. J. Ferguson, A. R. Katritzky, M. Moreno-Mañas, and M. J. T. Robinson, *J.C.S. Chem. Comm.*, 1976, 399.

[8] A. R. Katritzky, V. J. Baker, I. J. Ferguson, and R. C. Patel, *J.C.S. Perkin II*, 1979, 143.

[9] A. R. Katritzky, V. J. Baker, and F. M. S. Brito-Palma, in preparation.

[10] N. K. Wilson and J. B. Stothers, *Topics Stereochem.*, 1974, **8**, 58.