Tetrahedron Letters No. 43, pp 3803 - 3806, 1977. Pergamon Press. Printed in Great Britain.

THE SYNTHESIS AND CONFORMATIONAL ANALYSIS OF PERHYDRO-1,2,4-TRIAZINES AND PERHYDRO-1,3,4-THIADIAZINES AND A NOTE ON 1-METHYLMORPHOLINE AND 1,4-DIMETHYLPIPERAZINE[1]

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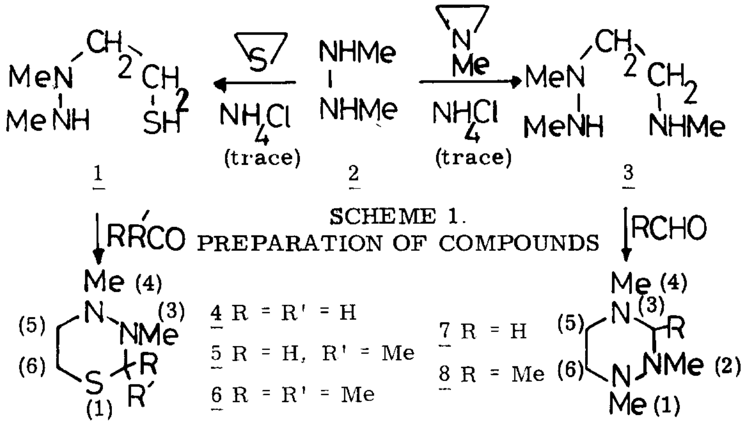
(Received in France 20 June 1977; received in UK for publication 12 September 1977)

1,2,4-Triazanes and 1,3,4-thiadiazanes are previously unknown classes of compound: we have now synthesised representatives of each (Scheme 1) by methods which utilise thiiran and N-methylaziridine and are extensions of our previously reported[2] synthesis of the 1,3,4-oxadiazane ring system.

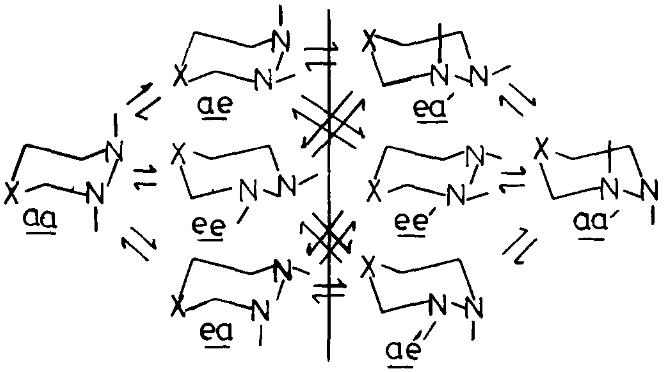


SCHEME 1.
PREPARATION OF COMPOUNDS

4 R = R' = H
5 R = H, R' = Me
6 R = R' = Me
7 R = H
8 R = Me

1,2,4-Trimethyl-1,2,4-triazane (7). The conformational equilibria for this compound are shown in the cube of Scheme 2, except that the ax/eq-4-N-Me inversion is not included: this last inversion is considered to remain fast at all temperatures measured; cf. 1,3-dimethyl-1,3-diazane has been shown to have a barrier of 7.0 ± 0.3 kcal mole^{-1} for the N-Me inversion.[3]

The 'H NMR spectrum of 7 at +20 °C shows the expected three N-Me peaks (at δ 2.51, 2.46, 2.16), the N-CH_2-N singlet (at δ 3.40) and N-CH_2- multiplet (at δ 2.74). Coalescence occurs on lowering the temperature at ca. -30 °C; at -50 °C the spectrum consisted of the three N-Me signals (δ 2.44, 2.36, 2.02), the N-CH_2-N (at δ 3.43, 3.24 ABq, $^2J_{HH}$ = 11 Hz), and the N-CH_2- (at δ 2.61 m) protons. Measurement of the N-CH_2-N peak at the coalescence temperature of -31 °C gives $\Delta G_c^{\ddagger}$ = 12.0 ± 0.3 kcal mole^{-1}: this refers to the lowest in energy of the six barriers cut by the line 'A' in Scheme 2. Two of the N-Me signals show a dynamic broadening and sharpening phenomenon at lower temperatures, -50 to -70 °C. We believe this corresponds to the barrier 7b ⇌ 7f, in support of the ^{13}C results.



A

X = S 4
X = NCH_3 7

SCHEME 2

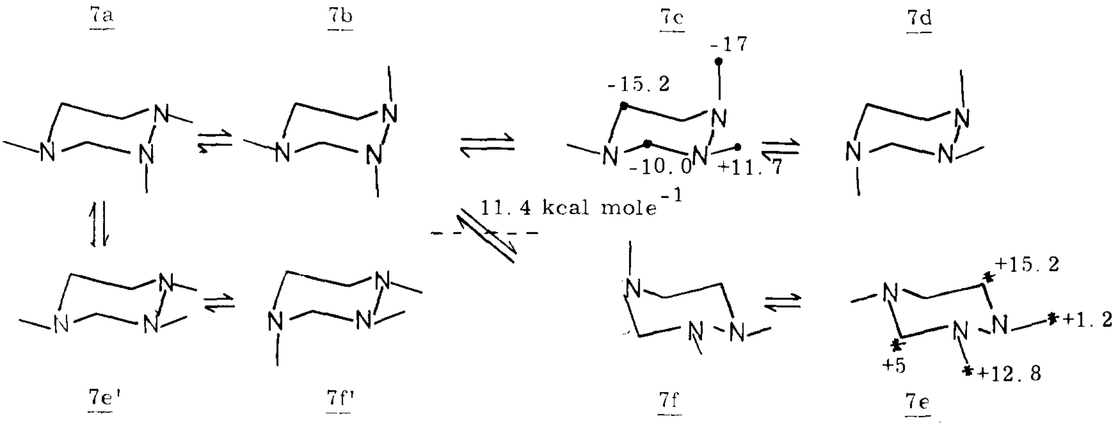
The ^{13}C NMR spectra of 7 at +20 °C shows the expected six peaks (Table). On lowering the temperature no coalescence occurs but two successive selective broadening and resharpening of peaks occur. This indicates[4] the existence of a biased equilibrium with the successive freezing out of two minor components. Scheme 3 gives the appreciably populated conformers for 7, excluding those with *syn*-diaxial methyl groups. We believe that the predominant conformer for 7 is 7a. Nelsen[5] has shown that 1,2-dimethyl-1,2-diazane exists as a 42:58 mixture of ae and ee forms at room temperature: the extra nitrogen (4) will increase the population of the ea form 7a, as has been found for 1,3,4-oxadiazane.[2]

The first broadening phenomenon at about -15 °C involves the 2-N-Me and the 3- and 6-ring carbons; examination of Scheme 3 shows that this is just what is expected for the freezing out of the "non-passing" ring inversion 7b ⇌ 7f (or the alternative passing *N*-inversion 7a ⇌ 7e′), and the separation of the minor forms 7e and 7f out of the equilibrium. In Scheme 3 the *C*-atoms which experimentally show broadening are indicated by *. Since signals for minor conformations were not observed at lower temperatures, differential chemical shifts for 7c , 7e relative to major form 7a are predicted from model compounds 1,2-dimethyl-1,2-diazane[5] and 1,3-dimethyl-1,3-diazane[3] (Scheme 3). The Anet equations[4] give ΔG_c^o 1.2 ± 0.1 kcal $mole^{-1}$ for the population of the minor forms 7e and 7f: we expect 7e to be rather more populated than 7f and the absence of broadening for N(4)-Me supports this. $\Delta G_c^{\ddagger}$ (minor to 7a) was calculated to be 11.4 kcal $mole^{-1}$ (Table).

TABLE. C-13 NMR (25.05 MHz) DATA[a] FOR 1,2,4-TRIMETHYL 1,2,4-TRIAZANE

Temp. (°C)	N(1)-C	N(2)-C		C(3)		N(4)-C	C(5)	C(6)
ca 30 δ (ppm)	42.5	32.9		77.1		43.0	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 [b]	q	q		t		q	t	t
Broadening data [c]								
	[d]					[d] [e]	[d]	[e]
t_c (°C)	-99 [f]	-13	-92	-19	-92		-99	-13
$\Delta\omega_{1/2}$ [g] (Hz)		22.1	32.1	10.7	20.5		9.8	26.1
$\Delta\nu$ [h] (ppm)		+12.8	+11.7	+5.0	-10.0		-15.2	+15.2
Pop. [i] (%)		6.9	9.1	8.5	8.2		2.5	6.9
ΔG^o_c (kcal mole^{-1})		1.34	0.82	1.17	0.87		1.27	1.35
$\Delta G^{\ddagger}_c$ (kcal mole^{-1})		11.2	7.7	11.4	7.7		7.3	11.1

[a] Solvent: CF_2Cl_2-acetone-d_6, 2:1. [b] Obtained from off resonance decoupling. [c] Anet's equations, Ref. 4. [d] No broadening effect near -10 °C. [e] No broadening effect near -90 °C. [f] Overlap precludes accurate assessment of broadening parameters. [g] Corrected for natural line width in absence of 'slow' exchange: natural line width = 3.9 Hz. [h] Obtained from model compounds: see Text. Sign of $\Delta\nu$ relative to shifts in 7a. [i] Pop. of minor conformation: 1st phenomenon (7e ⇌ 7f); 2nd phenomenon (7c ⇌ 7d).



SCHEME 3. CONFORMATIONS OF 7

The second broadening phenomenon around -95 °C involves the 1- and 2-N-Me and 3- and 5-ring carbon atoms. Application of the Anet equation[4] gives $\Delta G^{\ddagger}_c$ 7.5 ± 0.3 kcal mole^{-1}. This second dynamic process must represent the freezing out of one or more of the minor conformations 7b, 7c, 7d. We can exclude 7b as a large contributor, because the N(2)-Me shows a significant upfield shift on reducing the temperature (Table) whereas the N(2)-Me of 7b should itself be upfield of that for 7a.[5] Again examination of the experimentally observed (indicated by •) and expected broadenings indicates that 7c is the principal component of the minor isomers which freeze out.

3,4-Dimethyl-1,3,4-thiadiazane (4). The ^{1}H NMR shows at +50 °C ($CDCl_3$) N-Me singlets (at δ 2.55 and 2.47), N-CH_2-CH_2-S broad, diffuse multiplet (δ 2.77) and the N-CH_2-S singlet (at δ 4.38). On lowering the temperature coalescence occurs of the ring CH_2 peaks and for the N-CH_2-S (δ 4.9, 3.9 ABq, $^2\underline{J}_{HH}$ = 11.2 Hz) a barrier of 12.7 $\pm$ 0.3 kcal mole^{-1} was found for the lowest of the six barriers denoted by 'A' in Scheme 2. No further changes occur down to -78°C.

The ^{13}C proton noise decoupled NMR spectrum at 15 °C (CF_2Cl_2-acetone-d_6) shows N-Me signals at δ 28.9 [N(3)-C] and 43.7 ppm [N(4)-C] and ring carbon peaks at δ 58.1 [C(2)], 28.0 [C(6)] and 43.0 [C(5)]. The only temperature change observed was the reversible broadening of the 3- and 4-N-Me and C(2) and C(6) peaks at ca. -110 °C. This indicates that there is no appreciable amount of the ee conformation: its presence would have led to higher temperature broadening as observed for 7b ⇌ 7f ring inversion. It is apparent that we are 'freezing' out 4ae ⇌ 4aa ⇌ 4ea interconversion. No signals were observed for the minor conformation and therefore $\Delta\underline{\nu}$ for the Anet equations[4] were obtained, as first approximation, from 1,2-dimethyl-1,2-diazane.[5] A barrier of 6.8 kcal mole^{-1} is estimated for the minor to major inversion, with $\Delta\underline{G}^o_c$ = 1.35 kcal mole^{-1} (ca. 2% of minor form 4ea). The major form is expected to be the N(3)-Me axial and N(4)-Me equatorial (4ae) and this is confirmed by the upfield shift of the N(3)-Me signal.

1-Methylmorpholine and 1,4-dimethylpiperazine. The utility of the broadening phenomenon in biased conformational equilibria is underlined by this work. However, we emphasise that great care must be taken to avoid spurious broadening phenomena arising from machine faults. We recently reported[6] results obtained on a XL-100 machine for three compounds. While those for tropane have been entirely confirmed using the FX-100 spectrometer, we now believe that the apparently reproducible broadenings we found for 1-methylmorpholine and 1,4-dimethylpiperazine were artifacts and we wish to withdraw this part of our previous paper. We thank Prof. Anet for his help with this.

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