knowledged. The authors are indebted to Professor T. Yonezawa for encouragement of this work. They wish to thank Professor H. Kato and Dr. H. Fujimoto for helpful discussions.

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Conformational Interconversions in Hexahydropyridazine Derivatives

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Abstract: Variable-temperature ^{13}C NMR data for 1,2-dimethylhexahydropyridazine (1), its *cis*- and *trans*-3,6-dimethyl derivatives, and 3,4-dimethyl-3,4-diaza-*trans*-bicyclo[4.4.0]decane are reported. These data show that the equatorial, equatorial *N*-methyl conformation of 1 is about 0.3 kcal/mol lower in enthalpy than the equatorial,axial conformation, and that $\Delta G^{\ddagger}$ for the two different nitrogen inversions possible for 1 differ by about 4.8 kcal/mol, which is interpreted to be principally caused by lone-pair–lone-pair repulsion.

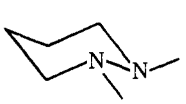
Although the conformations of six-membered rings have been by far the most important and best studied, an understanding of the conformational equilibria involved in azacyclohexanes has been slow to develop, largely because of the difficulty in separating nitrogen inversion from ring inversion, and the lack of experimental techniques which can directly observe and identify different conformations. A capsulation of published conformational work on 1,2-dimethylhexahydropyridazine (**1**) illustrates this point. Anderson[1] concluded that **1** exists solely in the diequatorial methyl conformation **1ee** because the ^{1}H NMR *N*-methyl signal remained a singlet, even at temperatures where two *N*-methyl signals were observed

Table I. ^{13}C Chemical Shift for Hexahydropyridazine Derivatives (ppm from internal Me_4Si)

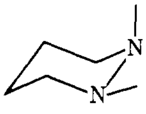
Compound	Temp, °C	Concn, M	Signal: NCH$_3$	C(3,6)	C(4,5)	Other	Assignment
1	33	3[a]	40.91	54.06	23.37		Equilibrating
	−68	3[a]	44.78 (A)	58.41 (A)	25.55 (A)		1ee
			35.60 (B)	48.09 (B)	20.13 (B)		1ae ⇌ 1ea
	−121	1.5[b]	44.68 (A)	58.21 (A)	25.36 (A)		1ee
			43.55 (C)	54.21 (C)	(ca. 25.4) (C)		1ae frozen
			26.46 (C)	42.96 (C)	15.64 (C)		
3	49	0.9[a]	40.99	59.60	39.92	30.47; 26.73	Equilibrating
	−43	0.9[a]	44.52 (A)	64.51 (A)	42.23 (A)	30.11, 26.53	3ee
			37.08 (B)	54.00 (B)	37.08 (B)		3ae ⇌ 3ea
4	34	2.5[a]	31.64	51.22	29.71	20.52	Equilibrating
	−127	1.3[b]	40.22	56.98	34.39	20.78	4ae′ frozen
			21.81	46.44	24.60	20.24	
5	58	1.3[a]	36.03	51.96	26.69	20.04	Equilibrating
	−65	1.3[a]	40.39	55.45	30.04	26.25	5ae frozen
			29.86	46.77	22.01	18.74	
	−119	0.7[b]	40.47	55.57	29.88	21.28	5ae frozen
			29.88	47.20	21.90	18.52	

[a] In acetone-d_6. [b] Acetone-d_6 sample diluted with CF_2Cl_2 to concentration shown.

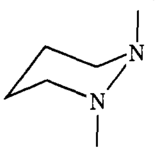
for **2**, a fact which requires that both ring and nitrogen inversion for **2** be slow on the NMR time scale. Jones, Katritzky, and co-workers[2a] determined the dipole moment of **1** to be too high for **1ee** to be the only conformation present at room temperature, and from a combination of low-temperature ^{1}H NMR and dipole moment studies on derivatives of **1** concluded that **1** exists as a 36:34:30 mixture of **1aa**:**1ea**:**1ee** at room temperature.[2b,c] They were able to rationalize Anderson's NMR spectrum of **1** by assuming that only ring inversions and nitrogen inversions which force methyl groups to pass each other in the transition state for the conformational process were slow enough to be frozen out at the temperature employed.[2b,c] The spectrum of **2** was not commented upon. Armed with new NMR data in which Anderson saw a small second *N*-methyl singlet in the ^{1}H NMR spectrum at very low temperature, the English group then revised the room-temperature conformational percentages for **1** to 62:20:18,[2d] which was also consistent with the dipole moment data.



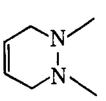
1ee



1ea



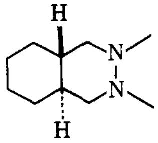
1aa



2

We report ^{13}C NMR results which show that **1ee** is in fact the stablest conformation of **1**[3] and, from the spectra of more highly substituted **1** derivatives, that electronic interaction and not steric repulsion is the factor causing substantially different barrier heights for the two types of nitrogen inversions.

Results



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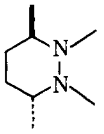

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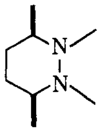


5

We report ^{13}C chemical shift data at various temperatures for **1** and the related compounds studied here (**3**–**5**) in Table I. For **1**, the room-temperature spectrum of three lines broadened and was replaced by two three-line spectra (set A and set B) as the temperature was lowered (see Figure 1). Since the lines of set B broadened and split to a spectrum consisting of six equal intensity lines (set C), B must consist at least largely of the unsymmetrical conformer **1ae**, and because all of the lines of set A are downfield of the averaged lines of B, A can only reasonably be **1ee**. In the range where spectra A and B were observed, we determined the relative amounts of these species by integration (both electronic and by cutting and weighing the peaks), and at the upper end of this range an independent measurement of the relative amounts of A and B present could be made by simulation of the spectra, since the A/B ratio influences the appearance of the spectrum. At temperatures where A and B had coalesced to a single three-line spectrum, chemical shift interpolation was used to estimate the amounts of A and B. Each technique gives three independent A/B determinations at each temperature, one for each type of carbon. The averaged data at each temperature appear in Table II, and all data points are included in the log K_{eq} vs. $1/T$ plot shown as Figure 2. It is clear that there is more scatter in the integration numbers than the chemical shift interpolation, although it is not true that the latter data are necessarily more accurate, for systematic error is introduced because we cannot reasonably correct for nonconformationally caused chemical shift temperature dependence. The percent **ee** values obtained by the different methods agree reasonably well, and the plot of Figure 2 yields for $K_{eq} = (\mathbf{1ee})/(\mathbf{1ae})$, $\Delta H° = -0.37$ kcal/mol, $\Delta S° = -0.6$ eu. The conclusion that $\Delta S°$ is small seems quite firm; the maximum and minimum slopes that can be drawn which still touch data points give only a ±1 eu difference in $\Delta S°$. It will be noted that there is a −1.4 eu symmetry contribution to $\Delta S°$ for this equilibrium.

The diazadecalin **3** gave qualitatively similar behavior to **1**, the initial spectrum of equilibrating **3** (five types of carbon) broadening and resharpening to unequal sized doublets for the NCH_3, NCH_2, and CH signals. We did not observe broadening or double signals for the methylene carbons of the carbocyclic ring. We could not obtain spectra below −43° because **3** crystallized out of solution. Both chemical shift interpolation above coalescence and integration below coalescence gave ratios of the two conformations which were consistent within experimental error (see Table II) and showed that K_{eq} for **3** is only slightly lower than that for **1**.

Arguments for the conformational assignments for **3**–**5** (Table I) appear in the Discussion section. The spectra were simulated in the temperature ranges where conformational broadening was occurring, yielding the activation parameters listed in Table III.

Discussion

1,2-Dimethylhexahydropyridazine (1). It is useful to consider the diagram showing interconversion of the eight chair con-

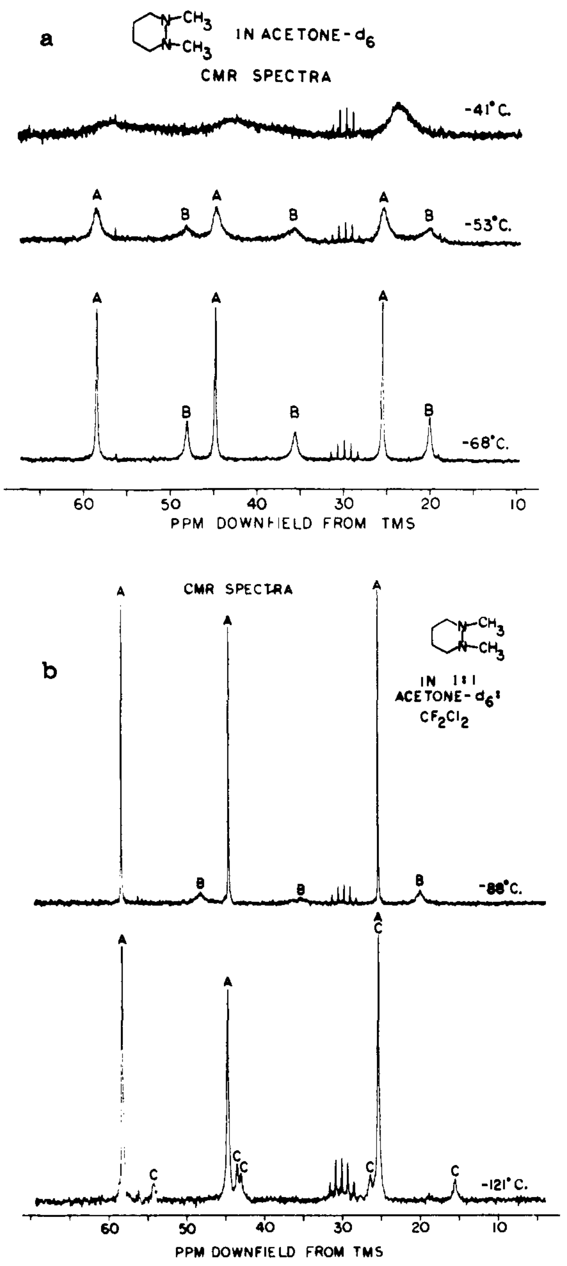


Figure 1. ^{13}C NMR of 1 at various temperatures.

formations of **1** given as Figure 3[4] before the ^{13}C experimental results are analyzed. Examination of models convinces us (as it has others[1,2]) that ring and nitrogen inversions will occur independently of each other, since coupling of the motions involved would lead to higher activation barriers. Each conformation can invert the ring or either of the two nitrogens, so the conformations may be placed at the corners of a cube, having nitrogen inversions as the sides of two squares in parallel planes, and the ring inversions forming the other four edges of the cube. The opposite corners of the cube have mirror image conformations. Figure 3 is the diagonal view of this cube which is most convenient for this discussion. Because of the symmetry of the conformations, there are four different conformational changes possible for **1**, two different ring inversions (horizontal equilibria in Figure 3) and two different nitrogen inversions (diagonal equilibria).

As Jones, Katritzky, and co-workers pointed out,[2] the processes which force methyl groups to pass each other, that is, the four identical nitrogen inversions and two identical ring inversions broken by the heavy line bisecting Figure 3, must both become slow to isolate the four conformations on the left from their enantiomeric conformations on the right, which will cause the NCH_2 ^1H NMR signal to separate into a broadened AB quartet, but leave the NCH_3 signal a singlet, because the four conformations on each side of the heavy line are still interconverting. Thus Anderson[1] measured the activation energy of the lowest of the processes, **1ae** $\rightleftharpoons$ **1ee′** (N-inversion) or **1ae** $\rightleftharpoons$ **1ea′** (ring inversion), or the two processes coupled. Freezing out the ca. 12-kcal/mol processes broken by the heavy line of Figure 1 will not, however, affect the ^{13}C NMR spectrum. The

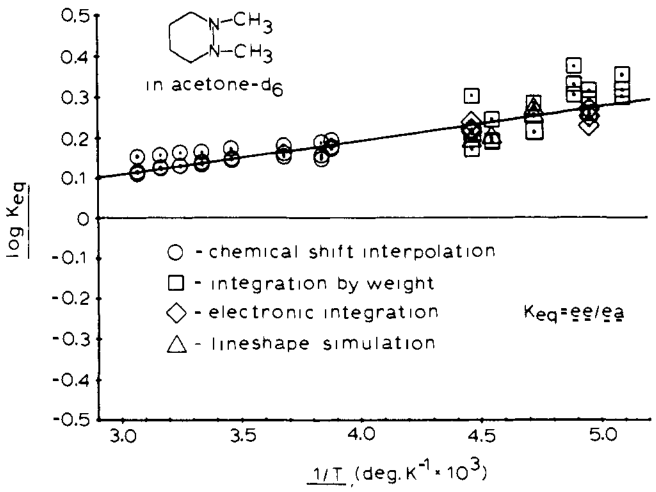


Figure 2. Plot of K_{eq} vs. $1/T$ for 1, showing all data points.

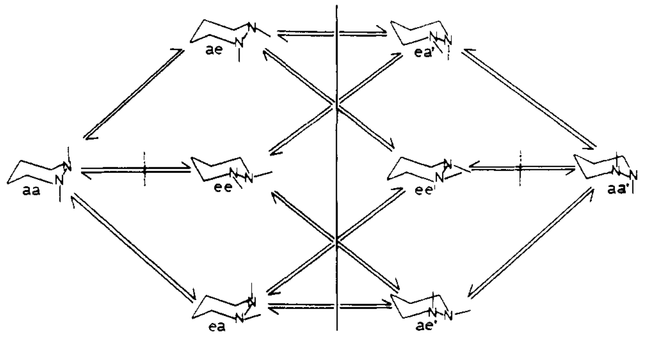


Figure 3. Conformational interconversions for **1**.

Table II. Estimations of Conformational Populations

Compd	Temp, °C	% ee	Method[a]
1	53.4	57.1	A
	43.1	57.5	A
	35.1	57.9	A
	26.7	58.2	A
	16.1	58.7	A
	−1.0	59.3	A
	−12.3	59.2	A
	−15.1	60.0	A
	−49.0[b]	62.6 (62.5)[61]	B(C)[D]
	−53.2	61.6 [61]	B[D]
	−61.3	63.1 [65]	B[D]
	−68.5	68.2	B
	−71.0[b]	65.8 (63.7)	B(C)
	−76.5	67.6	B
3	49.5	54	A
	37.9	54	A
	33	54	A
	−12.8	(57)	(C)
	−18.7	(55)	(C)
	−32.8	(57)	(C)

[a] Method A is chemical shift interpolation; B, cut and weigh; C, electronic integration; and D, simulation (see text). [b] At 67.9 MHz; all other data at 25.2 MHz.

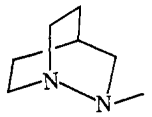
Table III. Activation Parameters for Conformational Processes in Hexahydropyridazine Derivatives

Compd	Temp range, °C	κ used	No. data points	$\Delta G^{\ddagger}(T)$, kcal/mol[a]	T	$\Delta G^{\ddagger}(25°)$, kcal/mol[a]	$\Delta H^{\ddagger}$, kcal/mol[a]	$\Delta S^{\ddagger}$, eu[a]	Assignment[b]
1	−15 to −68	½	14	10.30 ± 0.07	−30	9.9 ± 0.2	11.9 ± 0.6	6.7 ± 2.6	R (1ee ⇌ [1ae ⇌ 1ea])
	−15 to −68	½	14	10.07 ± 0.07	−30	9.7 ± 0.2	11.6 ± 0.6	6.2 ± 2.6	R ([1ae ⇌ 1ea] ⇌ 1ee)
	−75 to −121	½	9	7.56 ± 0.04	−100	7.0 ± 0.3	8.4 ± 0.5	4.6 ± 2.6	N (1ae ⇌ 1ea)
3	49 to −19	1[c]	10	12.60 ± 0.07	2	12.5 ± 0.07	13.6 ± 0.8	3.7 ± 2.9	N (3ee ⇌ 3ea′)
	49 to −19	1[c]	10	12.71 ± 0.07	2	12.6 ± 0.07	13.6 ± 0.8	3.3 ± 2.9	N (3ea′ ⇌ 3ee)
4	−50 to −112	½	8	7.85 ± 0.05	−100	7.6 ± 0.2	8.1 ± 0.3	1.5 ± 1.8	N (4ae ⇌ 4ea)
5	33 to −30	½	16	11.80 ± 0.13	−100	11.7 ± 0.16	12.3 ± 1.1	2.0 ± 4.1	See text

[a] Errors quoted are statistical errors at the 95% confidence level. [b] R is ring reversal; N is nitrogen inversion as the rate-limiting step. [c] A single nitrogen inversion performs this interconversion, so the transmission coefficient (κ) is 1. For the other examples, an intermediate which must partition "forward" and "backward" with equal probability is involved, so κ = ½.

observed ^{13}C NMR behavior is just what is expected from Figure 3. As the temperature is lowered, the first process frozen out is the **1aa** ⇌ **1ee** ring inversion, which separates **1ee** from the equilibrating mixture of **1ae** ⇌ **1aa** ⇌ **1ea.** That the assignment of set A lines to **1ee** and set B to **1ae** is correct is assured by their behavior upon further lowering the temperature, for set A sharpens, but at low enough temperature, set B broadens as the **1ae** ⇌ **1ea** interconversion becomes slow, eventually causing emergence of the six-line set C spectrum of frozen **1ae.** We see no lines attributable to **1aa** at low temperature, and since the lines for this species would be expected to occur upfield of those of the other conformations, if a significant amount of **1aa** were present at higher temperatures, we would have expected that the set B lines would not have occurred so close to the average of the set C lines. We cannot, of course, rule out a few percent of **1aa** by this argument, but we have no evidence for the presence of the diaxial conformation.

The activation parameters for the two conformational processes frozen out appear in Table III (since the **1ae** ⇌ **1ea** equilibrating mixture is slightly higher in energy than **1ee,** slightly different activation parameters are involved for the two ring reversals). The nitrogen inversion process which separates **1ae** from **1ea** has a $\Delta G^{\ddagger}$ at −100° of 7.5 kcal/mol, quite close to the nitrogen inversion barrier in the bicyclic hydrazine **6**, $\Delta G^{\ddagger}$ (−100°) = 7.8 kcal/mol.[5]



6

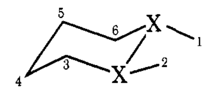
3,4-Dimethyl-3,4-diazabicyclo[4.4.0]octane (3). The two higher energy conformational changes undergone by **1** do not affect its ^{13}C NMR spectrum. Anderson[1] measured $\Delta G^{\ddagger}$ of the faster of these processes by ^{1}H NMR, but our inability to distinguish which one prompted us to try to measure the difference in barrier heights for the "easy" and "difficult" nitrogen inversions of **1** by an indirect method. We selected the diazadecalin **3** as a model for **1** in which both ring reversals were ruled out, but in which there are only small geometric differences near the nitrogen atoms. We believe that the similarity of free energy differences between the **ee** and **ea** conformations for **1** and **3** (Table II) show that **3** is a good model for **1**; the percent **ee** of **1** varies from about 57% at 50° to 67% at −75°, while that for **3** is ca. 54–57% between 50 and −33 °C. This corresponds to about a 0.3-kcal/mol difference in $\Delta H°$, and under 1 eu difference in $\Delta S°$. We measured activation parameters for the high-energy nitrogen inversion of **3** (Table III) but were unable to measure the low-energy barrier because of solubility problems. Assuming that the measured barrier for **3** is a good model for the corresponding unmeasurable one of **1**, the difference in $\Delta G^{\ddagger}$ (25°) for the "easy" and "difficult" nitrogen inversions of **1** is 4.8 kcal/mol, a rather large difference. Jones, Katritzky, and co-workers[2a-d] have argued that the cause of this difference is steric repulsions because *N*-methyl groups do not have to pass in the low barrier, but do in the higher one.[2e] The $\Delta G^{\ddagger}$ observed for **1** by Anderson is rather lower than that for nitrogen inversion of **3,** suggesting that the ring reversal of **1** which crosses the heavy line in Figure 3 may be faster than the nitrogen inversion.

3,6-Methylated 1,2-Dimethylhexahydropyridazines. If the NMe,NMe steric interaction were really so large, one should see a large fraction of this interaction in a CMe,NMe interaction, so we also investigated compounds **4–6,** which have such interactions present.

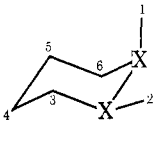
For the *trans*-3,6-dimethyl compound **4,** only one conformational process was observed, each peak in the high-temperature spectrum broadening and resharpening as a symmetrical doublet. The low $\Delta G^{\ddagger}$ measured for this process (Table III) makes it apparent that what we have observed is the freezing out of the **ae** ⇌ **ae** nitrogen inversion. No peaks corresponding to the **ee** conformation, which is the predominant one for **1**, were ever observed, nor was broadening seen as the temperature was lowered through the region where the **ee** ⇌ **ae** (equilibrium) process would freeze out. We conclude that **4** exists almost exclusively in an axial,equatorial conformation. Referring to Figure 4, there are two different axial,equatorial conformations, and the one labeled **ea′** and **ae′** is obviously more stable than the one labeled **ae** and **ea,** which has a 1,3-diaxial methyl-methyl interaction. This figure also makes it clear that the lower energy nitrogen inversion is all that is required to interconvert **ea′** with **ae′**. Making the comparison at −100°, where our experimental accuracy is greatest, $\Delta G^{\ddagger}$ of **1** is 7.56, and **4,** 7.85 kcal/mol. It is clear that forcing an *N*-methyl group on nitrogen in a chair six-membered ring to pass an equatorial *N*-methyl group on the adjacent carbon does not raise $\Delta G^{\ddagger}$ appreciably, and that the difference in $\Delta G^{\ddagger}$ for the two types of nitrogen inversions of **1** cannot be attributed to such a steric effect. The same conclusion was drawn for nitrogen inversion in the 2-methyl-2-azabicyclo[2.2.2]-octane series, where introduction of a C(1) methyl group had only a small effect on $\Delta G^{\ddagger}$.[5]

The *cis*-3,6-dimethyl compound **5** also shows only a single conformational process, each high-temperature ^{13}C singlet freezing to a 1:1 doublet, but the activation energy involved is far higher. Once the initial process is frozen out, further cooling does not lead to conformationally caused broadening. We assign the observed conformation to the lowest energy equatorial,axial ones (**5ae, 5ea′**) on the basis of chemical shifts (see below). Reference to the conformational cube for **5** (Figure 5) shows the reason for **5** having a considerably higher barrier than **4.** Conformations **5ae** and **5ea′** are in opposite sides of the "high" barriers and thus cannot interconvert by the low-energy nitrogen inversion, which allowed interconversion of the stablest equatorial,axial conformations of **4.** The observed $\Delta G^{\ddagger}$ (25°) of 11.7 kcal/mol is significantly lower than

Table IV. Chemical Shift Differences (ppm) for Dimethylcyclohexanes and 1,2-Dimethylhexahydropyridazine (1)

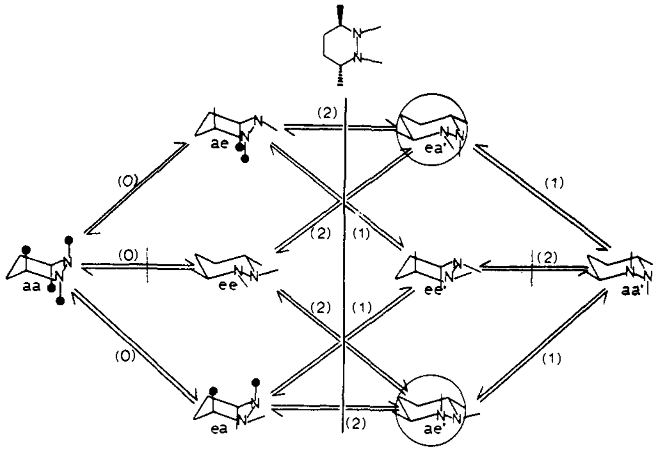


ee



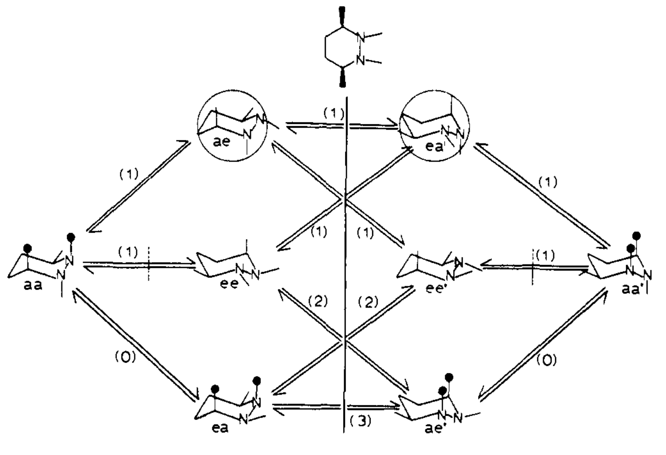
ae

	X = CH $\Delta\delta$ (ae–ee)	X = N $\Delta\delta$ (ae–ee)	$\Delta\delta_{ee}$ X=CH—X=N	$\Delta\delta_{ae}$ X=CH—X=N
C(3)	−7.7	−15.2	21.6	14.1
C(4)	0.0	0.0	−2.0	−2.0
C(5)	−7.0	−9.8	−2.0	−4.8
C(6)	−2.4	−4.0	21.6	20.0
Me(1)	−9.0	−18.2	23.9	14.7
Me(2)	0.3	−1.2	23.9	22.4



(number of CH_3-CH_3 crossings)

Figure 4. Conformational interconversions for 4.



(number of CH_3-CH_3 crossings)

Figure 5. Conformational interconversions for 5.

the 12.5 kcal/mol observed for the high-energy nitrogen inversion of **3**, but we cannot distinguish whether a comparable nitrogen inversion, or the ring reversal which interconverts **5ae** and **5ea′** is rate limiting; it seems possible that these processes have rather similar $\Delta G^{\ddagger}$, both contributing to the rate of interconversion. One notes again that the barrier is not raised by the presence of the α-methyl groups.

Chemical Shifts. Part of the utility of ^{13}C NMR in conformational work is the well-recognized upfield shift caused by steric crowding; the effect is large enough so that an axially substituted cyclohexane has unambiguous upfield shift for the axial substituent, as well as the β-ring carbons undergoing 1,3-diaxial interactions.[6] Schneider and Hoppen[7] have shown that the β-carbon shifts do not correlate with the size of the cyclohexane substituent, since electronically induced shifts are fairly substantial. We have assigned the upfield member of the doublets produced upon freezing at the C(3,6), C(4,5) and Me(1), Me(2) peaks of equilibrating **1ae** $\rightleftharpoons$ **1ea** to the Me(1), C(3), and C(5) signals (Me(1) is the axial methyl group—see Table IV). Making these assignments, one obtains the **1ae–1ee** chemical shift differences given in Table IV, where they are compared with the similar shift difference for the related hydrocarbons, taken from the literature.[8] The shifts obtained for the hydrazines generally parallel those for the hydrocarbons, although all hydrazine shifts are significantly larger in size.

We used the observed shift changes upon replacing the methine carbons of *trans*- and *cis*-dimethylcyclohexane with nitrogens to give hydrazines **1ee** and **1ae**, respectively (see the last two columns of Table IV), to estimate the chemical shifts for various conformations of **5**, and enable assignment of the observed one. Since the required 1,2,3,4-tetramethylcyclohexane models are unknown, we estimated chemical shifts for these compounds from the Grant parameters,[6] which reproduce the spectra for frozen *cis*- and *trans*-dimethylcyclohexane quite successfully (root-mean-square deviations of 0.39 and 0.57 ppm). Then the shifts from the last two columns of Table IV were added to "convert" the hydrocarbons to hydrazines. We lack good numbers for the shift expected at Me(3) and Me(6) of **4** and **5** upon going from hydrocarbon to hydrazine, so we used the C(4) correction for Me(3) and the C(5) correction for Me(6), an obviously poor assumption. Table V contains the deviations of the shifts calculated in the above manner from those observed for three conformations of **5**. We included the Me(3) and Me(5) values in parentheses because of the modeling problem mentioned. We note that the **5ae** conformation gives a substantially lower deviation than **5ee** or **5ae′** (which is destabilized by a 1,3-diaxial Me,Me interaction anyway, and was included to see what sort of deviations would be given by an incorrect conformation). We therefore assigned the observed conformation of **5** as **5ae** in the above discussion of activation parameters. The unsymmetrical conformation of **4** which was observed can only reasonably be **4ae′**, which gave a satisfyingly low deviation (see the last column of Table V).

Lone-Pair–Lone-Pair Destabilization. If methyl-methyl interaction cannot explain more than a small fraction of the ca. 4.8 kcal/mol difference in $\Delta G^{\ddagger}$ values for the two types of nitrogen inversion in **1**, what causes the difference? Not only the methyls, but the lone pairs on nitrogen must pass each other in the **1ee–1ae′** ("difficult") nitrogen inversion, but the lone pairs on nitrogen are nearly perpendicular at the **1ae–1aa** transition state, as is illustrated in Figure 6. We believe that it is lone-pair–lone-pair repulsion in the transition state which

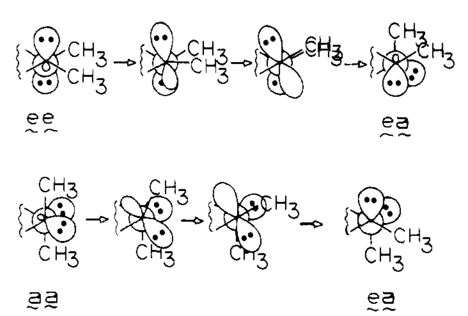
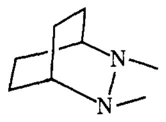


Figure 6. Diagram contrasting lone-pair-lone-pair interactions for the high- and low-barrier nitrogen inversions in hexahydropyridazines.

raises the $\Delta G^{\ddagger}$ for the "difficult" nitrogen inversion. Essentially this point has been made for exocyclic vs. cyclic hydrazines by Dewar and Jennings,[9] and we have observed that the barrier for "double nitrogen inversion" for **7** is $\Delta G^{\ddagger}$ (298°) 11.9 kcal/mol, whereas that for nitrogen inversion of **6** is only 7.1 kcal/mol, although it is not clear that nitrogen inversion is the barrier measured for **7**.[5]



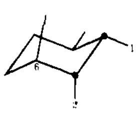
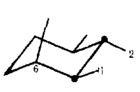
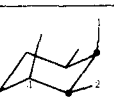
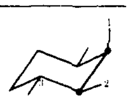
7

If an sp^2-sp^3 lone-pair-lone-pair interaction destabilizes the half-planar transition state for nitrogen inversion by approximately 4.8 kcal/mol, one would expect to see measurable (though smaller) destabilization for sp^3-sp^3 lone-pair interaction in ground-state hydrazines in which the lone-pair-lone-pair dihedral angle is near 0 or 180°. We suggest that this is the reason that **1ee** is so close in enthalpy to **1ae**, despite the fact that **1ae** is destabilized sterically by two 1,3 diaxial MeN-CH interactions. Unfortunately, it is difficult to estimate how destabilizing the steric interaction in **1ae** will be. Although it could be raised from the 1.7 kcal/mol for axial methylcyclohexane by the presence of the shorter C-N and N-N bonds in the ring, it should be lowered by the greater ease of deformation at nitrogen than at carbon, and we are unable to evaluate the relative sizes of these effects. Another factor which prevents ready quantitation of the size of the lone-pair-lone-pair destabilization in **1ae** is that there is likely to be a difference in the 1,2 Me,Me interaction depending on whether the methyls are axial,equatorial or equatorial,equatorial. Buttressing effects seem important, since there is an obvious aversion to having three adjacent equatorial methyl substituents in these systems; no **ee** conformations were detected for **4** or **5**.

This work establishes the fine balance of conformational preferences for these hexahydropyridazines, but a quantitative understanding of the steric and electronic factors influencing the balance of the preferences will have to be reserved for the future. It would be of great interest to see if the molecular mechanics method would be able to handle this problem.

Comparison with Photoelectron Spectroscopy. We have investigated **1, 4,** and **5** by photoelectron spectroscopy (PES),[10] and previously concluded that in the vapor phase **1ee** was present in higher concentration than **1ae,** and that both **4** and **5** had less than 1% **ee** conformations. These results agree with the ^{13}C results in solution. Although it appeared from PES that **1ee** predominates somewhat more in the vapor phase than ^{13}C NMR has shown it does in solution, a lack of knowledge of the cross sections for emission of the n_+ and n_- bands of **1ee** and **1ae** make this only a tentative result. We believe that the important conclusion is that only minor changes in conformational ratios apparently occur even in going from as polar a solvent as acetone to the vapor phase. We believe that the conformational preferences observed are not greatly affected by solvation differences.

Table V. Chemical Shift Differences (Observed – Calculated) for 1,2,3,6-Tetramethylhexahydropyridazines

Carbon	 **5ae**	 **5ee**	 **5ae′**	 **4ae′**
C(3)	0.75	–5.56	6.44	0.15
C(4)	2.26	–5.59	–2.11	0.56
C(5)	–0.84	–1.98	4.44	0.51
C(6)	0.34	–8.24	–1.47	1.67
Me(1)	3.28	–11.38	10.05	1.98
Me(2)	0.67	–0.79	0.67	0.42
Me(3)	(3.13)	(3.10)	(8.62)	(2.63)
Me(6)	(4.63)	(8.59)	(5.91)	(4.87)
Dev[a]	2.47	6.59	5.90	2.18
Dev[b]	1.36	6.63	5.30	1.12

[a] Root-mean-square sum of the deviations. [b] As *a*, but omitting Me(3) and Me(6).

Experimental Section

3,4-Dimethyl-3,4-diaza-*trans*-bicyclo[4.4.0]decane-2,5-dione. *trans*-1,2-Cyclohexanedicarboxylic anhydride[11] (8.5 g, 0.0552 mol), *sym*-dimethylhydrazine (3.31 g, 0.0552 mol), and dry benzene (300 ml) were refluxed through a Soxhlet extractor containing Linde 3A molecular sieves for 24 h. Removal of solvent gave 11.18 g of white solid, which was recrystallized from 1.5 l. of hexane, mp 134–140 °C (67%). Spectral data: NMR ($CDCl_3$) δ 1.0–1.6 (4 H, m), 1.84 (2 H, m), 2.18 (4 H, m), 3.26 (6 H, s); ir (CCl_4) 1687 cm^{-1}; mass spectral peak match (calcd for $C_{10}H_{16}N_2O_2$, 196.12117) 196.12074 (2.2 ppm error).

3,4-Dimethyl-3,4-diaza-*trans*-bicyclo[4.4.0]decane (3). A solution of 6.20 g (0.0316 mol) of the dione in 200 ml of dry tetrahydrofuran was added to a slurry of 7.3 g (0.193 mol) of lithium aluminum hydride in 200 ml of dry tetrahydrofuran and refluxed under nitrogen for 48 h. After quenching with 7.3 ml of H_2O, 7.3 ml of 15% sodium hydroxide, and 22 ml of H_2O, the solution was filtered, dried with magnesium sulfate, and concentrated, and the product was obtained as an oil (4.58 g) which crystallized upon standing. Three sublimations at 1 mm gave 3.66 g (69%) of **3**, mp 35–40 °C. Spectral data: NMR ($CDCl_3$) δ 0.75–1.90 (10 H, m), 2.2–2.7 (4 H, m), 2.45 (6 H, s); ir (CCl_4) no C=O, mass spectral peak match (calcd for $C_{10}H_{20}N_2$, 168.16265) 168.16267 (0.1 ppm error).

NMR Measurements. A Varian XL 100 was used for most of the measurements, but a Brucker 270 instrument was used to eliminate overlapping of the broadened set A and set B peaks in the electronic integrations of **1**. The data-handling techniques and variable-temperature measurements methods used have been discussed.[5]

The conformational equilibrium constant for **1**, K_{eq} = **ee**/(**ea** $\rightleftharpoons$ **ae**), was measured in two temperature ranges. The chemical shift interpolation method of Eliel[12] (eq 1) was employed to estimate K_{eq} at temperatures in the fast exchange region, where the values of δ_{ee} and $\delta_{ea \rightleftharpoons ae}$

$$\%\,\mathbf{ee} = \frac{\delta_{obsd} - \delta_{ea \rightleftharpoons ae}}{\delta_{ee} - \delta_{ea \rightleftharpoons ae}} \times 100 \qquad (1)$$

for each type of carbon were obtainable from the slow exchange spectrum. (The spectrum at –66 °C was used for this purpose, where the **ea** $\rightleftharpoons$ **ae** process was still averaged. Corrections for temperature dependence of δ_{ee} and $\delta_{ea \rightleftharpoons ae}$ were impossible because of the limited temperature range in which both δ_{ee} and $\delta_{ea \rightleftharpoons ae}$ were sharp.) In the slow and intermediate exchange regions where peak overlap was not a problem, electronic integration and integration by peak weight were employed to measure K_{eq}. In the intermediate exchange region where peak overlap was a problem, direct line-shape simulation was utilized.

For the use of these last three methods, we must necessarily assume identical T_1 and NOE enhancement within each of the three sets of two lines, i.e., for corresponding carbons in the two conformations.

That this assumption is warranted was initially indicated by the similarity in K_{eq} values obtained from each of the three line pairs at a given temperature. Further verification was obtained by use of the gated ^{1}H-noise decoupling technique for the suppression of the nuclear Overhauser effect (NOE)[13] at -56 °C (67.9 MHz), which yielded percent **ee** values within 1% of the normally obtained data at this temperature. Use of long delay times (e.g., 80 s, 90° pulse), such that essentially complete relaxation of each nucleus was achieved, and NOE suppression yielded percent **ee** values with considerably more scatter ($\pm 4\%$) due to low signal/noise but with a mean identical with that obtained in the other methods at -56 °C.

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(4) (a) Figure 4 is topologically identical with Jones' and Katritzky's representation,[2] but easier to understand. (b) As Professor Mislow has pointed out to us, his group has investigated several systems (diarylmethanes, triarylboranes, spirocyclic phosphoranes) which also have eight symmetry-related conformations, which they placed at the corners of a cube considerably prior to the work reported here, and for which the conformational interconversions were analyzed by far more elegant group-theoretical treatments. See D. Gust, P. Finocchiaro, and K. Mislow, *Proc. Nat. Acad. Sci. U.S.A.*, **70**, 3445 (1973); D. Gust and K. Mislow, *J. Am. Chem. Soc.*, **95**, 1535 (1973); P. Finocchiaro, D. Gust, and K. Mislow, *ibid.*, **96**, 3198 (1974); and K. Mislow, *Acc. Chem. Res.*, **9**, 26 (1976).

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Bifunctional Catalysis of the Dedeuteration of Acetone-d_6 by Conformationally Constrained Derivatives of *N,N*-Dimethyl-1,3-propanediamine[1]

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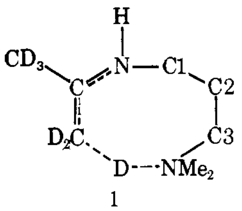
Abstract: Bifunctional catalysis of the dedeuteration of acetone-d_6 by the monoprotonated forms of nine primary-tertiary diamines has been studied. Each catalyst uses its primary amino group to transform the ketone to an iminium ion from which the deuterium is removed internally by the tertiary amino group to give an enamine with a $-NMe_2^+$ substituent. The deuterium is then removed from the $-NMe_2^+$ group by attack of a base. Rate constants have been obtained for formation of the iminium ions, as have rate and equilibrium constants for the formation of enamines and rough relative rate constants for removal of deuterium from the $-NMe_2^+$ groups. In the case of the eight 1,3-diamines studied, the transition state for enamine formation is most stable relative to acetone-d_6 and monoprotonated diamine when there is eclipsing around the bond between the carbon atom to which the primary amino group is attached and the adjacent carbon atom, especially when the C-NH_2 bond is eclipsed with the C-$CNMe_2$ bond. Bifunctional catalysis is also observed with a monoprotonated 1,4-diamine, *o*-(dimethylaminomethyl)benzylamine, but it is much less effective than it would otherwise be because the reactant is so highly stabilized by simultaneous coordination of the added proton with both amino groups. Such internal hydrogen bonding in a monoprotonated diamine, which makes *N,N,N′,N′*,2,2-hexamethyl-1,3-propanediamine and *o*-bis(dimethylaminomethyl)benzene much more basic than they would otherwise be, does not increase the rate at which such diamines remove deuterons from acetone-d_6 and hence results in large deviations from the Bronsted equation for the monofunctional base-catalyzed reaction.

Studies of the dedeuteration of acetone-d_6 in the presence of diamines of the type $Me_2N(CH_2)_nNH_2$, where *n* is 2, 3, 4, and 5, and of the conjugate acids of such diamines showed that monoprotonated *N,N*-dimethyl-1,3-propanediamine is the best catalyst.[2,3] This was attributed to internal attack by the dimethylamino group on deuterium in the intermediate iminium ion.

There are two conformers for the transition state **1** for such a process in which the carbon-deuterium bond being broken is approximately perpendicular to the plane described by the three carbon atoms from acetone and the iminium nitrogen atom. In what appears to be the more stable of these two conformers, the C(1)-N bond from the diamine is approximately eclipsed with the C(2)-C(3) bond. In the other conformer the C(1)-N bond is approximately eclipsed with a C(2)-H bond. To obtain catalysts in which such eclipsing was approximated in the reactants, *cis*- and *trans*-2-(dimethylaminomethyl)cyclopentylamine were prepared and their monoprotonated forms found to be considerably better catalysts than monoprotonated 3-dimethylaminopropylamine.[2,3] In order to learn more about



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