Conformational Analysis of Bridgehead Diazadecalin Derivatives by ^{13}C Nuclear Magnetic Resonance

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Abstract: A variable temperature ^{13}C NMR conformational study of several diazadecalin derivatives is reported. The relative energy of conformations with diequatorial alkyl groups (ee) and axial, equatorial alkyl groups (ae) on a hexahydropyridazine ring varies widely with substitution. Linking the alkyl groups in a six-membered ring strongly favors ee conformations, and only ee was detected for 1,6-diazabicyclo[4.4.0]decane (**5**). The presence of α-methyl groups and β,β' unsaturation favors ae conformations, leading to a range of K_{eq} = [ee]/[ae] values. No ee was detected for *cis*-7,10-dimethyl-1,6-diazabicyclo[4.4.0]-dec-3-ene (**10**), and measured values for $\Delta G°$ (ee–ae) at 25 °C (positive when ae is favored at equilibrium) were +0.8 (*trans*-7,10-dimethyl-1,6-diazabicyclo[4.4.0]dec-3-ene, **9**), +0.1 (*cis*-2,5-dimethyl-1,6-diazabicyclo[4.4.0]decane, **12**), −0.3 (*trans*-2,5-dimethyl-1,6-diazabicyclo[4.4.0]decane, **11**), and −0.7 kcal/mol (1,6-diazabicyclo[4.4.0]dec-3-ene, **13**). Activation parameters for conformational change were calculated from the NMR spectra for **9–13**, and ranges for rate constants derived quoted. Nitrogen inversions must be coupled with ring reversal for these systems, and it is observed that the nitrogen inversion coupled with unsaturated ring reversal (**9, 10, 13**) or unsubstituted ring reversal (**11, 12**) is significantly more rapid than that requiring reversal of the saturated or substituted ring.

Introduction

The conformational equilibria for 1,2-dialkyl hexahydropyridazines have received considerable study,[1] and it has been established by ^{13}C NMR work[2] that the dimethyl compound, **1**, exists as a mixture of the diequatorial methyl form, **1ee**, and the axial, equatorial form, **1ae**, with the former slightly predominating (K_{eq} = 1ee/1ae = 1.7 at −49 °C[2b]); the **1aa** form has not been detected. There is good reason to believe that
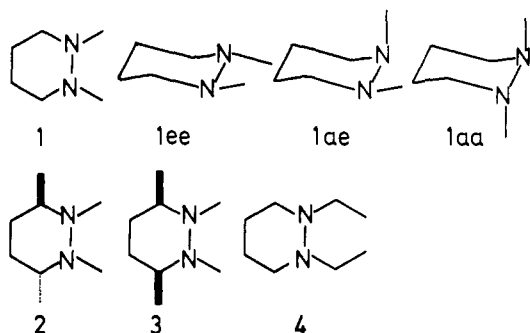
single nitrogen inversion and ring reversal without nitrogen inversion will be faster than combinations of these processes,[2b] so that the eight symmetry-related conformations of **1** may be placed at the corners of a cube, and the interconversions between them follow the edges of the cube (Figure 1). In the view shown, horizontal lines represent ring reversals, and the diagonal ones, nitrogen inversions. The rate of the faster of the two types of equilibria represented by the bold lines in Figure 1 was measured by ^{1}H NMR by Anderson,[3] and most likely represents the ring reversal, as indicated, because the $\Delta G^{\pm}$ for the ee → ae nitrogen inversion in a close model[2b] was measured to be 12.6 kcal/mol at 2 °C. The barriers measured by ^{13}C NMR[2b] for the remaining two interconversion equilibria are also shown in Figure 1.

The ee,ae equilibrium constants for hexahydropyridazines are quite sensitive to substitution at the carbons attached to nitrogen. Replacement of one C_α hydrogen by methyl causes ae conformations to predominate, and the disubstituted compounds **2–4** do not have detectable amounts of ee conformations.[2b,4] The bicyclic hydrazines **5** and **6** exist overwhelmingly in ee conformations, but only ae conformations were detected for tetrahydropyridazine **7** and **8**.[1]
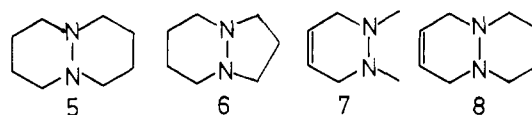
We report here ^{13}C NMR measurements of equilibrium and rate constants for conformational interconversion of several 1,6-diazabicyclo[4.4.0]decane derivatives. A principal reason for undertaking this study was to allow quantitative testing of the recently introduced low-temperature cyclic voltammetry method for studying conformational equilibria.[5] We chose bicyclo[4.4.0]decane derivatives for this test because ae conformations are unavailable for these compounds, thus eliminating the ca. 10 kcal/mol ee′ ⇌ aa ring reversal which allows rapid interconversion of ee and ae forms in monocyclic hexahydropyridazines—the conformational equilibria are restricted to the higher $\Delta G^{\pm}$ bold lines ("passing" equilibria) of Figure 1. Conformational barriers are also raised by the necessity of reversing both six-membered rings to interconvert axial, equatorial forms, as has been well established for *cis*-decalin derivatives.[6] We wanted to have a series of compounds with various sizes for K_{eq} = (ee)/(ea), which we expected to achieve by pitting the ee-favoring N,N'-alkyl group cyclization against the ae-favoring presence of α-methyl groups and β,β' unsaturation. We employed acetonitrile-d_3 as the solvent in this work, instead of the acetone-d_6 used previously,[3,4] to use the same solvent for the electrochemical study, allowing a more direct comparison of the methods. Acetonitrile has far better electrochemical properties than acetone. Further distinct advantages for acetonitrile in this work are the lack of solvent carbon interference (the methyl carbon signals are close to the Me$_4$Si methyl, but do not interfere with hydrazine peaks, in contrast to acetone) and an increased high-temperature limit.

Results and Discussion

Compound Preparation. The new compounds prepared for this study are **9–14**.[7] Reductive alkylation of 1,2,3,6-tetrahydropyridazine with hexane-2,5-dione by sodium cyanoborohydride proved to be somewhat sluggish, but conditions were worked out which gave a 40% yield of a mixture of **9** and **10**, which were readily separated by preparative VPC. Although a similar reductive alkylation of hexahydropyridazine gave the expected mixture of **11** and **12**, we were unable to separate
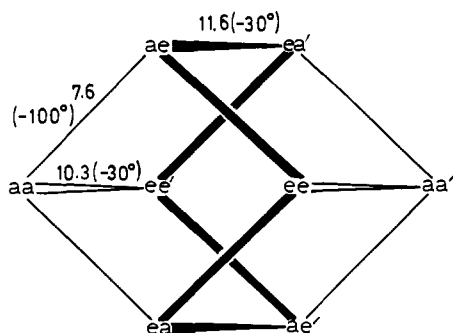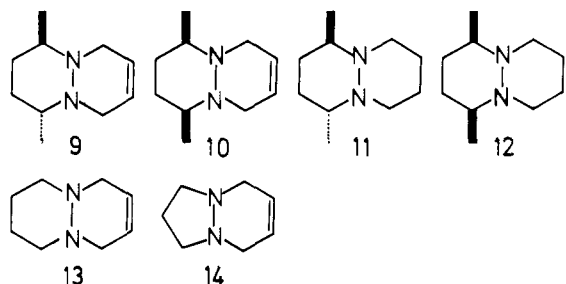
Figure 1. Conformational diagram for **1**, showing activation energies in kcal/mol at the temperatures shown for the interconversions indicated.

them, and were forced to prepare them by hydrogenation of the corresponding unsaturated compounds, **9** and **10**. Compound **13** was conveniently prepared by lithium aluminum hydride reduction of the tetrahydropyridazine–succinic anhydride condensation product **15**.

Chemical Shift Assignments. The assignment of which of the tetrahydropyridazine reductive alkylation product isomers was **9** and which **10** was carried out by examination of their ^{13}C NMR spectra. Both isomers gave the expected five-line patterns for rapidly conformationally equilibrating mixtures at high temperature, although even at 73 °C, the carbons next to nitrogen were noticeably broadened. The isomer of shorter VPC retention time (A) constituted about one-third of the mixture obtained from the reductive methylation, and had higher field carbon absorptions for its saturated ring carbons than did the longer retention time, major isomer (B). This is consistent with A being the cis methyl isomer **10**, since **10** must have one axial methyl group in each conformation. As the temperature is lowered and conformational interconversions become less rapid, the lines for both isomer A and B broaden and disappear into the baseline. At −9 °C, reappearance of broad lines was observed, and these lines sharpen as the temperature is lowered still further. At −23 °C, isomer B shows a set of ten lines of clearly greater intensity than a minor set of five lines (see Figure 3). Reference to the conformational diagrams of Figure 2 shows that only the trans isomer 9 has conformations with a twofold symmetry axis—isomer B is **9**. The $C_{2,5}$, $C_{7,10}$, and C_{Me} lines of the symmetrical minor conformation of **9** all appear at lower field than the corresponding lines of the major conformation, which is only consistent with the minor conformation being the expected one, CeeC (DeeD, the other symmetrical conformation of **9**, would have much higher field absorptions, and is also considerably destabilized by having two axial methyl groups in the saturated ring; no lines attributable to this conformation were observed). Isomer A, **10**, gives a single ten-line spectrum at low temperature, and the chemical shifts observed are only consistent with the observed species being the CeaD/DaeC racemic pair conformations; no lines for other conformations were seen. The chemical shifts measured appear in Table I. The conformations of **2** and **3** were previously shown[2b] to be those illustrated in
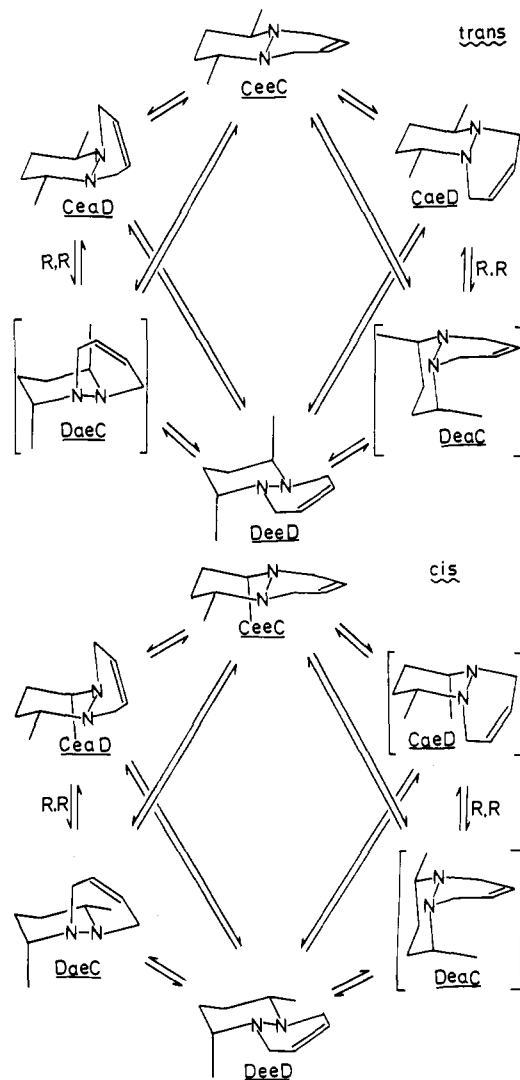
Figure 2. Conformational diagrams for **9** (trans) and **10** (cis) showing the conformations destabilized by 1,3-diaxial alkyl,methyl interactions in brackets. The left and right capital letters in the conformational designations give the ring reversal form for the left and right rings, respectively (arbitrarily chosen as C,C in the top structure; ring reversal converts C to D), and the small letters refer to axial or equatorial alkyl substitution on the left ring (front nitrogen appears first).

Table II. The small sizes of the deviations in chemical shift observed at Me_2, Me_5, C_3, and C_4 which are far from the site of substitution difference, coupled with the similar sizes of the shift differences at C_2, C_5, N_1C_{10}, and N_2C_7, make it clear that the ae conformation observed for the trans compounds **2** and **9** correspond, as do those for the cis compounds **3** and **10**.

The assignment of the lines for the trans isomer in the fully saturated series, **11**, is straightforward because the diequatorial conformation has a twofold symmetry axis which the axial, equatorial conformation lacks, so that identification of which lines belong to which conformation is easy in spite of an equilibrium constant near one. Assignments were far more difficult for the cis isomer, **12**, which gives 20 lines of nearly equal intensity in its low-temperature NMR spectrum. Good estimates for the axial, equatorial conformer carbon shifts can be made because the axial, equatorial isomer of **10** is available as a model (note the small differences between corresponding carbons of axial,equatorial **9** and **11**). To estimate the shifts for **12** CeeC/DeeD, because neither **3** nor **10** showed an ee conformation, we lack a good model with cis methyl groups, so we used the methyl shift parameters of Dalling and Grant[8]
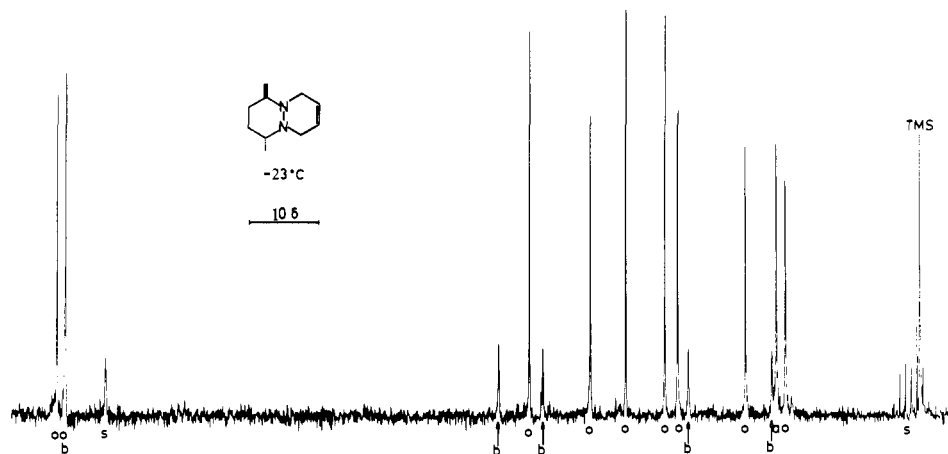
Figure 3. ^{13}C NMR spectrum of **9** at −23 °C. Major conformation (CeaD) peaks are marked (a), and those for the symmetrical minor conformation (b). The vinyl carbon of the minor conformation is not resolved from the upfield vinyl of the major conformation in this spectrum, but was resolved partially at lower temperature. The (s) peaks are caused by the CD$_3$CN used as solvent.

Table I. ^{13}C Chemical Shifts of 1,6-Diaza-2,5-dimethylbicyclo[4.4.0]decane Derivatives (ppm Downfield from Me$_4$Si, in Acetonitrile-d_3) and Related Compounds
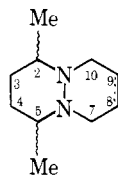
Compd	Temp, °C	Me	$C_{3,4}$	$C_{7,10}$	$C_{2,5}$	$C_{8,9}$	Assignment
9 (isomer B)	74	20.39	31.36^a	45.71^a	52.62^a	124.25	Equilibrating
(1.6 M)	−23	⎰20.71 ⎱19.42	⎰35.06 ⎱25.16	⎰47.76 ⎱36.92	⎰56.60 ⎱42.61	⎰124.76 ⎱123.53	CeaD (major)
		21.39	33.52	54.66	61.09	Unres	CeeC (minor)
11	72	20.92	33.31^a	49.91^a	56.32^a	24.48^a	Equilibrating
(0.9 M)	−25	⎰20.08 ⎱19.75	⎰34.94^b ⎱25.62^c	⎰49.28 ⎱35.07^b	⎰57.28 ⎱41.54	⎰26.35^c ⎱17.65	CeaD
		21.37	33.98	53.46	59.97	25.34	CeeC
10 (isomer A)	73	19.75	27.03^a	46.79^a	49.56^a	126.88	Equilibrating
(1.2 M)	−26	⎰21.05 ⎱18.60	⎰30.41 ⎱22.66	⎰48.05 ⎱43.84^b	⎰53.86 ⎱44.15^b	⎰125.44 ⎱123.89	CeaD
12	71	17.92	28.97	50.74	54.22	24.07	Equilibrating
(0.7 M)	−32	⎰20.72^b ⎱18.44	⎰29.89^c ⎱23.69	⎰49.46 ⎱42.88	⎰54.10^d ⎱44.08	⎰25.97^f ⎱17.29	CaeD
		⎰20.47^b ⎱11.17	⎰31.68^c ⎱28.00	⎰56.04^e ⎱54.69^d	⎰61.78 ⎱56.80^e	⎰25.59^f ⎱25.48^f	CeeC
13 (13-d_4)^g	72^a	None	24.31 (+0.11)	54.73 (−0.13)	55.41 (−)	123.93 (−0.16)	Equilibrating
(2.3 M)	−31 (−36)		25.44 (−0.11)	53.62 (−0.20)	52.20 (−)	123.14 (−0.35)	
	Minor		15.94 (+0.16)	40.22 (0.00)	42.93 (−)	Unres	ae (minor)
	Major		25.04 (0.00)	56.80 (−0.24)	57.70 (−)	123.72 (−0.25)	ee (major)
14	33	None	22.74^h	55.73^i	54.10^i	124.77	ee
(2.4 M)	−10		22.58^h	55.67^i	54.41^i	124.69	ee

^{a} Broadening caused by conformational equilibration still noticeable. $^{b-f}$ These assignments may be reversed. ^{g} The numbers in parentheses are $\Delta\delta = \delta(\mathbf{13}) - \delta(\mathbf{13}\text{-}d_4)$. ^{h} Numbering must be different for this bicyclo[4.3.0]nonane system. This is the single CCH$_2$C carbon. ^{i} NCH$_2$C carbons, not assigned.

on the unmethylated **5**ee spectrum to estimate shifts for this conformation. A visual comparison of the observed with the estimated shifts is given in Figure 4, where it may be seen that the methyl shift parameters gave rather larger deviations than did comparison with the unsaturated compound; the shifts for carbons 2, 3, 4, 5, 7, and 10 of **12**ee were all estimated about 1–2 ppm smaller than the observed lines. The assignments

made in Figure 4, which are the most logical based on these estimates, also give the closest agreement to the averaged high-temperature spectra.

The unmethylated, unsaturated compound **13** gave a low-temperature spectrum showing a clear predominance of the symmetrical diequatorial conformations over the four equivalent axial,equatorial conformations, but small chemical shift
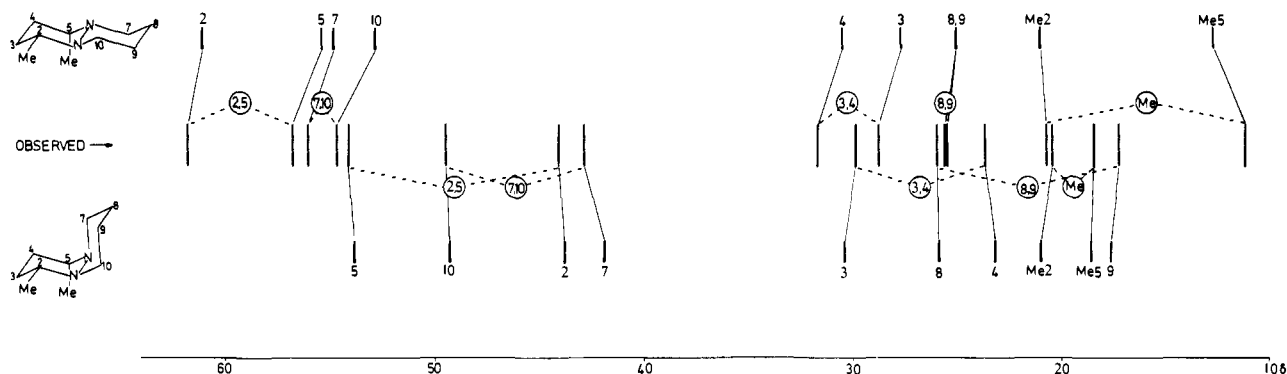
Figure 4. Diagram showing the chemical shift assignments for **12**. See text for the methods of estimating chemical shifts for the two conformers.

Table II. Chemical Shift Differences Observed for Axial, Equatorial Conformations of Bicyclic (**9, 10**) and Monocyclic (**2, 3**) Hexahydropyridazine Derivatives

trans ea
R = H 2
R = (CH=) 9
R = (—CH$_2$—) 11

cis ea
R = H 3
R = (—CH=) 10
R = (—CH$_2$—) 12

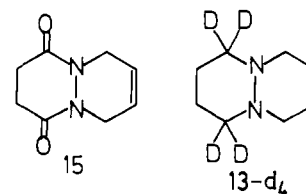| Position	Δδ (2–9)	Δδ (2–11)	Δδ (3–10)	Δδ (3–12)^a
Me$_2$	+1.4 to −0.5	+0.2 to +1.0	+0.2	+0.5
Me$_6$	+1.4 to −0.5	+0.2 to +1.0	+0.1	+0.3
C$_3$	−0.7	−0.6	−0.2	+0.3
C$_4$	−0.6	−1.0 (or −1.8)	−0.5	−1.5
C$_2$	+3.8	+4.9	+2.7	+1.5
C$_5$	+0.4	−0.3	+1.7	+2.7
N$_1$CH$_2$R	−7.5	−9.1	−7.8	−9.2
N$_2$CH$_2$R	−15.1	−13.2 (or −13.1)	−14.0	−13.0

^{a} Using the assignments of Table I.

Table III. Comparison of % ee Values Calculated by Chemical Shift Interpolation with and without Temperature Corrections for δ_{av} ee and δ_{av} ae^a

Carbons	Δδ$_{av}$ (ee−ae)^b	% ee, uncor^b	% ee, cor^c
2,5	10.5	50.5	47.6
7,10	9.2	49.5	46.3
3,4	3.5	63.2	40.4
8,9	3.9	62.5	40.3
Me	3.5	43.7	48.7

^{a} For **12** at 71 °C. ^{b} Using the −32 °C spectrum as the source of δ_{av} ee and δ_{av} ae. ^{c} Calculating the δ_{av} values at 71 °C using a linear extrapolation from values observed at −40.2, −34.4, and −31.9 °C.

differences between C$_{2,5}$ and C$_{7,10}$ in both conformations precluded assignment of these peaks with confidence. We therefore prepared **13**-d_4 by lithium aluminum deuteride reduction of **15**; because the deuterium splitting was not decoupled, signals for the carbons bearing deuterium were so broadened that we did not detect them, allowing the assignment to be made. Compound **14** showed only a single conformation by ¹³C NMR, which can only be **14**ee from the ob-

served chemical shifts, although we cannot distinguish which of the N*C* signals is which from available data.

Equilibrium Constants. The values of K_{eq} = (ee)/(ae) were measured at temperatures far below the coalescence temperature by integration of peaks for corresponding carbons in ee and ae conformations, where this was possible; in some cases peaks overlapped too much for accurate integration. For integration to be accurate, similar T₁ and NOE enhancement for corresponding carbons in different conformations is required. Use of the gated ¹H-noise technique[8b] to suppress NOE and long delay times to allow complete relaxation gave very similar results as in our previous work.[2b] The most convincing evidence that the above values are correct remains the excellent agreement (to with 2%) of % ee when different carbons of the same molecule are analyzed. At temperatures far above the coalescence temperature, the chemical shift interpolation (csi) method of Eliel[9] was employed. Because chemical shifts for hydrazine carbons which are not being influenced by changing equilibrium constants vary up to several tenths of a δ unit over a 100 °C temperature range,[10] one expects the accuracy of the csi method to be less when Δδ$_{av}$ (ee−ae) is smaller than when it is large. Such an effect was found by Bovey and co-workers[11] in the a,e equilibrium for cyclohexyl fluoride. They noted that serious errors occurred in applying the cis method to the ¹H spectrum, but not for the ¹⁹F spectrum, where Δδ is larger. This effect is clearly noted in all of our data, one example appearing in Table III. If the −32 °C low-temperature spectrum of **12** is used for the base data in a csi calculation, although excellent agreement is noted between the % ee values obtained for the large Δδ carbons, C$_{2,5}$ and C$_{7,10}$, the three carbons with smaller Δδ values deviate a great deal, the total range in calculated % ee being over 19%. When the δ_{av}ee and δ_{av}ae used for the csi were recalculated by a linear extrapolation of the shifts observed in low-temperature spectra recorded over an 18 °C temperature range (we are unfortunately limited in range by conformational broadening at the high-temperature end and solvent freezing at the low-temperature end) to the high temperature of the csi calculation, the C$_{3,4}$ and C$_{8,9}$ carbons gave far lower % ee values, and C$_{Me}$ a significantly higher value, while the large Δδ carbons were less affected. Although it appears that our crude temperature extrapolation may have "overcorrected" to some extent, it seems clear that the temperature extrapolated csi % ee values, which vary over an 8% range in % ee, are more accurate. All of our csi data for the
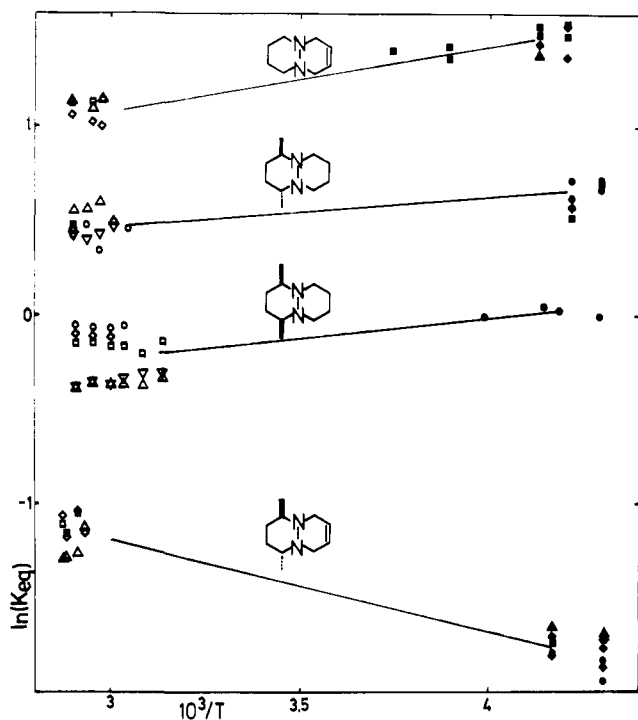
Figure 5. Van't Hoff plot of K_{eq} data for **9, 11, 12,** and **13.** The filled symbols are csi points, and the open ones integration points. $C_{7,10}$; $C_{2,5}$; $C_{3,4}$; $C_{8,9}$; C_{Me}.
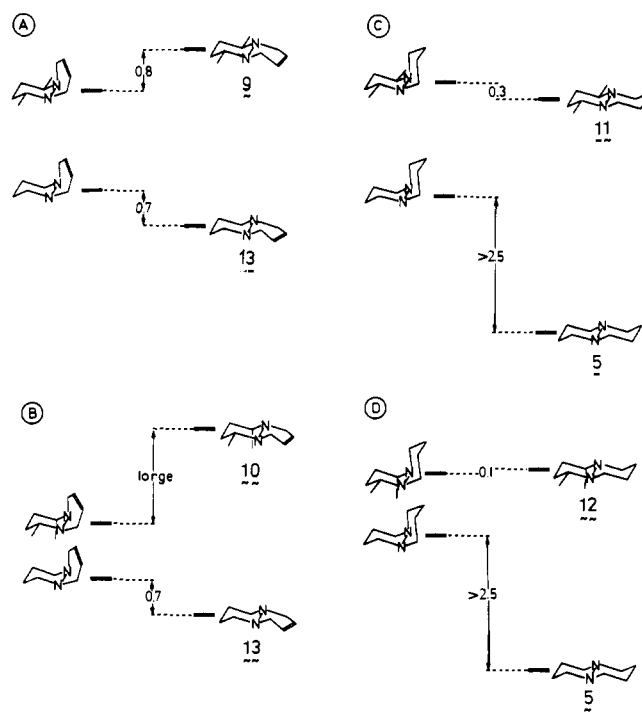

Figure 6. Pairwise comparisons of ee,ae energy differences for bridgehead diazadecalin derivatives. The vertical displacements between the methylated and unmethylated compounds are completely arbitrary.

**Table IV.** Thermodynamic Parameters for Some Bicyclic Hydrazines

Compd	$\Delta H°$, kcal/mol	$\Delta S°$, eu	$\Delta G°$ (25 °C)	$\Delta G°$ (−25 °C)
9	+0.90 (10)[a]	+0.31 (39)[a]	+0.81 (2)[a]	+0.82 (2)[a]
10	Very pos			
11	−0.26 (10)	+0.16 (34)	−0.31 (2)	−0.30 (2)
12	−0.39 (21)	−1.63 (74)	+0.09 (3)	+0.01 (3)
13	−0.61 (10)	+0.40 (35)	−0.72 (2)	−0.70 (2)
14	Very neg			
5	Very neg			
1	−0.38 (9)	−0.6 (4)	−0.19 (3)	−0.22 (2)
16[b]	−0.81 (15)	−2.9 (6)	+0.05 (3)	−0.9 (3)

[a] The values in parentheses in Tables IV and V are the statistical uncertainty in the last decimal place quoted, propagated at 95% confidence level, and refer only to deviations from the least-squares line through the data. [b] These values differ from those previously reported.[2b] Temperature extrapolation (see text) has been applied to obtain the present values.

other compounds were treated with similar linear temperature extrapolations, and fell in 6% or less ranges in % ee when different carbons were compared. Temperature extrapolations to improve csi data have previously been employed by Berlin and Jensen,[12] although their use does not seem to have become very general.

Because of the uncertainty in % ee measurements derived from NMR data, there is a good deal of scatter present in a Van't Hoff plot (a 1% uncertainty in % ee makes ln K_{eq} uncertain to ±0.04 at 50% ee, ±0.05 at 30 and 70% ee, and ±0.11 at 10 or 90% ee). Our data for **9, 11, 12,** and **13** are graphed in Figure 4, where it may be observed that we actually have nearly a two-point plot to represent the temperature variation of K_{eq}, because although several measurements were made by csi at high temperature, and several by integration at low temperature, the temperature range available for each type of measurement is usually small compared to the experimental scatter and temperature gap between them. We are gratified that the csi and integration measurements agree as well as they do. Since $S°$ for ee and ae conformations should be similar, $\Delta S°$ should be small, and the Van't Hoff lines should slope as they do, toward intercepts near zero at infinite temperature.

To indicate the relative precision (only) of the data represented in Figure 5, $\Delta G°$, $\Delta H°$, and $\Delta S°$ values determined from them are given in Table IV with statistical deviations propagated at the 95% confidence level. We emphasize that these deviations only relate to scatter in the Van't Hoff plot, and are not necessarily real error limits on these quantities. Nevertheless, if there had been seriously different systematic errors between the csi and integration K_{eq} measurements, this should have resulted in large $\Delta S°$ values; these data are internally quite consistent. For comparison with our earlier work[2b] data for **1** and **16** have been included, with the precision values calculated.
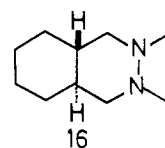
In an attempt to directly observe the ae conformation of **5**, a 2 M solution was cooled to −35 °C, and 66 000 transients were collected. No peaks attributable to **5ae** were observed near 17 and 36 ppm (where lines for **5ae** can be confidently
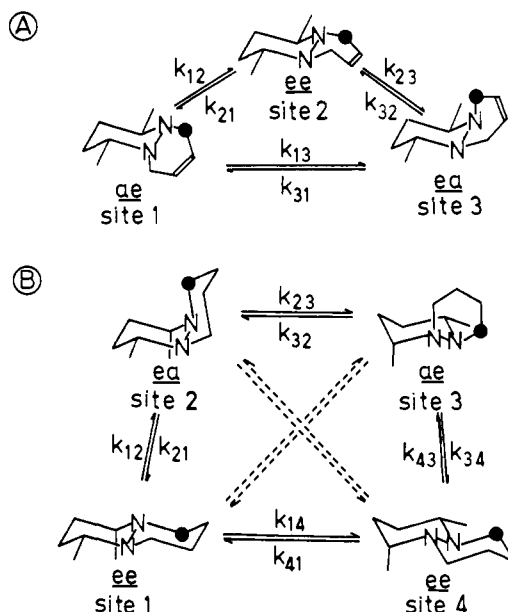
Figure 7. (A) Diagram showing an example of the three sites for a carbon of **9**, and the kinetic scheme used for spectral simulation (**11** and **13** are analogous). (B) The four carbon sites for **12**, and kinetic schemes used for analysis.

predicted to occur, from the known δ values of **12ae**). We are confident that we could have been able to detect a 0.5% amount of **5ae** under these conditions, establishing that $\Delta G°$ (-35 °C) ≥ -2.5 kcal/mol for **5**. Similarly comparing $\Delta G°$ values for **5** and **13** indicates that the ae-favoring effect of β,β' unsaturation is somewhat less important than α,α'-dimethylation, but still substantial (≥ 1.8 kcal/mol).

In considering the effects of adding methyl groups and introducing unsaturation upon K_{eq}, it is useful to refer to the $\Delta G°$ (25 °C) differences shown diagrammatically pairwise in Figure 6. The effect of adding trans methyl groups to the unsaturated system (**13 → 9**) is to add two $CH_{3e}C,NCH_{2e}$ (EE) interactions in **9ee**, but one CH_{3e},NCH_{2a} (EA) interaction and one EE interaction in **9ae**. Referring to Figure 6A, EE is about 1.5 kcal/mol larger than EA. This energy difference is considerably larger than would be seen in hydrocarbon analogues, and results from the presence of the six-ring hydrazine unit. X-Ray work[13] has shown that the amount of flattening at nitrogen depends upon the lone pair–lone pair dihedral angle, and that the dihedral angles between diequatorial substituents at nitrogen are rather smaller than those between axial,equatorial substituents. The data reported here confirm that the EE steric interaction is also significantly larger than is the AE one, and establishes the size of the difference. Addition of cis methyls (**13 → 10**, see Figure 6B) resulted in observation of only **10ae**. Because **10** CeaD/DaeC lacks the EA interaction of the trans compound, it is not surprising that the ae,ee energy gap is larger for **10** than for **9**. The unmethylated, saturated compound **5** is far more stable in the ee than in the yet undetected ae conformation, apparently some 2.5 kcal/mol stabler, from the results of our unsuccessful ^{13}C search **5ae**. The double bond of **13** flattens the hexahydropyridazine ring, greatly reducing the 1,3-diaxial RN,CCH$_2$ interaction present in the saturated series ae forms, as Anderson pointed out long ago.[3]

Addition of trans methyl groups (**5 → 11**, Figure 6C) results in the ee conformation being only 0.3 kcal/mol lower in energy than the ae conformation, making it appear that the EE-EA energy difference ($\geq$ about 2.2 kcal/mol) is appreciably larger than in the unsaturated series. Cis dimethylation in the saturated series (Figure 6D) results in the stablest ae conformation of **12** being slightly lower in energy than **12ee**. Cis dimeth-

ylation has only a slightly greater effect than that of trans dimethylation at destabilizing the ee form, and the magnitude of the effect is comparable to the ee-stabilizing effect of linking the alkyl groups of a dialkylhexahydropyridazine in a second six-membered ring.

Activation Barriers. For monocyclic six-membered ring hydrazines the nitrogen inversions which equilibrate ae and ea forms (by going through the undetected aa form) are rapid enough that the carbon signals of the equilibrating ae/ea mixture become sharper at lower temperatures than those at which significant broadening for ee $\rightleftharpoons$ [ae/ea] interconversion (which occurs most rapidly by ring reversal) is observed. This allows determining rates for these two different conformational processes as two-site problems in different temperature ranges.[2] In contrast, the bicyclic compounds considered here cannot attain aa conformations, and ae $\rightleftharpoons$ ea and ee $\rightleftharpoons$ [ae/ea] broadening occur in the same temperature range. The conformational interconversions involve either nitrogen inversion coupled to ring reversal (abbreviated N,R, the diagonal equilibria of Figure 2) or two coupled ring reversals (R,R, the vertical equilibria). Figure 7A shows the three sites a given carbon equilibrates between for the trans dimethyl saturated compound **9** (**11** and **13** are analogous), and Figure 7B the four sites for the cis dimethyl compound **12** (**10** is analogous). The NMR spectrum is sensitive to the rates at which sites interconvert (k_{ij} in Figure 7), although inspection of the complete conformational diagrams of Figure 2 will show that each of the NMR rates corresponds to two or more possible pathways.

The NMR spectrum is also sensitive to K_{eq}, and in a rather similar conformational situation Yang and Bushweller[14] have recommended measuring K_{eq} by using it as an independent variable in the region of kinetic broadening, where the rate constants are also measured. We found that the K_{eq} values determined by interpolation from the higher temperature csi (which overlap with the kinetic points) and lower temperature integration measurements give good fit to our observed spectra throughout the temperature range employed for kinetics. This serves as an additional check upon the K_{eq} data reported in the previous section, although we did not observe that the kinetic simulations were particularly sensitive to K_{eq} in most of the broadening range.

The observed spectra for **9, 11,** and **13** were fit successfully over the entire kinetically useful temperature range by setting $k_{13} = 0$ and just varying k_{12} (and hence k_{21}, which is related by K_{eq}). Similarily, the spectra for **12** were fit well with $k_{14} = k_{13} = k_{24} = 0$. For **10**, where only axial, equatorial conformations were observed, only the rate of **10ae → 10ea** is obtainable—the spectra contain no information on the pathway. The simulated rate constants gave reasonable Eyring plots, and the activation parameters thus obtained appear in Table V.

The good fit observed by setting $k_{13} = 0$ does not, of course, mean that such processes do not occur. Equivalently good fits for **9, 11,** and **13** were calculated when k_{13} was allowed to increase to a certain limit, if k_{12} was dropped accordingly, to keep the lifetime of a carbon at site 1 the same. The sensitivity of each spectrum to the relative sizes of k_{12} and k_{13} is dependent both on temperature (spectra below T_c are more sensitive) and on the carbons observed (large $\Delta \nu$ carbons are more sensitive). The minimum tolerable k_{12}/k_{13} rate ratios for **9, 11,** and **13** calculated at various temperatures which are collected in Table VI illustrate both points. Sample Eyring plots showing the $k_{12}(k_{13} = 0)$ data along with the k_{12} range resulting if the minimum acceptable k_{12} values are employed appear in Figure 8. Although the NMR data only give ranges for k_{12}, the range is rather narrow compared to the statistical error inherent in the experiment at the low-temperature end, and there is no evidence from our experiments that the k_{13} processes contribute at all. For **13**, the k_{12} rate constant corresponds to N,R (unsaturated). The k_{13} process is the sum of R,R (CeaD $\rightleftharpoons$

Table V. Activation Parameters for Conformational Change in Bicyclic Hexahydropyridazines

Compd	Process	$\Delta G^{\ddagger}$ (25 °C)	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
9[a]	$k_{12}\,(k_{13}=0)$[f]	14.43 (3)	15.8 (3)	+4.5 (11)
	$k_{21}\,(k_{13}=0)$	14.03 (3)	14.9 (3)	+2.8 (11)
11[b]	$k_{12}\,(k_{13}=0)$[f]	13.45 (6)	13.6 (7)	+0.5 (23)
	$k_{21}\,(k_{13}=0)$	14.18 (6)	13.8 (7)	−1.2 (23)
13[c]	$k_{12}\,(k_{13}=0)$[f]	14.05 (4)	16.4 (6)	+8.0 (21)
	$k_{21}\,(k_{13}=0)$	15.16 (4)	17.2 (7)	+6.8 (21)
10[d]	10ae $\rightleftharpoons$ 10ea	13.75 (8)	13.8 (10)	0.0 (34)
12[e]	$k_{23}\,(k_{14}=k_{24}=0)$[g]	13.39 (5)	15.3 (6)	+6.2 (18)
	$k_{12}\,(k_{14}=k_{24}=0)$	12.30 (5)	13.8 (6)	+5.2 (18)
	$k_{21}\,(k_{14}=k_{24}=0)$	12.24 (5)	14.1 (6)	+6.2 (18)

[a] Data used: C_{Me} at −6.0, 9.1, 16.5, 23.5; $C_{7,10}$ at 67.0, 74.0; $C_{3,4}$ at 51.7, 61.2, 67.0, and 74.0 °C; total T range 80 °C, 11 simulations. [b] Data used: C_{Me} at −12.8, −8.0, 1.2; $C_{2,5}$ at 1.2, 17.3, 62.1; $C_{8,9}$ at 17.3, 33.0, 44.3, 52.3; $C_{7,10}$ at 72.3; $C_{3,4}$ at 17.3, 21.6, and 33 °C; total T range 85.1 °C, 14 simulations. [c] Data used: $C_{3,4}$ at 21.1, 27.7, 33.2, 45.6, 54.0 °C for **13**, $C_{7,10}$ at 72.3, 69.0, 57.6, 48.4, 41.2, 30.6, 23.4, and 18.3 °C; $C_{3,4}$ at 48.4, 41.2, 30.6, and 23.4 °C for **13-d_4**; total T range 54.4 °C, 17 simulations. [d] Data used: C_{vinyl} at −7, −3.3, 2.0, 9.8; $C_{3,4}$ at 37.4, 39.4, 45.7, 55.7, 56.2 °C; total T range 63 °C, 9 simulations. [e] Data used: C_{Me} at 32.0, 42.1, 51.3; $C_{3,4}$ at 32.0, 51.3; $C_{8,9}$ at 56.6; $C_{2,5}$ at 42.1, 51.3, 56.6, 61.3, 71.0 °C; total T range 39.0 °C, 11 simulations. [f] See Figure 7A. [g] See Figure 7B.

DaeC in the analogue of Figure 2) and N,R (saturated). As shown in Table VI, N,R (unsaturated) is at least five times as fast as either of the k_{13} processes. N,R (unsaturated) is substantially faster than N,R (saturated), presumably reflecting the great difference in ring reversal rates of cyclohexene and cycohexane (5.3 and 10.8 kcal/mol, respectively, at 25 °C[15]). The R,R process is also slow compared to N,R (unsaturated).

For the saturated trans-dimethyl compound, Table VI indicates that k_{13} is only one-fifth or less the rate of k_{12}, which corresponds to N,R of the unsubstituted ring. The most direct site 1 → site 3 mechanism corresponding to k_{13} is successive N,R of the dimethylated ring at each nitrogen; this process therefore is slow compared to successive N,R of the unsubstituted ring. This presumably indicates that part of the destabilization of the bis-axial methyl intermediate in the N,R (disubstituted) pathway appears in the transition state for this process. We suggest, then, that the barriers listed in Table V for **9**, **10**, and **13** are dominated by N,R (unsaturated) for **9**, and N,R (unsubstituted) for **11** and **12**.

The rate constants given for compound **12** in Table V are not accurate, because of several problems with the data. The spectral simulation here is a four-site problem (see Figure 7B) and the spectrum is only sensitive to the k_{23}/k_{12} ratio at low temperatures, so for lack of another way to proceed, this ratio was held constant at all temperatures. We also set $k_{14} = 0$, which seems a reasonable assumption because of serious steric destabilization of the CaeD/DeaC forms, which would be intermediates in conversion of a site 1 to a site 4 carbon without going through sites 2 and 3. Spectral fit was attained setting $k_{13} = 0$ as well, suggesting that N,R (substituted) is a higher energy process than N,R (unsubstituted) for the cis-disubstituted ring of **12** as well as for the trans one of **11**. The accuracy expected for the rate constants quoted for **12** in Table V is clearly lower than for other cases.

The lowest energy N,R processes of **9–13** are substantially higher in activation energy than even the "passing" R and N processes of monocyclic hexahydropyridazines, which is not surprising because nitrogen inversion and ring reversal must be coupled in **9–13**. A simple nitrogen inversion would lead to a destabilized, boat conformation in one of the rings. The ring reversal barrier for *cis*-decalin has an analogous coupling of two ring reversals, and has been discussed in detail by Gerig and Roberts[6a] and by Grant and co-workers,[6b] who measured the barrier to be $\Delta G^{\ddagger}$ (25 °C) = 12.6 kcal/mol, $\Delta H^{\ddagger}$ = 13.6 (7) kcal/mol, $\Delta S^{\ddagger}$ = +3.5 (30) eu ($\kappa = \frac{1}{2}$), significantly above the cyclohexane barriers. A possible pathway for the coupled N,R barrier in *cis*-diazadecalin is shown in Figure 9, in which
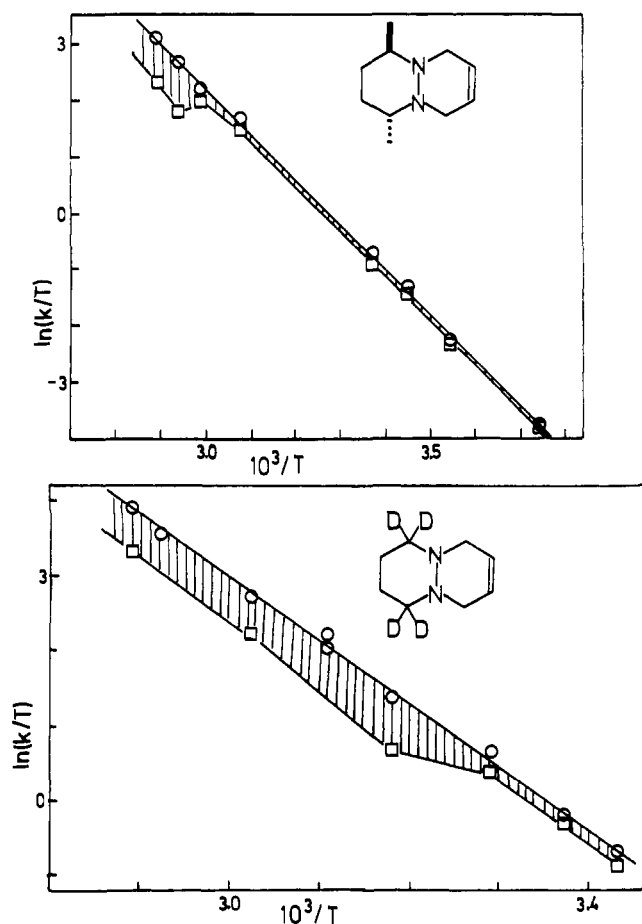

Figure 8. Eyring plots of kinetic data for **9** (above) and **13-d_4** (below). The circles show k_{12} calculated with $k_{13} = 0$, and the squares the minimum values of k_{12} compatible with the data. The shaded areas represent equally probable values of k_{12} from the spectra simulations at each temperature.

transformation of one ring to its boat/twist boat form precedes nitrogen inversion. We chose to picture this because such a ring reversal process is expected to have an activation energy near the ca. 10 kcal/mol of 1,2-disubstituted cyclohexanes and the "nonpassing" ring reversal of 1,2-dimethylhexahydropyridazine, while the nitrogen inversion preceding ring deformation would be a "passing" one, which ought to be higher in activation energy. The highest barrier to be surmounted in the

Table VI. Minumum k_{12}/k_{13} Ratios Consistent with ^{13}C NMR Spectra for **9, 11**, and **13**

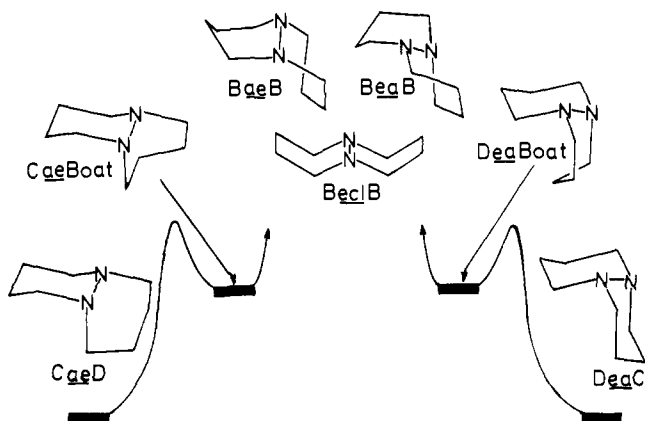| Compd	Carbons	Temp, °C	(k_{12}/k_{13}), min	Compd	Carbons	Temp, °C	(k_{12}/k_{13}), min
9	7,10	74	0.8	**11**	3,4	22	2
	7,10	67	0.7		2,5	17	3
	3,4	61	5		Me	1	5
	3,4	52ʳ	5		Me	−8	7
	3,4	24	5	**13**	2,5	73	1.3
	Me	17	7		2,5	58	1.5
	Me	9	5		2,5	48	1.5
	3,4	−6	5		2,5	41	1.0
11	7,10	72	1.2		2,5	31	3
	2,5	61	1.5		2,5	23	6
	8,9	52	0.3		2,5	18	5
	8,9	33	0.3				

Figure 9. Suggested pathway for double nitrogen inversion for a cis bridgehead diazadecalin. BeclB refers to the bis-boat structure indicated, which has eclipsed lone pairs and alkyl groups.

transformation of CaeD to DeaC is expected to lie somewhere between the BaeB and BeaB forms shown in the center of the figure, perhaps near the eclipsed boat,boat form, although, as stated above, there is experimental evidence that the N,R (unsubstituted) process is lower in activation energy than the N,R (substituted) one. It is, we believe, by no means obvious whether one or two potential surface maxima are involved in various cases, and we have set $\kappa = 1$ for all of our calculations.

Experimental Section

cis- and *trans-*7,10-Dimethyl-1,6-diazabicyclo[4.4.0]dec-3-ene (**9** and **10**). A solution of 4.56 g (40 mmol) of 2,5-hexanedione and 4.80 g (80 mmol) of glacial acetic acid in 50 mL of acetonitrile was added over 5 h to a stirred mixture of 3.36 g (40 mmol) of 1,2,3,6-tetrahydropyridazine, 2.52 g (40 mmol) of NaBH₃CN, and 50 mL of acetonitrile at 80 °C. After the mixture was stirred at 80 °C for an additional 2 h, sodium hydroxide pellets were added until the mixture was basic to litmus, and the solid was filtered off. The solution was extracted with 4 × 50 mL of pentane, the pentane layer dried over magnesium sulfate, and the solvent removed by rotary evaporation giving 2.55 g (38%) of a mixture of **9** and **10**. The isomers were separated by preparative VPC (XF-1150 Chromosorb W column), the peak of shorter retention time (33% by thermal conductivity peak area) being shown to be **10** (cis) by ^{13}C NMR, and the longer retention time VPC peak **9** (trans, 67% of the mixture). **9:** ^{1}H NMR (acetone-d_6) δ 1.01 (d, $J = 5$ Hz, 5 H), 1.48 (br s, 4 H), 2.6–3.2 (m, 4 H), 3.4–7.2 (m, 2 H), 5.72 (s, 2 H); mass spectral parent 166.147 00 (−1.2 ppm error) (calcd for C₁₀H₁₈N₂, 166.146 79). **10:** ^{1}H NMR (acetone-d_6) δ 1.10 (d, $J = 7$ Hz, 6 H), 1.2–2.1 (m, 4 H), 2.8–3.8 (m, 6 H), 5.72 (s, 2 H); high-resolution mass spectrum 166.147 00 (−1.2 ppm error).

*trans-*2,5-Dimethyl-1,6-diazabicyclo[4.4.0]decane (**11**). A solution of 250 mg of **9** in 50 mL of pentane was treated with 250 mg of 10%

Pd/C and hydrogenated at 35 psig initial pressure using a Parr hydrogenator. Filtration and concentration gave 98% of **11:** ^{1}H NMR (acetonitrile-d_3) δ 0.95 (d, $J = 6$ Hz, 6 H), 1.2–1.7 (m, 8 H), 2.1–3.2 (m, 6 H); mass spectral parent 168.162 64 (0.0 ppm error) (calcd for C₁₀H₂₀N₂, 168.162 65).

*cis-*2,5-Dimethyl-1,6-diazabicyclo[4.4.0]decane (**12**). Preparation was analogous to that of **11**, using **10** as starting material: ^{1}H NMR (acetonitrile-d_3) δ 1.10 (d, $J = 7$ Hz, 6 H), 1.27–1.8 (m, 8 H), 2.8 (m, 6 H); mass spectral parent 168.162 82 (1.0 ppm error) (calcd for C₁₀H₂₀N₂, 168.162 65).

1,6-Diazabicyclo[4.4.0]dec-8-ene-2,5-dione (15). A mixture of 50 mL of xylene, 2.09 (22.8 mmol) of 1,2,3,6-tetrahydropyridazine, and 2.28 g (22.8 mmol) of succinic anhydride was refluxed over a Dean-Stark trap until water ceased to separate (6 h) and concentrated by rotary evaporation. Recrystallization from benzene gave 1.50 g (40%) of **15:** mp 192–198 °C; ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 2.60 (s, 4 H), 4.19 (s, 4 H), 5.89 (s, 2 H); mass spectral parent 166.074 23 (1.1 ppm error) (calcd for C₈H₁₀N₂O₂, 166.074 41).

1,6-Diazabicyclo[4.4.0]dec-3-ene (13). A mixture of 1.37 g (36 mmol) of lithium aluminum hydride in 200 mL of dry THF was refluxed through a Soxhlet extractor initially containing 2.0 g g (12 mmol) of **15** for 15 h. After cooling to room temperature, 1.5 mL of H₂O, 1.5 mL of 15% NaOH, and 4.5 mL of H₂O were added dropwise. After filtration and removal of solvent, 1.8 g of crude **13** was obtained, mp 47–50 °C, and purified by preparative VPC: NMR (acetonitrile-d_3) δ 1.60 (s, 4 H), 2.2–3.6 (m, 8 H), 5.66 (s, 2 H); mass spectral parent 138.115 70 (5.4 ppm error) (calcd for C₈H₁₄N₂, 138.116 44). NMR at 70 °C: δ 5.65 (t, $J = 1.2$ Hz, 2 H) which collapses when the 3.08 (br s, 4 H₂,₂,₅,₅) signal is saturated, 2.63 (br s, 4 H), 1.58 (m, 4 H).

1,6-Diazabicyclo[4.4.0]dec-3-ene-7,7,10,10-d_4 (13-d_4) was prepared from 1.0 g (6 mmol) of **15** and 0.68 g (18 mmol) of lithium aluminum deuteride by the same method used for **13**, giving 0.5 g (58%) of an oil, which was purified by VPC. ^{1}H NMR at 70 °C (acetonitrile-d_3) completely lacked the δ 2.63 peak for the hydrogens on C₇ and C₁₀, and the fine splitting in the δ 1.58 peak for the hydrogens on C₈ and C₉ was collapsed; mass spectral parent 142.140 88 (0.8 ppm error) (calcd for C₈H₁₀D₄N₂, 142.140 99).

1,6-Diazabicyclo[4.3.0]non-3-ene (14). A mixture of 2.93 g (35 mmol) of 1,2,3,6-tetrahydropyridazine, 5.0 g of potassium carbonate, and 7.07 g (35 mmol) of 1,3-dibromopropane in 100 mL of 95% alcohol was stirred at ambient temperature for 18 h and filtered. The ethanol was mostly removed by rotary evaporation, and the residue was extracted into pentane, dried wih magnesium sulfate, and concentrated to 0.75 g of an oil containing **14**, which was separated by VPC: NMR (acetonitrile-d_3) δ 1.6–2.0 (m, 2 H), 2.69 (t, $J = 6$ Hz, 4 H), 3.12 (s, 4 H), 5.66 (s, 2 H); mass spectral parent 124.100 05 (−0.5 ppm error) (calcd for C₇H₁₂N₂, 124.099 99).

NMR Measurements. The spectrometer and temperature-measuring equipment have been previously described.[2b] All NMR samples were run in acetonitrile-d_3 in sealed tubes, degassed immediately after collection from the final VPC purification. The simulations were performed by visually matching calculated spectra to the experimental ones. Calculations were performed on a Hewlett-Packard 9820A calculator using a multisite chemical exchange program written by W. Ehrhardt (University of Wisconsin) employing the equations of Reeves and Shaw.[16] The program was checked for accuracy by using

the considerably more expensive DNMR 3[17] in selected three- and four-site examples; no difference in the simulated curves was found.

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Low-Temperature Cyclic Voltammetry. 3. Quantitative Comparison of Cyclic Voltammetry and Nuclear Magnetic Resonance as Methods for Conformational Equilibrium and Rate Constant Measurements

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Abstract: Low-temperature CV measurements of equilibrium and rate constants for conformational change in 1,6-diazabicyclo[4.4.0]dec-3-ene, its cis and trans 7,10-dimethyl derivatives, and their saturated analogues, the *N,N'*-dimethyl and diethyl derivatives of 3,4-diazabicyclo[4.4.0]decane, 1-ethyl-2-methylhexahydropyridazine, 1,2-diethylhexahydropyridazine, and 2-methyl-1,2-diazabicyclo[4.4.0]decane, are reported. A comparison is made with NMR conformational results for these compounds.

In previous work,[1] it has been established that several six-membered ring hydrazines show a kinetic resolution of the oxidation peaks for conformations with axial, equatorial alkyl groups (Hae, shown below for 1,2-dimethylhexahydropyridazine, **1**) from those with diequatorial groups (Hee, below)

Hae   Hee

in cyclic voltammetry (CV) experiments. The oxidation of Hae is slow and electrochemically irreversible while that of Hee is more rapid and nearly reversible. Digital simulations of kinetic Scheme I gave good fit to the observed CV curves.[1b,c] In this scheme the electrode merely samples the concentrations of Hee and Hae, and the conformational change takes place in solution, entirely unaffected by the presence of the electrode. The digital simulations give a value for a kinetic parameter $K_{eq} \cdot \sqrt{k_t}$, where $K_{eq} = [Hee]/[Hae]$, and $k_t = k_{ee \to ae} + k_{ae \to ee}$. The values of the kinetic parameters obtained for **2–4** were consistent with ^{13}C NMR derived conformational data,[1b,c]

Scheme I
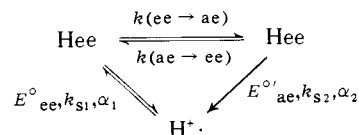
suggesting that Scheme I is a useful picture of what is happening, and that CV can be useful for conformational analysis.

Several factors combined to make our work on **2–4** less than

1   **2**   **3**   **4**
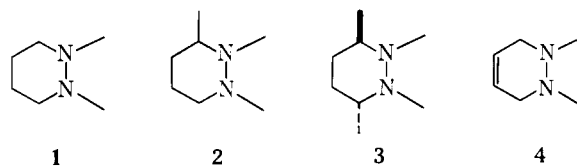
a quantitative comparison of the CV and NMR methods for conformational analysis of these compounds. The low temperatures necessary to observe the second (Hae) oxidation peak required the use of butyronitrile (not suitable for NMR work)