about the structures of the complexes, particularly with phenylglycine methyl ester salts as guests. The naphthalene rings in CPK molecular models of **41** are perpendicular to the best plane of the oxygens. The ring currents of the naphthyl groups provide magnetic probes for the placements of the methyls, the methines, and the ortho protons of the amino ester guests. Likewise, the phenyl group of the phenylglycine ester provides a probe for the placement of the methyls and of the central methylene protons of **41**. The structure of each diastereomeric complex turned out to be approximately what was expected from CPK molecular model examination.[27b]

Hopefully, better binding hosts such as **39** will provide higher chiral recognition, which must derive from a complementary arrangement of steric barriers for one diastereomeric complex and of high steric inhibition of complexation for the other. High binding free energies of hosts for small guests such as $NH_4^+$ are probably a prerequisite for high chiral recognition. The high free-energy cost of the organization required for chiral recognition must be paid for by a high intrinsic binding potential of the host. However, if binding energies become very high, the advantages of very rapid rates of complexation–decomplexation are lost, and the uses to which complexation can be put are limited.

These studies demonstrate that, with the inspiration of biological systems and the help of scale molecular models, organic-to-organic complexes can be designed which, when synthesized, show the anticipated molecular organization. If complexation is a central feature in the operation of biological systems, then hosts which are designed and synthesized by organic chemists could become the theme of much research in the future.

# Conformational Studies of Hexahydropyridazine Derivatives

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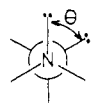
*Received December 13, 1976*

The preference of many compounds with adjacent heteroatoms for adopting conformations in which the lone-pair orbitals on the heteroatoms are nearly perpendicular has been discussed as the "gauche effect".[1] There are two principal factors which have been used to rationalize this preference: repulsion between the lone-pair orbitals[2] and attractive lone-pair–adjacent-bonding-pair interaction.[3] Although the relative importance of these two factors is not yet known, it is clear that there is a significant torsional barrier to rotation about a heteroatom–heteroatom bond and that this barrier, which is not steric in origin, involves the lone-pair electrons. Hydrazines provide attractive systems for quantitative study of the influence of lone-pair–lone-pair dihedral angle ($\theta$ in I) on conformational equilibrium and rate constants. The identical energies of the lone-pair orbitals in the (hypothetical) absence of interaction and the relatively large orbital–orbital overlaps expected because of the relatively short N–N bond length should make the torsional effect larger than in most other cases.[4] For derivatives of 1,2-dimethylhexahydropyridazine (**1**), the well-known

**1** **1ee** **1ae** **1aa**

steric requirements of the six-membered ring will limit the available conformations to chair forms with equatorial and/or axial disposition of the substituents (**1ee**, **1ae**, and **1aa**), isolated from each other by reasonably substantial kinetic barriers.

It may be noted that **1ee** is required to have $\theta$ near 180°, and thus is electronically destabilized by a large lone-pair–lone-pair repulsion and the lack of an adjacent bonding orbital anti to either lone pair. **1ae** and **1aa**, on the other hand, have the electronically preferred gauche lone-pair orientation ($\theta$ near 60°) but are clearly sterically destabilized by the presence of axial substituents on the six-membered rings. Because of the conflicting steric and electronic effects, conformational study of six-ring hydrazine derivatives would be expected to reveal the relative sizes of these effects. We describe here work which has led to the measurement of equilibrium and rate constants for conformational



I

Stephen F. Nelsen was born in Chicago and received his undergraduate training at the University of Michigan, where his interest in organic chemistry was stimulated principally by Martin Stiles. After earning his Ph.D. degree at Harvard University with P. D. Bartlett in 1965, he joined the faculty at the University of Wisconsin, where he is professor of chemistry. His research involves the study of reaction mechanisms, largely in free radical and radical ion reactions, and emphasizes the importance of the influence of conformational geometry upon reaction rate.

(1) S. Wolfe, *Acc. Chem. Res.*, **5**, 102 (1972).

(2) M. J. S. Dewar and W. B. Jennings, *J. Am. Chem. Soc.*, **95**, 1562 (1973).

(3) (a) L. Radom, W. J. Hehre, and J. A. Pople, *J. Am. Chem. Soc.*, **94**, 2371 (1972); (b) N. D. Epiotis, *ibid.*, **95**, 3087 (1973); (c) R. C. Bingham, *ibid.*, **97**, 6743 (1975); (d) T. Brunck and F. Weinhold, *ibid.*, **99**, in press. We thank Professor Weinhold for discussion of this work prior to publication.

(4) Both large overlap and small $\Delta E$ are required to maximize orbital–orbital interactions: R. Hoffmann, *Acc. Chem. Res.*, **4**, 1 (1971).

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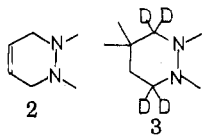
interconversion of a number of six-ring hydrazines.

## $^1$H NMR and Dipole Moment Studies on 1,2-Dimethylhexahydropyridazine

The relatively rapid ring reversal and nitrogen inversion processes occurring in six-ring compounds containing heteroatoms lead to difficulties in interpretation of experiments designed to elucidate conformational equilibria for such compounds.[5] A summary of the conformational work on **1** should well illustrate these difficulties.[6] In 1969 Anderson[7] concluded from $^1$H NMR work that **1** exists entirely in the **1ee** conformation. Although the *N*-methylene hydrogens equilibrate by a process with $\Delta G^{\ddagger}$ of 11.6 kcal/mol, the *N*-methyl signal remained a singlet even at temperatures where both N-inversion and ring reversal were slow on the NMR time scale for the corresponding tetrahydropyridazine, **2**.



**2** **3**

Jones, Katritzky, and co-workers[8] pointed out in 1971 that the dipole moment of **1**, 1.49 D, is higher than would be expected for **1ee** and also that the conformational analysis for **1** was more complex than had been previously considered. Because **1** has two nitrogens which can invert and a ring which can reverse, there are eight symmetry-related conformations. Therefore, the necessary condition for observation of different chemical shifts for the two *N*-methylene hydrogens is slowing of two conformational processes, which they postulated to be the ring reversal and nitrogen inversion requiring methyl groups to pass each other. They also postulated that these "passing" processes, the faster of which would be Anderson's 11.6-kcal/mol barrier, were significantly slower than the ring reversal and nitrogen inversion which do not require methyl passing, and estimated that the barrier for these more rapid nonpassing barriers was about 8 kcal/mol. Consequently, these processes were not slowed down sufficiently at the temperatures Anderson employed to allow observation of more than one *N*-methyl signal.[9] The low-temperature $^1$H NMR of **3** unambiguously showed peaks for both ee and ae conformations, and, from the dipole moments of **1** and **3**, it was calculated that **1** was a 30:34:36 mixture of **1ee**:**1ae**:**1aa**.[8] New higher field NMR data of Anderson showed that the *N*-methyl signal for **1** actually does separate into two signals below −74°, a minor peak (assigned[10] to **1ee**) about one-seventh the area of the major one appearing 0.06 ppm upfield of it, and Jones,

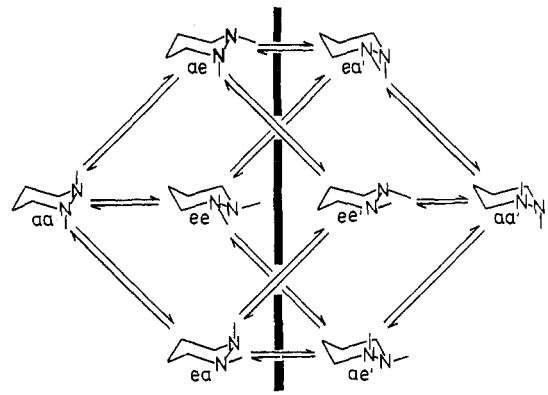



**Figure 1.** Diagram showing conformational interconversion for **1**.

Katritzky, and co-workers[10] revised their estimate to 18:20:62 **1ee**:**1ae**:**1aa** on the basis of these data in 1974. A nonpassing ring reversal barrier of 11 ± 1 kcal/mol, a reasonable value for this process, was consistent with the observed spectra.

## Photoelectron Spectroscopic Detection of Hexahydropyridazine Conformations

In 1973–1975 photoelectron (PE) spectroscopy was applied to the question of hydrazine conformation by Nelsen and Buschek[11] and by Rademacher.[12] They found that the energy separation between the two highest occupied orbitals of hydrazines (principally symmetric and antisymmetric lone-pair combinations) is dependent upon $\theta$, showing a large value of about 2.3 eV near $\theta = 0$ and 180°, and a minimum[13] of about 0.5 eV in the vicinity of $\theta \sim 90°$. Because the time scale of the PE experiment is very short, one observes the superposition of spectra for conformations with different $\theta$ values when these are present, instead of a time-averaged spectrum, as is frequently the case with NMR experiments. For **1**, three PE peaks appeared in the lone-pair region; these were assigned to a pair having a 2.3-eV separation, corresponding to **1ee** ($\theta \sim 180°$), and a pair with about a 1-eV separation, corresponding to **1ae** and/or **1aa** (both of which would have $\theta \sim 60°$, and therefore similar PE peak separations). The lowest energy ionizations for both types of conformations overlap, resulting in the observation of only three lone-pair ionization peaks. The **1ee** peaks were approximately three times as intense as those corresponding to gauche conformations, implying a predominance of **1ee** in the vapor phase. The PE curves cannot, unfortunately, be readily quantitated to give exact percentages of the two classes of conformations, because the cross sections for electron expulsion are probably slightly different for different conformations; the cross sections differ slightly even for the symmetric and antisymmetric lone-pair combination orbitals of a single conformation.[11e] In retrospect, however, no exception to the statement that the pre-

(5) For a good review of conformational work on monoheteroatom six-ring compounds, see J. B. Lambert and S. I. Featherman, *Chem. Rev.*, 611 (1975).

(6) For a good review of hydrazine conformational work through 1973, see Y. Shvo in "The Chemistry of Hydrazo, Azo, and Azoxy Groups", S. Patai, Ed., Wiley, New York, N.Y., 1975, Part 2, pp 1017–1095.

(7) J. E. Anderson, *J. Am. Chem. Soc.*, **91**, 6374 (1969).

(8) (a) R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *Chem. Commun.*, 644 (1971); (b) R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *J. Chem. Soc., Perkin Trans. 2*, 34 (1972).

(9) R. A. Y. Jones, A. R. Katritzky, and R. Scattergood, *Chem. Commun.*, 644 (1971).

(10) R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, *J. Chem. Soc., Perkin Trans. 2*, 406 (1974).

(11) (a) S. F. Nelsen and J. M. Buschek, *J. Am. Chem. Soc.*, **95**, 2011 (1973); (b) S. F. Nelsen, J. M. Buschek, and P. J. Hintz, *ibid.*, **95**, 2013 (1973); (c) S. F. Nelsen and J. M. Buschek, *ibid.*, **96**, 2392 (1974); (d) S. F. Nelsen and J. M. Buschek, *ibid.*, **96**, 6982 (1974); (e) S. F. Nelsen and J. M. Buschek, *ibid.*, **96**, 6987 (1974).

(12) (a) P. Rademacher, *Angew. Chem.*, **85**, 410 (1973); (b) P. Rademacher, *Tetrahedron Lett.*, 83 (1974); (c) P. Rademacher, *Chem. Ber.*, **108**, 1548 (1975); (d) P. Rademacher and H. Koopman, *ibid.*, **108**, 1557 (1975).

(13) S. F. Nelsen, V. E. Peacock, and G. R. Weisman, *J. Am. Chem. Soc.*, **98**, 5269 (1976).

dominant conformation in solution (determined by $^{13}C$ NMR) is also the predominant one in the vapor phase (determined by PE spectroscopy[11,13]) has yet been found. It is therefore clear that changing from the vapor to solution phase does not have a major effect on the **ee**/**ae** equilibrium constant.

### Elucidation of the Conformational Mixture for 1 by $^{13}C$-NMR Spectroscopy

The conformational interconversions for **1** are conveniently considered by reference to Figure 1. The eight conformations of **1** have been placed at the corners of a cube having nitrogen inversions as the sides of two parallel faces (one ring reversal form on each face), with the ring reversals forming the other four edges.[14,15] Diagonally opposite corners of this cube are occupied by mirror image conformations. The skewed projection shown in Figure 1 was chosen because it retains the symmetry properties of the three-dimensional system and also places the higher activation energy equilibria (Jones and Katritzky's methyl passing equilibria) at the center of the diagram, crossing the heavy vertical line. The fact that there are four, and only four, different conformational equilibria (passing and nonpassing, nitrogen inversion and ring reversal) may be verified by examination of this diagram (nitrogen inversions are the diagonal equilibria, and ring reversals the horizontal ones in Figure 1).

The conformational mixture actually present for **1** was elucidated unambiguously by the use of low-temperature $^{13}C$ NMR,[16] which has several advantages over $^{1}H$ NMR for this purpose. The chemical shift range is considerably expanded in $^{13}C$ NMR compared to $^{1}H$ NMR, making the likelihood of accidental overlap less, especially since, in proton-decoupled work, each carbon appears as a singlet. The most important advantage, however, is the well-known upfield shift caused by steric compression for carbons in axially substituted six-membered rings.[17] The chemical shifts alone allow correct assignment of carbons to **ee** and **ae** conformations where both are observed, independent of symmetry considerations. Even when the *N*-methyl singlets for **1** were partially resolved by $^{1}H$ NMR, the positions of the peaks did not allow assignment to the conformations. Although percentages for the conformational mixture of **1**, assigned using dipole moments and $^{1}H$ spectra, were made by a logical train of arguments,[8-10] an incorrect conclusion for the conformational mixture present was consistent with the data; there was no obvious way of telling from these data that serious mistakes had been made somewhere.

The carbon spectra of **1** are further simplified by a loss of information over that contained in the proton spectra, because the carbon spectrum is unaffected when the passing equilibria in Figure 1 (those crossing the central line) become slow; each type of carbon can still equilibrate among all conformational types by means of the nonpassing equilibria, which remain rapid. The carbon spectrum is first affected as the nonpassing ring reversal becomes slow on the NMR time scale, and separate signals are observed for **1ee** and the still rapidly equilibrating **1ae** $\rightleftharpoons$ **1aa** $\rightleftharpoons$ **1ea** mixture. The downfield set of lines may be confidently assigned to **1ee** because of the steric upfield shift effect, and it proved possible to verify the assignment by lowering the temperature still more, until **1ae** is no longer equilibrating rapidly with **1ea**. At this point the observed spectrum consists of a three-line spectrum of diequatorial form, superimposed upon the six-line spectrum of the axial,equatorial conformation.[16] No lines for **1aa** were ever observed at low temperature, nor were chemical shift changes attributable to a significant amount of **1aa** becoming populated at higher temperatures noted.

### ee/ae Equilibrium Constants

Two principal methods were used to extract $K_{eq}$ = [ee]/[ae] values from the NMR spectra. Well below the coalescence temperature for the diequatorial–axial, equatorial interconversion, where resolved lines are observed for the two types of conformations, integration of the peak areas was employed. Well above the coalescence temperature, where only one line is observed for each type of carbon, Eliel's method[18] of weighted averaging of the "frozen" chemical shifts was employed. A significant increase in accuracy is attained by temperature extrapolation of the low-temperature chemical shift data to determine the expected shifts at the high temperatures where Eliel's method was employed. Such temperature extrapolation was first used by Berlin and Jensen,[19] but its use has not been general. It is noticeably more important when smaller $\Delta\delta$ carbons (3–4 ppm) are employed than for larger $\Delta\delta$ ones (ca. 10 ppm).[20] Because each type of carbon yields an independent measurement of the same $K_{eq}$ value, an internal check is provided. A stringent check on the values obtained is provided by calculations of $\Delta S°$ for the equilibrium. The entropy content of **ae** and **ee** isomers should be similar, and the $\Delta S°$ values calculated are, indeed, small.[20] In the intermediate temperature region, where great broadening of the lines is observed, the simulation of the spectrum is sensitive to $K_{eq}$ as well as the rate constants, and $K_{eq}$ may be independently measured by direct simulation.[21] However, in our more recent work, we have simply interpolated $K_{eq}$ from the high- and low-temperature ranges and found that good fit is obtained.

Equilibrium constant data for several six-ring hydrazines, illustrating the remarkable sensitivity of $\Delta G°$ to substitution pattern,[20-22] is presented in Table I. As Anderson showed,[7] tetrahydropyridazine **2** is exclusively ae, presumably because one 1,3-diaxial Me,H interaction present in **1ae** is removed by introduction of the

(14) Mislow[15] has developed elegant group theory methods and notation to aid the analysis of several systems with eight (and higher numbers of) conformations in which the interconversion situation is more complex because of the existence of low-energy pathways to directly interconvert conformations along the diagonals of the cube. The situation is simpler for **1**, where the coupling of nitrogen inversion and ring reversal or two nitrogen inversions which would be necessary for such diagonal interconversions rather clearly lead to prohibitively high activation energy transition states.

(15) (a) D. Gust, P. Finocchiaro, and K. Mislow, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 3445 (1973); (b) D. Gust and K. Mislow, *J. Am. Chem. Soc.*, **95**, 1535 (1973); (c) A. Finocchiaro, D. Gust, and K. Mislow, *ibid.*, **96**, 3198 (1974); (d) K. Mislow, *Acc. Chem. Res.*, **9**, 26 (1976).

(16) S. F. Nelsen and G. R. Weisman, *J. Am. Chem. Soc.*, **96**, 7111 (1974).

(17) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **96**, 1874 (1974), and references therein.

(18) (a) E. L. Eliel, *Chem. Ind. (London)*, 568 (1959); (b) E. L. Eliel and R. J. L. Martin, *J. Am. Chem. Soc.*, **90**, 682, 689 (1968).

(19) A. J. Berlin and F. R. Jensen, *Chem. Ind. (London)*, 998 (1960).

(20) S. F. Nelsen and E. L. Clennan, to be submitted to *J. Am. Chem. Soc.*

(21) S. F. Nelsen and G. R. Weisman, *J. Am. Chem. Soc.*, **98**, 3281 (1976).

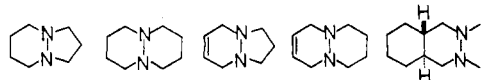
(22) G. R. Weisman and S. F. Nelsen, *J. Am. Chem. Soc.*, **98**, 7007 (1976).

Table I
Equilibrium Data for Some Hexahydropyridazine Derivatives

| Compound | $K_{eq}$,[a] −25 °C | $\Delta G°$, −25 °C, kcal/mol[b] | Temp range, °C | $\Delta H°$, kcal/mol[b] | $\Delta S°$, eu[b] |
|---|---|---|---|---|---|
| **4-6** | Too large to measure | | | | |
| **7** | 4.1 | −0.69 (2) | +72 to −33 | −0.7 (1) | −0.2 (4) |
| **12** | 1.8 | −0.30 (2) | +72 to −24 | −0.3 (1) | +0.2 (3) |
| **1** | 1.6 | −0.22 (2) | +53 to −77 | −0.4 (9) | −0.6 (4) |
| **8**[c] | 1.2 | −0.11 (3) | +48 to −43 | −0.8 (2) | −2.9 (6) |
| **13** | 1.0 | +0.01 (3) | +72 to −40 | −0.4 (2) | −1.6 (7) |
| **14** | 0.19 | +0.82 (2) | +74 to −33 | +0.9 (1) | +0.3 (4) |
| **16** | 0.1 (−82 °C) | | | | |
| **2, 10** | Too small to measure | | | | |
| **11, 15, 17** | | | | | |

[a] $K_{eq} = ee/ae$. [b] Numbers in parentheses are statistical errors in the last place quoted, calculated at the 95% confidence level, and relate only to the scatter of the experimental points in a van't Hoff plot. [c] These differ slightly from the previously published[21] numbers, because temperature extrapolation has been included in the Eliel method points used in these calculations. The data for 1 have not been so corrected because of a solvent problem and are presumably less accurate because of this. 1 and 8 both have a −1.4 eu increment in $\Delta S°$ on symmetry grounds.

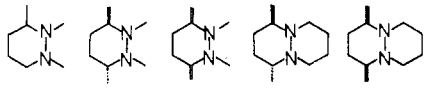
4,5 unsaturation. Linking the *N*-alkyl groups to give a second five- or six-membered ring (as in **4** and **5**) has



4 5 6 7 8

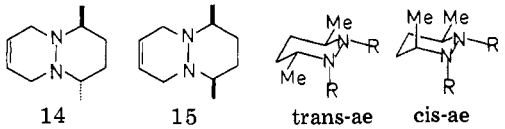
the opposite effect of preferentially stabilizing the ee form. Although the bicyclic tetrahydropyridazine **6** did not contain a detectable amount of the ae form, **7** has an easily measured, though minor, fraction of the ae form. A high-sensitivity search for the ae form of **5** was unsuccessful; if, however, the signal-to-noise ratio had been more favorable, we feel that 0.5% of **5ae** would have been detected[20] (corresponding to $\Delta G° < -2.4$ kcal/mol at −49 °C). This quantity, when combined with the $\Delta G°$ (−25 °C) of −0.7 kcal/mol for **7**, allows estimation of the ae-favoring effect of unsaturation to be >1.7 kcal/mol at −25 °C.

Not surprisingly, the presence of the $\beta,\beta'$-diequatorial substituents in **8**, which are far from the nitrogens, does not affect $K_{eq}$ markedly.[21] Introduction of $\alpha$ substituents is quite another matter, and even the presence of one $\alpha$-methyl, in **9**, results in predominance of ae



9 10 11 12 13

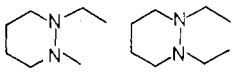
conformations (as shown by PE spectroscopy;[11e] the NMR spectrum was too complex for analysis[22]). Both *trans*- and *cis*-dimethyl substitution in **10** and **11** gave exclusively ae conformations.[21] Pitting *N*-alkyl linking against ring methylation in **12** and **13** resulted in comparable amounts of ee and ae conformations being observed, and similar bis-$\alpha$-methyl substitution on the tetrahydropyridazine **7** resulted in a significantly smaller increment in $\Delta(\Delta G°(-25°C))$, 1.5 kcal/mol for **14** vs. **7**, compared to >2.2 kcal/mol for **12** vs. **5**. We




14 15 trans-ae cis-ae

unfortunately were unable to detect the ee conformation of **15**, so we are not able to estimate how positive $\Delta G°$ actually is for **15**.[20] The greater ae-favoring effect of cis over trans methylation in **12**, **13** and **14**, **15** seems reasonably rationalized by noting that trans-ae has an additional gauche MeN,NR interaction compared to cis-ae ($CH_{3ax}C,NR_{ax}$ groups anti), relative to the ee forms.

Most interestingly, methylation at the exocyclic $\alpha$ carbon of **1** has an ae-favoring effect similar in magnitude to that at the endocyclic $\alpha$ carbon. Thus **16** is

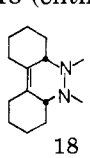


16 17

only about 9% ee at low temperature, and the diethyl compound **17** does not show a detectable amount of the ee conformation. We have estimated the change in $\Delta G°$ upon replacement of one methyl of **1** by an ethyl group to be about 0.9 kcal/mol (near −95°C), and a lower limit of 1.8 kcal/mol was obtained for replacement of both methyls by ethyl groups.[22] Observation of such large effects on $\Delta G°$ by the seemingly trivial replacement of ethyl for methyl requires adjacent nitrogens, as was shown by investigation of the $\alpha$-alkyl piperidine analogue;[22] no effect at all on $\Delta G°$ has been noted in comparing dimethyl- to diethylcyclohexanes.[23]

## Structure Determination

The equilibrium constants in the previous section make it clear that Me(eq)N–NMe(eq) steric interaction is larger than Me(ax)N–NMe(eq) interaction, and also that for $\alpha$-methylated compounds e,e interactions are significantly larger than a,e in six-ring hydrazines. These observations were put in quantitative structural terms by determination of structures by x-ray single-crystal analysis,[24] which showed that for **8** (which is entirely ee in the solid) the MeN–NMe dihedral angle is about 64°, while for **18** (entirely ae in the solid) the



18

MeN–NMe dihedral angle is 72°. The CN–NC internal

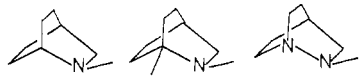
(23) S. S. Berman, V. K. Zakharevko, and A. A. Petrov, *Neftekhimya*, 7, 703 (1969); *Chem. Abstr.* 68, 86737j (1969).
(24) S. F. Nelsen, W. C. Hollinsed and J. C. Calabrese, *J. Am. Chem. Soc.*, 99, 4461 (1977).

Table II
Nitrogen Inversion Barriers for Some Hydrazines and Amines

| Compound | Process | $\Delta G^{\ddagger}$,[a] $T$, °C | $\Delta H^{\ddagger}$,[a] kcal/mol | $\Delta S^{\ddagger}$,[a] eu |
|---|---|---|---|---|
| 1 | ae → aa[b] | 7.56 (4), −100 | 8.4 (5) | +4.6 (26) |
| 2 | ae → aa[b] | 8.17 (4), −103 | 8.8 (2) | +3.9 (19) |
| 10 | ae → aa[b] | 7.85 (5), −100 | 8.1 (3) | +1.5 (18) |
| 19 | | 6.51 (7), −127 | 7.3 (10) | +5.6 (68) |
| 20 | | 6.63 (7), −121 | 7.7 (9) | +6.9 (55) |
| 21 | | 7.86 (6), −113 | 8.7 (5) | +5.4 (25) |
| | ee → ea′[c] | 12.60 (7), +2 | 13.6 (8) | +3.7 (29) |
| 8 | ea′ → ee[c] | 12.71 (7), +2 | 13.6 (8) | +3.3 (29) |

[a] kcal/mol; numbers in parentheses are statistical errors in the last place quoted, propagated at the 95% confidence level, and refer only to scatter of the data in an Eyring plot. [b] "Non-passing" nitrogen inversion. [c] "Passing" nitrogen inversion.

dihedral angles are quite comparable (65 and 67°, respectively), but the difference in CC–NN angles (64 and 48°, respectively) presumably leads to the substantial differences in the size of $\alpha$-methylation effects observed. It is interesting to note the substantially different degrees of flattening at the nitrogens (see $\beta$ in II) in the

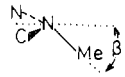


19 20 21

ee hydrazine 8 ($\theta \sim 180°$, large lone-pair–lone-pair interaction), $\beta = 59°$, compared to $\beta = 49°$ and 48° at the two nitrogens of the ae hydrazine 18 ($\theta \sim 74°$, smaller lone-pair–lone-pair interaction), coupled with a significant increase in the N–N bond length for 8 compared to 18 (0.036 Å, nine standard deviations). Both changes are in the direction expected for significant lone-pair-induced electronic destabilization of the ee compound, although steric differences obviously cannot be ignored.[24]

## Rate Constants for Conformational Change

**Nitrogen Inversion Barriers.** Jones, Katritzky, and co-workers[8,9] originally pointed out that there were two different nitrogen inversion barriers for 1, postulating that the higher activation energy "passing" barrier (crossing the heavy line in Figure 1) was raised in energy because of adjacent methyl–methyl interaction in the transition state. They subsequently realized from study of other 1,2-dimethyl-substituted heterocycles[25] that the amount of barrier raising attributable to such a steric interaction is smaller than the observed difference in $\Delta G^{\ddagger}$ values for 1, as is illustrated by the small barrier changes for *N*-methyl inversion in the nonpassing barriers for 1 and **10**[21] and in the bicyclic amine model compounds **19** and **20**[26]



II

(Table II). The second example in each case requires a passing *N*-methyl–*C*-methyl interaction, but $\Delta G^{\ddagger}$ is raised by less than 0.5 kcal/mol in the presence of the flanking methyl group.

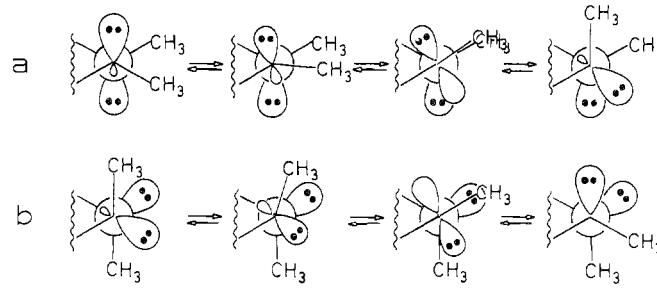


**Figure 2.** Diagram contrasting lone-pair–lone-pair interactions for the high- and low-barrier nitrogen inversion of hexahydropyridazines. (a) The **ee** ⇄ **ae′** conversion (high barrier). (b) The **aa** ⇄ **ea** conversion (low barrier).

The nitrogen inversion barrier for bicyclic hydrazine **21** and the nonpassing N-inversion barrier of 1 are within experimental error of being the same. For **21** the transition state for N inversion must have the lone pair at $N_1$ nearly perpendicular to that of $N_2$, which should be approximately p-hybridized, and for 1 the lone pairs bear a very similar spatial relationship (see Figure 2). Comparison of the barriers for **19** and **21** shows that replacement of the $\alpha$ carbon by a nitrogen, with its lone pair essentially orthogonal to that of the inverting nitrogen at the transition state, increases the inversion barrier by approximately 1.4 kcal/mol in a six-membered ring. Dewar and Jennings[2] observed similar barrier increases upon replacement of N for C in comparing *N*-methyl cyclic amines with those of the *N*-amino compounds; they noted that the lone pairs ought also to be perpendicular in the transition state for these cases. We note that these considerations lead to an estimation of the inversion barrier of *N*-methylpiperidine of under 6.5 kcal/mol; this estimate is rather less than two recent estimations of this barrier[27,28] and is a point of current contention in the literature.[25]

Experimental distinction of the higher energy, passing N-inversion barrier from that of the passing ring-reversal barrier of 1 cannot be achieved by NMR studies because both barriers must be frozen out to affect the spectrum, although the lower of the two is the 11.6-kcal/mol barrier measured by Anderson.[7] We therefore have used the nitrogen inversion barrier for 8 to measure this number. We believe this inversion to be an excellent model for 1, in which ring reversal is precluded by the second six-membered ring, because of the similarity in $K_{eq}$ (Table II). There is about a 5-kcal/mol increase in both $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ over the nonpassing barrier; only about 0.5 kcal/mol of this increase can be attributed to the difference in steric interactions. As shown in Figure 2, there is a large overlap between the lone pairs at the "passing" transition state ($\theta$ formally near 30°). We believe that the >4-kcal/mol electronic destabilization of the transition state for passing nitrogen inversion compared to the nonpassing one is the best experimental measure of the electronic portion of the "gauche effect" for nitrogen lone pairs (one tetrahedral, one planar) yet available.

The nonpassing nitrogen inversion barriers for the *N*-ethyl compounds **16** and **17** were significantly lower than for 1, precluding measure of $\Delta G^{\ddagger}$, because spectra

(25) I. J. Ferguson, A. R. Katritzky, and D. M. Reed, *J. Chem. Soc., Chem. Commun.*, 255 (1975).
(26) S. F. Nelsen and G. R. Weisman, *J. Am. Chem. Soc.*, **98**, 1842 (1976).
(27) H. Kessler and D. Liebfritz, *Tetrahedron Lett.*, 4297 (1970).
(28) F. G. Riddell and H. Labaziewicz, *J. Chem. Soc., Chem. Commun.*, 766 (1975).

with the ae,ea interconversion slow on the NMR time scale were not obtained, although broadening for slowing this process could be observed to start near −120°C.[22] The lower barrier to N inversion seems consistent with a flattening at *N*-ethyl- compared to *N*-methyl-substituted nitrogen which seems to be implied by the large $\Delta(\Delta G^\circ)$ effects observed in comparing **1**, **16**, and **17**, but quantitation of these ideas has not been achieved.

The barriers observed for the bridgehead bicyclo[4.4.0]decyl systems **7** and **12–15** are particularly high, over 14 kcal/mol. The presence of the second ring precludes occupation of aa conformations, collapsing the conformational diagram to an octahedron which lacks two sides,[20] with all processes employing higher activation energy passing barriers. Furthermore, ring reversal must accompany either nitrogen inversion or reversal of the other ring to give stable conformations, as has been discussed for *cis*-decalin by Roberts[29a] and by Grant.[29b] Because broadening for ae,ee and ae,ea interconversion occurs in the same temperature range for these compounds, the experimental spectra turn out to be relatively insensitive to the ratio of rate constants for these two processes, and only a range of acceptable rates (if one is increased, the other must be decreased to maintain fit) is obtained at a given temperature.[20]

**Ring Reversal.** The ring-reversal process in cyclohexane derivatives has been the most studied conformational equilibrium. Cyclohexane itself has $\Delta G^\ddagger$ (−67°) of 10.2 kcal/mol.[30] A large body of evidence[31] has established that attaining the half-chair form is the highest barrier to be surmounted ($\Delta H^\ddagger$ = 10.8 kcal/mol) and that twist-boat forms are intermediates. The elegant cryogenic deposition experiment of Squillacote, Sheridan, Chapman, and Anet[32] has allowed direct measure of $\Delta H^\ddagger$ for conversion of twist-boat cyclohexane to the chair form to be 5.3 kcal/mol, in excellent agreement with calculations which also predict the boat transition states between the twist boat forms to lie 0.1 to 1.8 kcal/mol[30,31] above the twist-boat forms. These results make it clear that attaining the half-chair form is the highest barrier to ring reversal.

Wolf and Campbell[33] pointed out that cis-1,2-disubstituted cyclohexanes can ring-reverse by going to the half-chair form which does not increase the 1,2-substituent interaction, and that considerable destabilization of the eclipsed boat transition state which must be attained to achieve ring reversal can occur before the ring reversal barrier would be increased. They found $\Delta G^\ddagger$ for *cis*-1,2-dicarboethoxycyclohexane-$d_6$ to be 10.7–10.8 kcal/mol, and $^{13}C$ NMR measurement by Dalling, Grant, and Johnson[34] gave $\Delta H^\ddagger$ = 9.5 ± 0.7 kcal/mol, $\Delta S^\ddagger$ = −3.5 ± 3 eu ($\Delta G^\ddagger$(25 °C) = 10.3 kcal/mol) for *cis*-1,2-dimethylcyclohexane.

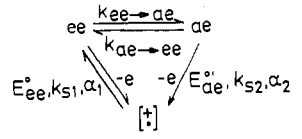
The ring-reversal barriers measured for hexahydropyridazine derivatives are summarized in Table III.

Table III
Ring Reversal Barriers for Some Hexahydropyridazine Derivatives

| Compound | Process | $\Delta G^\ddagger$,[a] *T*, °C | $\Delta H^\ddagger$,[a] kcal/mol | $\Delta S^\ddagger$,[a] eu |
|---|---|---|---|---|
| 1 | ee → [ae,ea][b] | 10.30 (7), −30 | 11.9 (6) | +6.7 (26) |
| | [ae,ea] → ee[b] | 10.10 (7), −30 | 11.6 (6) | +6.6 (26) |
| 16 | ee → [ae,ea][b] | 9.6, −74[c] | | |
| | [ae,ea] → ee[b] | 10.4, −74[c] | | |
| 1 | ae ⇄ ea′[d] | 11.6, −30 | | |
| 11 | ae ⇄ ea′[e] | 12.13 (13), −30 | 12.3 (1) | +0.6 (41) |

[a] kcal/mol; numbers in parentheses are statistical errors in the last place quoted, propagated at the 95% confidence level, and refer only to scatter of the data in an Eyring plot. [b] Nonpassing ring reversal. [c] Measured only at a single temperature by line-shape simulation. [d] $^1H$ NMR measurement by Anderson;[7] see text for assignment as the passing ring reversal. [e] A passing barrier, which might be either ring reversal or nitrogen inversion.[21]

Scheme I




The 10.3-kcal/mol $\Delta G^\ddagger$ barrier for nonpassing ring reversal observed for **1ee**[21] is experimentally the same as for cyclohexane itself, as expected from the above discussion. The single temperature rate estimate obtained for the same process in the methyl,ethyl analogue **16**[22] is also consistent with this number.

Because the minimum passing barrier for **1** is that observed by $^1H$ NMR,[7] the passing ring-reversal barrier is at least 1.3-kcal/mol higher in $\Delta G^\ddagger$ than the nonpassing ring-reversal barrier. It seems unlikely that the passing ring-reversal barrier is greater than this, because the passing nitrogen inversion barrier for **8**, which seems to be a good model for **1**, is rather higher, implying that the $^1H$ NMR experiment measured the ring-reversal barrier.

The higher passing ring-reversal barrier for **1** indicates that the eclipsed boat transition state has replaced the half-chair transition state as the highest barrier between the mirror image chair forms. This eclipsed boat barrier includes both eclipsed *N*-methyls and lone pairs.

## Low-Temperature Cyclic Voltammetry

A new, nonspectroscopic technique employing low temperature cyclic voltammetry (CV) is proving useful for conformational studies of hexahydropyridazine derivatives.[35–38] Like other tetraalkylhydrazines,[13] these compounds give nearly electrochemically reversible (fast electron transfer, long-lived radical cation) CV curves at room temperature, but in many cases a second, irreversible oxidation wave appears at higher voltage than

(29) (a) J. T. Gerig and J. D. Roberts, *J. Am. Chem. Soc.*, 88, 2791 (1966); (b) D. K. Dalling, D. M. Grant, and L. F. Johnson, *ibid.*, 93, 3678 (1971).
(30) F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, 89, 760 (1967).
(31) (a) F. A. L. Anet and R. Ault, in "Dynamic Nuclear Magnetic Resonance Spectroscopy", L. M. Jackson and F. A. Cotton, Ed., Academic Press, New York, N.Y., 1975, p 543. (b) J. E. Anderson, *Fortsch. Chem. Forsch.*, 45, 139 (1974).
(32) M. Squillacote, R. S. Sheridan, O. L. Chapman, and F. A. L. Anet, *J. Am. Chem. Soc.*, 97, 3244 (1975).
(33) S. Wolf and J. R. Campbell, *Chem. Commun.*, 874 (1967).
(34) D. K. Dalling, D. M. Grant, and L. F. Johnson, *J. Am. Chem. Soc.*, 93, 3678 (1971).
(35) S. F. Nelsen, L. Echegoyen, and D. H. Evans, *J. Am. Chem. Soc.*, 97, 3530 (1975).
(36) S. F. Nelsen, L. Echegoyen, E. L. Clennan, D. H. Evans, and D. A. Corrigan, *J. Am. Chem. Soc.*, 99, 1130 (1977).
(37) D. H. Evans and S. F. Nelsen, "Characterization of Solutes in Non-Aqueous Solvents", G. Mamantov, Ed., Plenum Press, New York, N.Y., in press.
(38) S. F. Nelsen, E. L. Clennan, and D. H. Evans, to be submitted to *J. Am. Chem. Soc.*

the room temperature oxidation waves when the CV experiment is performed at low temperature and/or fast scan rate. It was shown empirically, by studying the relative size of the two waves at low-temperature, fast scan rate conditions, that the first wave corresponds to oxidation of the ee hydrazine (nearly electrochemically reversible) and the second wave to oxidation of the ae hydrazine (totally irreversible; the resolution of the two waves is caused by the far slower heterogeneous electron-transfer rate constant for the ae oxidation). No second wave is observed under any conditions for the exclusively ee compounds **4**–**6**, while for the predominantely ae compounds **2**, **9**, **10**, **14**, **15**, and **17**, the first wave greatly decreases in size relative to the second at fast scan rates and low temperatures. Professor Evans wrote programs for simulation of the CV curves which would result if the simplest scheme consistent with the data,[35] Scheme I below, occurs. Here the conformational equilibrium occurs normally in solution, and the electrode simply samples the relative amounts of ee and ae compound diffusing to it. These simulations reproduce the experimental CV curves quite well.[36-38] In cases where the conformational interconversion is slow compared to the CV experiment, and the ratio of the sizes of the two oxidation waves is scan rate independent (a condition currently achievable only when the $\Delta G^{\ddagger}$ separating ae and ee conformation is above about 11 kcal/mol), the simulations give $K_{eq}$. In temperature–scan-rate regions where the relative sizes of the two oxidation peaks are scan rate dependent, the simulations evaluate a mixed kinetic parameter, $K_{eq}(k_{ee\rightarrow ae} + k_{ae\rightarrow ee})^{1/2}$. Since the NMR and CV experiments frequently are sensitive to different conformational equilibria, these techniques are frequently complementary. As an example, because no ee conformation is observable by NMR for **2**, no information on the equilibrium constant is available by NMR studies, but measurement of the kinetic parameter by CV provides an upper limit on acceptable values for $K_{eq}$.[36] For **7**, where the experimental NMR curves are insensitive to the $k_{ee\rightarrow ae}/k_{ae\rightarrow ea}$ rate ratio,[20] the CV experiment, which is only sensitive to the former process, is in principle superior for extraction of the rate constants.[38] Although still in its initial steps of development, low-temperature CV provides an additional powerful method for conformational analysis of these compounds.

## Conclusions

The most quantitative means of obtaining rate and equilibrium constants for conformational change in hexahydropyridazines is $^{13}C$ NMR, although the symmetry of the molecule is very important in determining the complexity of the spectra observed, and thus the ease of analysis. Three of the four possible conformational interconversion rates for **1** have been measured directly by a combination of $^{1}H$ and $^{13}C$ NMR, and the fourth inferred by use of a model compound, **8**. The barrier for nitrogen inversion has been shown to be sensitive to the lone-pair configuration at the noninverting nitrogen, and the electronic and steric components of this difference at least roughly separated. The remarkable sensitivity of both rate and equilibrium constants in these systems to substitution changes has been documented quantitatively, and their origin in both steric and electronic effects has been studied by several methods. Conformations of these hydrazines have been studied by two methods developed in the course of this work, PE spectroscopy (which proves not to be as easily quantitated, but provides rapid, rough estimations of $K_{eq}$ in the vapor phase, even when conformational interconversion is too fast for NMR methods) and low-temperature cyclic voltammetry (a more quantitative solution method which can give information not attainable by NMR). Accurate solid-state structural information was provided by single-crystal x-ray spectroscopy. These studies provide a much more quantitative picture of the factors involved in determining conformational equilibria in these examples of compounds experiencing the "gauche effect" than was previously available.

*The work reported here has been supported by the National Science Foundation, the Petroleum Research Fund, administered by the American Chemical Society, and the Wisconsin Alumni Research Foundation. It is a pleasure to thank my able coworkers who participated in the unraveling of hexahydropyridazine conformations: P. J. Hintz, J. M. Buschek, G. R. Weisman, Dr. L. Echegoyen, E. L. Clennan, V. E. Peacock, and W. C. Hollinsed, as well as Professor D. H. Evans, without whom the electrochemical method would not have been developed.*