Conformation of Cyclohexadecane

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Abstract: The ^{1}H and ^{13}C NMR spectra of cyclohexadecane are temperature dependent below about −100°. Cyclohexadecane-*1*-^{13}C was synthesized and used to obtain clear ^{13}C NMR spectra, which show the presence of three resonances in the ratio of 1:2:1 at −152°. Iterative strain-energy calculations indicate that the [4444] conformation is 1.9 kcal/mol more stable than the [3535] conformation. It is concluded that cyclohexadecane exists predominantly in the [4444] conformation, and that the barrier to pseudorotation is 6.7 ± 0.2 kcal/mol.

Cyclohexadecane belongs to the family of "large-membered" rings in which transannular nonbonded repulsions are absent.[1] An examination of the conformations of this hydrocarbon using ordinary molecular models (e.g., Dreiding models) is not very fruitful, and the molecule appears to be exceedingly floppy, even if nonbonded atoms are kept reasonably far apart. Semiquantitative strain-energy calculations carried out by Dale,[2] however, suggest that the diamond-lattice "square" or [4444] conformation is distinctly lower in energy than any other conformation. The next best conformation is the "rectangular" or [3535] conformation that does not fit the diamond lattice. It has been suggested that the infrared spectrum[3] of cyclohexadecane in the crystalline phase at low temperatures is consistent with the [4444] conformation, but that the spectrum in the liquid phase indicates the presence of more than one conformer, possibly a mixture of the square and rectangular forms.[2,4]

We now report a study of the temperature dependence of the ^{13}C and ^{1}H NMR spectra of cyclohexadecane, as well as quantitative strain-energy calculations on the [4444] and [3535] conformations.

Experimental Section

Synthesis of Cyclohexadecane-*1*-^{13}C. Trimethylsilyl bromide (0.35 ml) was added to a stirred suspension of dry silver cyanide-^{13}C [prepared from silver nitrate solution and sodium cyanide-^{13}C (0.11 g)] in anhydrous ether (2 ml). The solution was stirred for 20 min at room temperature, and then cyclopentadecanone (0.5 g) in ether (2 ml) and a catalytic amount of zinc iodide were added. After 20 hr, the solid (AgBr) was removed by filtration and washed with ether. The combined filtrate was added to an excess of lithium aluminum hydride (0.4 g) in ether (35 ml), and the solution was refluxed for 20 hr under a nitrogen atmosphere. The excess reagent was carefully destroyed by the addition of water, followed by 30% acetic acid (50 ml). The ether was removed by distillation, and neutral products were removed by extraction with pentane. Sodium nitrite (0.4 g) was added to the aqueous phase, and the solution was allowed to stand for 5 hr. The solution was extracted with pentane, the organic phase was washed with sodium carbonate solution and water, and the pentane was removed by evaporation. The crude C-16 ketone was purified by conversion to its crystalline sparingly soluble semicarbazone from which the purified ketone (ca. 75 mg) was regenerated in the usual way. Cyclohexadecanone-*2*-^{13}C (70 mg) was heated with a mixture of diethylene glycol (10 ml) and hydrazine hydrate (0.1 g) at a bath temperature of 200°, and the volatile components were allowed to distill. After cooling, potassium hydroxide (1 pellet) was added, and the mixture was heated under reflux for 6 hr at a bath temperature of 240–250°. Water was added to the cooled reaction product, and the product was extracted with pentane. Evaporation of the pentane left a crystalline residue of cyclohexadecane-*1*-^{13}C which was washed with water and allowed to dry. Model experiments on unlabeled substrates showed that the scheme described above gave a product (mp 59–60.5°; lit.[5] mp 62–63°) which exhibited single lines in the ^{1}H NMR and ^{13}C NMR spectra at room temperature.

NMR Spectra. NMR spectra were obtained on a superconducting solenoid spectrometer operating at 59 kG.[6] The proton spectra were obtained with standard 5-mm sample tubes in a frequency-sweep mode. The ^{13}C spectra are Fourier transforms of accumulated free-induction decays and were obtained with 10-mm tubes with the magnetic field locked on a ^{19}F peak of the solvent.

Theoretical spectra were calculated by means of a computer program as described in an earlier paper.[6]

NMR Results and Discussion

The ^{1}H NMR spectra of cyclohexadecane at various temperatures are given in Figure 1. The spectrum at temperatures above −100° consists of a single line at 1.33 ppm downfield from tetramethylsilane. The resonance line broadens below −100°, and the line width at half-height at −152° is about 50 Hz. Although a substantial part of this broadening is surely due to dipole–dipole relaxation effects, some of the broadening very likely arises from a slowing down of conformational processes. However, resolution of chemical shifts does not occur, even in the high magnetic field of a superconducting solenoid. The examination of the ^{1}H spectrum of a highly deuterated cyclohexadecane that contains CHD rather than CH_2 groups would undoubtedly prove rewarding, as was indeed the case with cyclohexanone at very low temperatures.[7] In the present instance, however, it is possible to obtain important conformational information from the temperature dependence of the ^{13}C NMR spectrum, and thus we have not tried to analyze the ^{1}H spectrum of cyclohexadecane itself as we did not feel that this would lead to unambiguous results, even if spin-lattice relaxation times were measured to determine the broadening contribution due to dipole–dipole relaxation.

The low solubility of cyclohexadecane at temperatures below about −120° made an examination of the natural abundance ^{13}C NMR spectrum rather tedious. The use of supersaturated solutions was a partial answer to this problem, but free-induction decays could in general only be measured for a relatively short time before crystallization occurred, and this limited the signal-to-noise ratio that could be obtained. We therefore synthesized cyclohexadecane with one carbon enriched to 55% with ^{13}C. The synthetic scheme employed is a modification[8] of the Tiffeneau–Demjanov ring expansion reaction.[9] Cyclopentadecanone was allowed to react with trimethylsilyl cyanide-^{13}C to give the trimethylsilyl ether of the cyanohydrin. Reduction with lithium aluminum hydride followed by diazotization gave cyclohexadecanone-*2*-^{13}C. Wolff–Kishner reduction of the ketone then yielded cyclohexadecane-*1*-^{13}C.

Since there are 16 equivalent carbons in cyclohexadecane, and the natural abundance of ^{13}C is 1.1%, the signal-to-noise ratio resulting from the synthetic scheme described above is increased only by a factor of 4. However, there is a 16-fold saving in time, and this is very significant as the pe-

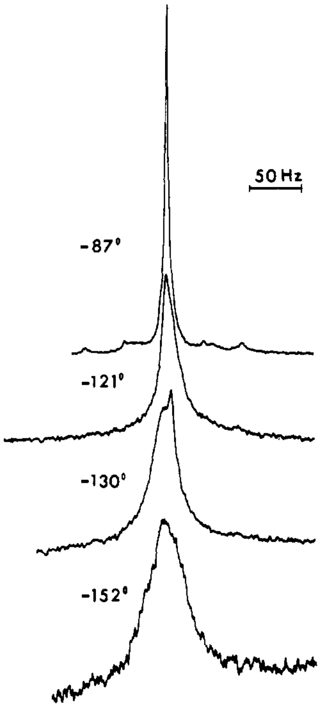

Figure 1. The 251-MHz ^1H NMR spectra of cyclohexadecane (0.1% in a 5:1 mixture of $CHCl_2F$ and $CHClF_2$) at various temperatures.

riod required to obtain spectra with a good signal-to-noise ratio at −152° was about 40 min with the enriched sample. Spectra at intermediate temperatures show broad lines and therefore exhibit smaller signal-to-noise ratios than those at either lower or higher temperatures. The ^{13}C spectra of the enriched sample are shown in Figure 2. It is clear that the spectrum changes from a single sharp line (δ 26.6 ppm) above about −100° to three lines in the intensity ratio of 1:2:1 at chemical shifts of 22.8, 26.8, and 27.0 ppm, respectively, at −152°.

The presence of three resonances in the ratio of 1:2:1 is immediately consistent with the [4444] conformation, whereas the [3535] conformation requires four lines in the ratio of 1:1:1:1 (Figure 3). It is of course conceivable that a coincidence of two of these resonances exists so as to give an apparent 1:2:1 triplet. Chemical-shift arguments presented below, however, support the [4444] conformation.

Carbon-13 chemical shifts in saturated hydrocarbons show regular features that are relatively well understood, at least from an empirical point of view.[10] In the conformations under discussion, two contributions to the ^{13}C NMR shifts should be of importance, namely the γ and the "vicinal-gauche" (Vg) effect. The γ effect results in an upfield shift of about 5 ppm for the terminal carbons in a gauche tetramethylene (or butane) fragment. The Vg effect occurs for the central carbons of the above-mentioned fragment and results also in an upfield shift but is somewhat smaller than the γ effect. A third effect, Vt, occurs for the central carbons in a transoid butane fragment, but its magnitude (ca. 0.8 ppm upfield) is very much smaller than that of either the γ or the Vg effect. It has been found that the γ effect varies considerably in magnitude and depends on the precise structure of the compound examined. Attempts to apply these effects to the observed chemical shifts[11,12] of cyclotetradecane, a compound that almost certainly exists in the diamond-lattice [3434] conformation, show that a good agreement cannot be obtained with a single γ value.[11,12] Furthermore, the chemical shifts in both the C_{14} and C_{16} cycloalkanes are appreciably temperature dependent. In cyclohexadecane, the chemical shift at −93° is 26.6 ppm, whereas the weighted average of the chemical shifts at −152° is 25.6 ppm. It is possible that the tetramethylsilane ^{13}C shift is itself somewhat temperature dependent, and that this accounts for part of the shift described above. A part of the observed shift may be due to the conformational looseness of large rings, and this will be discussed more fully below.

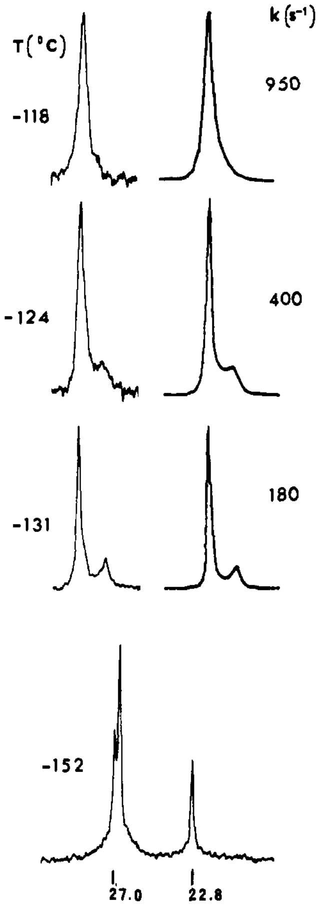

Figure 2. The 63.1-MHz ^{13}C NMR spectra of cyclohexadecane-*1*-^{13}C (0.5% in 5:2 mixture of vinyl chloride and dichlorofluoromethane) at various temperatures, with protons noise decoupled. The scale for the bottom spectrum is in parts per million downfield from tetramethylsilane. The upper spectra have scales ⅜ of that of the bottom spectrum. Calculated spectra are shown on the right.

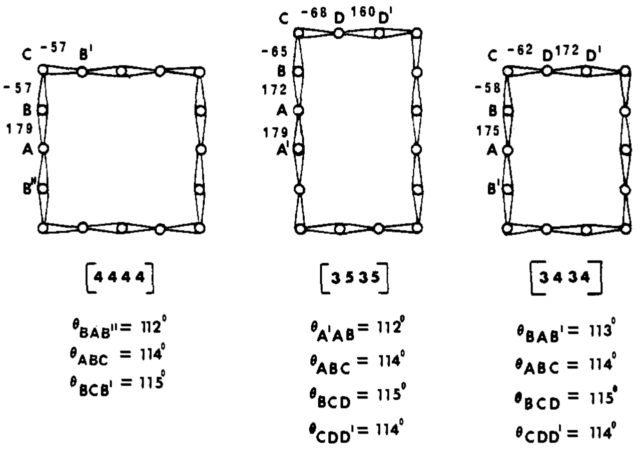

Figure 3. Wedge representations[2] of the [4444](D_{2d}) and [3535](D_2) conformations of cyclohexadecane and of the [3434](C_{2h}) conformation of cyclotetradecane. The ring torsional angles, shown on the drawings, and the internal angles (θ's) are derived from iterative strain-energy calculations. The letters A, B, C, D refer to carbon sites (circles).

Table I. Carbon-13 Chemical Shifts and Effects for $(CH_2)_{14}$ and $(CH_2)_{16}$

Conformational sites[a]	Obsd chemical shifts[b] $(CH_2)_{14}$	Obsd chemical shifts[b] $(CH_2)_{16}$	Chemical shift effects [3434]	Chemical shift effects [4444]	Chemical shift effects [3535]
A	23.3	22.8	$2\gamma + 2Vt$	$2\gamma + 2Vt$	$\gamma + 2Vt$
B	26.2[c]	26.8	$\gamma + Vg + Vt$	$\gamma + Vg + Vt$	$\gamma + Vg + Vt$
C	26.8[c]	27.0	$2Vg$	$2Vg$	$2Vg$
D	21.3		$2\gamma + Vg + Vt$		$2\gamma + Vg + Vt$

[a] As given in Figure 3. [b] In parts per million downfield from Me_4Si. [c] The assignments of the B and C resonances are not certain and could be reversed.

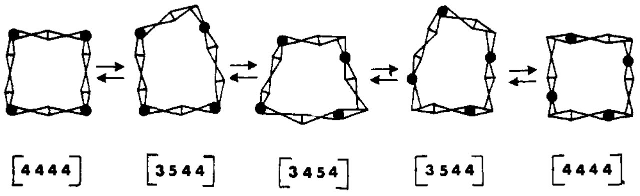

Figure 4. Pseudorotation itinerary for the [4444] conformation of cyclohexadecane. Intermediate, but not transition-state, conformations are shown, and black circles are carbon labels.

Despite the difficulties enumerated above, it is useful to compare the observed chemical shifts in the C_{14} and C_{16} cycloalkanes with the chemical-shift effects present in appropriate conformations, and this is done in Table I. It can be seen that the assumption of a single value for the γ effect implies that the average of the A- and C-site chemical shifts should be equal to the chemical shift of the B site. However, these numbers differ by 1.2 and 1.8 ppm for $(CH_2)_{14}$ and $(CH_2)_{16}$ (for the [4444] conformation), respectively. Nevertheless, the assignments made in Table I show a good agreement as far as the [3434] and [4444] conformations are concerned; i.e., carbons in similar sites have similar chemical shifts, and the maximum discrepancy is 0.6 ppm in a total chemical-shift spread of about 4 ppm. It should be noticed that the shift assignments made to the A sites in the [3434] form and to the B sites in the [4444] form are determined unambiguously by the relative populations of these sites.

The [3535] conformation would be expected to have its A-site chemical shift at a substantially lower field (3–5 ppm) than the corresponding chemical shift in the [3434] conformation because of the different number of γ effects in the two cases. The observed spectrum of $(CH_2)_{16}$ contains no resonances at such low fields. Additionally, the D-site resonance of the [3535] conformation should be at quite a high field and close to that of the resonance of the corresponding site in the [3434] conformation. Again, no such resonance is observed. Thus the [3535] conformation does not fit at all well the observed chemical shifts of cyclohexadecane at low temperatures.

Having established that cyclohexadecane most probably exists in the [4444] conformation, we may now consider the line-shape changes in the ^{13}C NMR spectrum at intermediate temperatures. The change from a 1:2:1 spectrum to a single line may take place in a variety of ways, depending on the precise mechanism of the exchange process. The lowest energy pseudorotation mechanism in the [4444] conformation involves, according to Dale's semiquantitative calculations,[13] the following itinerary: [4444] → [3544] → [3454] → [3544] → [4444] (Figure 4). Although the calculated barrier of 12.6 kcal/mol for this process is undoubtedly much too high, it is probably the best mechanism, as will be discussed further below. The mechanism leads to the following relative exchange probabilities:

$$P_{C\to B} = 1 \qquad P_{B\to A} = 0.5$$

$$P_{B\to C} = 0.5 \quad P_{A\to B} = 1$$

Table II. Relative Strain Energies of Cyclohexadecane Conformations

Conformation	Strain energies,[a] kcal/mol Dale[b]	Strain energies,[a] kcal/mol Present work
[4444]	0	0[c]
[3535]	1.2	1.9 (2.3)[d]
[3445]	3.2	
[3454]	3.4	

[a] Referenced to the [4444] conformation. [b] Reference 2. [c] Actual calculated strain energy is 9.8 kcal/mol. [d] For torsional angles of 174° for the middle bonds of the short sides of the [3535] form.

The populations of A, B, and C are in the ratio of 1:2:1, and the equations given above lead to equal lifetimes in each site and therefore to equal broadenings of the three resonances in the moderately slow exchange region. Unfortunately the near coincidence in the chemical shifts of the B and C sites prevents any simple broadening measurement. The total line shape at intermediate temperatures is consistent with this mechanism (Figure 2), even though the temperature dependence of the chemical shifts has been ignored.

The present analysis leads to a free energy of activation for the overall process described above of 6.7 ± 0.2 kcal/mol at −124°. The experimental line-shape data are not accurate enough to justify calculations of other activation parameters but, since entropy effects are expected to be small, the enthalpy of activation probably has a value close to that of the free energy of activation.

Iterative Strain-Energy Calculations

Dale has investigated the conformations that are available to cyclohexadecane using an "exploratory" semiquantitative method.[2] As stated previously, the diamond-lattice [4444] conformation is of lowest energy, and conformations calculated to be within 5 kcal/mol of this conformation are listed in Table II. Apart from the rectangular [3535] form, the remaining two conformations are relatively high in energy and are unlikely to be serious contenders for the ground-state conformation. As part of a general program to calculate the strain energies of conformations and conformational processes,[14] we have used Boyd's iterative strain-energy method[15] to try to obtain better estimates of the strain energies of the cyclohexadecane conformations. This method is based on empirical valence-force potentials and is similar in this respect to calculations carried out originally by Westheimer[16] and elaborated by Hendrickson,[17] Wiberg,[18] Lifson,[19] Allinger,[20] Schleyer,[21] and others. Because of the large number of atoms in cyclohexadecane and the correspondingly very large number of interactions, the present calculations have been limited to the [4444] and [3535] forms, and nonbonded interactions have been ignored at distances greater than 5 Å. The effect of this truncation, especially on *energy differences*, is expected to be negligible. The calculated energies are given in Table II, and the dihedral and torsional angles are shown in Figure 3.

For the [4444] conformation, the geometry is very close to that calculated by Dale, and to that of the ideal diamond-lattice conformation. The main distortion is that the internal angles at the corners, and next to the corners, are slightly larger than the unstrained value because of repulsive interactions of the gauche 1,4-butane type. Our calculations show that the [3535] form is 1.9 kcal/mol higher in energy than the [4444] form, whereas Dale[13] found a difference of 1.2 kcal/mol. While the geometries of the [4444] form in the two calculations are very similar, our results for the [3535] form give somewhat different ring torsional angles than those found by Dale. The biggest difference, however, is only 12°, and this occurs for the middle bonds (DD′) on the short sides of that conformation. Iterative calculations with the DD′ torsional angles fixed at the value given by Dale give an energy higher by 0.4 kcal/mol than that of our unconstrained [3535] form, and thus the latter conformation does not represent merely a local energy minimum of a [3535] geometry.

In view of the large number of individual iterative calculations required to define with confidence the pseudorotation energy surface in a compound as large as cyclohexadecane, we have decided not to carry out such a study at this stage. The considerations outlined below, however, allow a good estimate of the pseudorotation barrier to be made. The mechanisms envisaged by Dale for the lowest energy pseudorotation paths in cyclohexadecane and cyclotetradecane are very similar both in energy and in the actual conformational changes taking place.[13] The critical step always involves the "migration" of a corner position (C) from one carbon to an adjacent carbon. Three torsional angles change by about 120° in this process and must undergo eclipsing at some stage. One angle changes from ±60 to ±60°, a second from ±60 to 180° (−180° is the same as 180°), and the third torsional angle changes from 180 to ±60° (Figure 4), where the values given are to be considered approximate and may vary 10° or more in particular situations. Nevertheless, it is required that one torsional angle pass through 0°, and two others pass through 120°. Our experience with cyclotetradecane and cyclododecane conformational processes shows,[14] as would be expected intuitively, that the lowest energy path involves a sequential rather than a simultaneous eclipsing of these three torsional angles.

Extensive iterative calculations in the case of cyclotetradecane reveal that the barrier to pseudorotation is 8.0 kcal/mol,[22] much lower than the 12.8 kcal/mol obtained in "exploratory" calculations.[13] However, the general scheme proposed by Dale is strongly supported by the iterative calculations, and the energy discrepancy is not unexpected, especially when high-energy conformations are being considered. We may therefore deduce that pseudorotation in the cyclohexadecane [4444] conformation also should have a barrier of 7–8 kcal/mol, and this value is probably a maximum in view of the greater freedom for accommodating sequential torsional strains in the 16- as compared with the 14-membered ring. The agreement with the experimental barrier obtained from the ^{13}C NMR data is excellent. It is likely that the highest point in the pseudorotation itinerary of cyclohexadecane (Figure 4) occurs between the [4444] and the [3544] conformations, as determined in the exploratory calculations.[13]

Discussion

The ^{13}C NMR spectrum of cyclohexadecane indicates a preponderance of the [4444] conformation at low temperatures, a conclusion which is supported by iterative strain-energy calculations reported in this paper. Previous conclusions that this hydrocarbon is conformationally inhomogeneous rest on interpretations of infrared and thermodynamic data.

The infrared spectrum of cyclohexadecane shows broader bands in solution or in the solid state at room temperature than are observed in the solid below the solid–solid transition temperature of −2°.[3,4] The broadness of the infrared bands at higher temperatures does not agree well with a mixture of only two relatively rigid conformations, as pointed out by Dale.[4] It seems likely that the conformations of large-ring hydrocarbons are relatively nonrigid, and that librations can occur whereby some torsional angles change by an appreciable amount (say 10°) with only a small increase in strain energy. If this is indeed the case, the infrared data on cyclohexadecane would be consistent with a single conformation that is librating in solution (or in the crystalline state above the transition temperature) but is relatively rigid in the low-temperature crystalline phase. The higher temperature infrared data are of course also compatible with two or more librating conformations.

The entropy of fusion data[4] can be explained quite well by a single librating conformation in the liquid state, as such a conformation would have a relatively high entropy compared with that of the rigid conformation in the crystal below the transition temperature.

A number of cyclohexadecane derivatives, including cyclohexadecanone ethylene dithioketal, cyclohexadecane-1,9-dione bis(ethylene ketal), show spectral properties consistent with the [4444] conformation.[23] On the other hand, cyclohexadecanone and 2,2,10,10-tetramethyl-1,3,9,11-tetraoxacyclohexadecane show spectral properties which are inconsistent with the [4444] conformation[23] and, in these cases, it appears probable that the [3535] conformation is more or less populated. Cyclohexadecane may itself exist to a certain extent, perhaps up to 30%, in the [3535] conformation at room temperature especially as this conformation has a higher entropy than does the [4444] conformation, because it is chiral.[2] This would correspond to the [3535] conformation being only about 1 kcal/mol less stable in enthalpy than the [4444] conformation and would imply that the iterative calculations for the strain-energy difference between these two conformations are in error by about 1 kcal/mol, which is certainly not impossible. At low temperatures, the equilibrium would so favor the more stable conformation that it would be the only one observed. At the higher temperatures, the [3535] form is expected to interconvert rapidly with the [3544] form,[13] which is an intermediate in the pseudorotation of the [4444] form, and thus separate NMR signals for the [3535] and [4444] form will not be observed even if the population of the [3535] form becomes significant.

We thus conclude that cyclohexadecane exists in the [4444] conformation to the extent of at least 70% at room temperature, and that the next best conformation is the [3535], which comprises less than 30% of the total. At −150°, the square conformation is populated to at least 90%. Pseudorotation of the [4444] conformation via the [3544] and [3454] conformations as intermediates takes place with a free-energy barrier of 6.7 ± 0.2 kcal/mol and gives rise to exchanges between all hydrogen sites on the one hand and between all carbon sites on the other hand.

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Conformational Analysis. XXX.[1] Conformational Equilibrium of the *N*-Methyl Group in *N*-Methyl-*trans*-decahydroquinoline. The *N*-Methylpiperidine Problem

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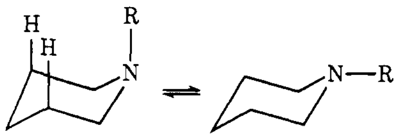
Abstract: The ^{13}C NMR signals of the methyl groups in *N*-methyl-*trans*-decahydroquinoline and some of its analogs with "mobile" *N*-methyl groups are compared with corresponding signals of *N*-methyl groups which are constrained, sterically, to remain in either the equatorial or the axial position. From these data, the conformational equilibrium *N*-methyl (axial) $\rightleftharpoons$ *N*-methyl (equatorial) is evaluated; the conformational energy $-\Delta G°$ is between 1.8 and 2.45 kcal/mol in chloroform and possibly somewhat larger in benzene. The appropriateness of the conformationally biassed (anancomeric) models is discussed. A less reliable value of $-\Delta G° = 1.35–1.77$ kcal/mol in chloroform was determined for the *N*-methylpiperidine equilibrium (Me-a $\rightleftharpoons$ Me-e), for which no suitable model for the Me-axial conformation is available.

The question as to the position of the N-H equilibrium in piperidine (eq 1, R = H) has been discussed extensively in the literature;[2] yet the answer is still controversial with



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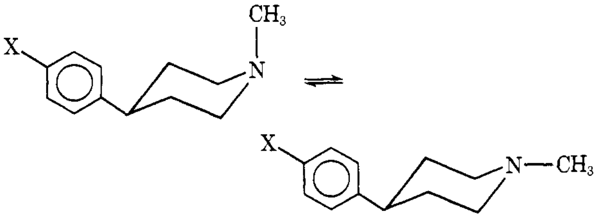
values reported ranging from +0.6 to −0.4 kcal/mol. Much less attention has been given to the *N*-methylpiperidine problem (eq 1, R = Me), even though the values reported, from −0.65 kcal/mol[3] to −1.61 kcal/mol,[4,5] span about the same range as those for the N-H compound (though they do not bracket the magic value of zero). Yet the widespread occurrence of *N*-methylpiperidines and their polycyclic homologs makes it very desirable to know whether 25 or 5% of their molecules exist in the conformation with axial *N*-methyl.

The most extensive studies of equilibrium 1 have involved studies of dipole moments as shown in (2).[3,6] In the original work,[6a] X was chlorine; later supporting experiments with X = NO_2 were reported.[6b] Since evaluation of the equilibrium shown in (2) from dipole moments depends on accurate calculation of the moments of the two conformers shown, which, in turn, depends on an accurate knowledge of the molecular geometry, later studies[3] included an optimization



(2)

of molecular geometry by molecular mechanical calculation; however, the refinement of the data produced thereby was relatively minor. Other studies of the equilibrium (eq 1) have involved infrared absorption intensity measurements of Bohlmann bands,[4] evaluation of the ratio of the protonated species formed when *N*-*cis*-3,5-trimethylpiperidine [a system similar to that in (1) but with ring reversal prevented by the methyl substituents] is quenched into trifluoroacetic acid,[2b] and an evaluation of the chemical-shift difference of the axial and equatorial protons at C-2,6 in variously substituted *N*-methylpiperidines.[2c] These studies have been subjected to various criticisms: the infrared study[4] on grounds that the *N*-isopropyl homolog, used as a standard for the intensity measurements of the Bohlmann bands, did not, itself, appear to be conformationally homogeneous (equatorial);[6b] the quenching study on grounds that the reaction may have been diffusion controlled, and partial equilibration of the salts may have occurred during