

Conformational Studies in the Cyclohexane Series. 1. Experimental and Computational Investigation of Methyl, Ethyl, Isopropyl, and *tert*-Butylcyclohexanes

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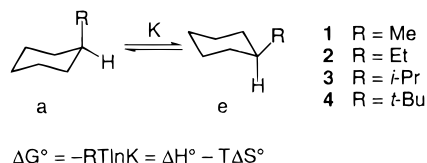
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The conformational enthalpy (ΔH°), entropy (ΔS°), and free energy ($-\Delta G^\circ$) of methyl- (**1**), ethyl- (**2**), and isopropylcyclohexane (**3**) have been reinvestigated both experimentally and computationally. A novel experimental approach to evaluation of highly biased conformational equilibria is described that obviates the need to measure large axial/equatorial isomer ratios directly in order to determine the equilibrium constant: the natural abundance ^{13}C signal for the C(2,6) resonance in the equatorial isomer of an alkylcyclohexane may be used as an internal reference, and the ratio of this band area to that of an enriched ^{13}C nucleus in the axial isomer gives K following correction for statistical differences and the differing ^{13}C -content of the signals being monitored. The experimental conformational enthalpies (ΔH°), determined at 157 K in independent studies at two laboratories, were found to be (kcal/mol) 1.76 ± 0.10 (Me), 1.54 ± 0.12 (Et), and 1.40 ± 0.15 (*i*-Pr); the corresponding conformational entropies (ΔS° , eu) were 0.2 ± 0.2 (Me), 1.3 ± 0.8 (Et), and 3.5 ± 0.9 (*i*-Pr). Computational studies at the QCISD level gave satisfactory agreement with the experimental results, but B3LYP gave energy differences that were too large, whereas MP2 gave differences that were too small. The computed structural data indicates that an axial alkyl substituent leads to local flattening of the cyclohexane ring but there was no evidence of a 1,3-synaxial interaction with the axial hydrogens at C(3,5).

Nearly a half-century has passed since Barton's seminal paper relating cyclohexane conformation to the physical and chemical properties of cyclohexanoid systems.² Over the ensuing years the conformational behavior of a large number of monosubstituted cyclohexanes has been investigated, the area has been extensively reviewed,^{3–5} and conformational energies, $-\Delta G^\circ$ (or "A values"),⁶ as well as conformational enthalpies (ΔH°) and entropies (ΔS°), have been determined for a variety of substituents.^{7,8} In light of the rapid development of ab initio computational methods, it was of interest to determine to what extent modern molecular orbital (MO) theory might be used to accurately describe the conformational behavior of monosubstituted cyclohexanes.⁹ Herein we report the results of a computational inves-

tigation of conformational equilibria in methyl- (**1**), ethyl- (**2**), isopropyl- (**3**), and *tert*-butylcyclohexane (**4**) at various levels of theory.



At the inception of this study it was recognized that methylcyclohexane (**1**) is a key compound in the conformational analysis of cyclohexane derivatives: it is the model against which other substituted-cyclohexanes are compared,⁴ and it has been used in the so-called "counterpoise" method,¹⁰ employing *cis*-1-methyl-4-substituted cyclohexanes, to provide information on the conformational preference of other groups.^{4,5,7,8} To the extent that the methyl group is a benchmark substituent in the conformational analysis of substituted cyclohexanes, the ability to quantitatively account for the equatorial preference of methylcyclohexane (**1**) is the sine qua non of a computational approach to understanding conformational equilibria in alkyl-substituted cyclohexanes.

The conformational equilibrium of methylcyclohexane (**1a** \rightleftharpoons **1e**) may be observed directly by low-temperature ^{13}C NMR, and several research groups have used this approach to determine the conformational energy of the

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(2) Barton, D. H. R. *Experientia* **1950**, *6*, 316.

(3) Eliel, E. L.; Allinger, N. L.; Angyal, S. J. *Conformational Analysis*; Wiley: New York, 1965.

(4) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 665–834 and references therein.

(5) Juaristi, E. *Conformational Behavior of Six-Membered Rings*; VCH Publishers: New York, 1995.

(6) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562.

(7) (a) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199. (b) Jensen, F. R.; Bushweller, C. H. *Adv. Alicycl. Chem.* **1971**, *3*, 139.

(8) Bushweller, C. H. In *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH Publishers: New York, 1995; pp 25–58.

(9) (a) Previous ab initio studies of monosubstituted cyclohexanes have been reviewed and the difficulties attending such calculations have been discussed; see: Cremer, D.; Szabo, K. J. In *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH Publishers: New York, 1995; pp 59–135. (b) Salzner, U.; Schleyer, P. v. R. *J. Org. Chem.* **1994**, *59*, 2138 and references therein.

(10) (a) Eliel, E. L.; Kandasamy, D. *J. Org. Chem.* **1976**, *44*, 3899.

(b) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959 and references therein.

methyl group.^{11–13} The currently accepted “best value” for the conformational energy of methyl in cyclohexane ($-\Delta G^\circ = 1.74$ kcal/mol)^{4,8} was determined by Booth and Everett from a ¹³C NMR study of the conformational equilibrium of **1** in CFC1₃–CDCl₃ (9:1 by volume) over a temperature range of 149–172 K using material enriched to 91 atom % ¹³C at the methyl carbon.¹¹ These authors reported a conformational enthalpy (ΔH°) of -1.75 ± 0.05 kcal/mol and a conformational entropy (ΔS°) of -0.03 ± 0.25 eu for the methyl group in **1**.¹¹ However, a reexamination of these data led us to question the accuracy of the derived values. Consequently, we have reinvestigated the conformational behavior of methyl- (**1**), ethyl- (**2**), and isopropylcyclohexane (**3**) in conjunction with the computational study.

Results and Discussion

Experimental Studies. The determination of the conformational energy difference between the axial and equatorial isomers of methylcyclohexane (**1**) by Booth and Everett involved measurement of the ratio of the intensities of the enriched ¹³CH₃ resonances in the two isomers (**1a** and **1e**).¹¹ The conformational equilibrium constants (*K*) reported in this study ranged from 426.7 at 149 K to 164.2 at 172 K.¹⁴ In an analogous analysis of the conformational equilibrium of isopropylcyclohexane (**3**), Booth and Everett reported that the equatorial/axial ratio for **3** was 723 at 149 K and 323 at 175 K.¹⁴ Clearly, even under ideal conditions, the accurate determination of an isomer ratio greater than ~100 is an extraordinarily difficult proposition, and it is possible that significant errors resulted from the measurement of these large ratios. Indeed, it has been argued that precise and accurate measurement of sizable equilibrium constants by integration of NMR peak areas is a futile exercise due to the very large error inherent in the determination of such a large ratio;¹⁵ better results are obtained when the ratio of the signals to be examined are in the range of 0.1–10.

(11) Booth, H.; Everett, J. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 255.

(12) (a) The axial conformer of methylcyclohexane (**1a**) was detected at -110 °C in the ¹³C NMR of a neat sample in an elegantly simple experiment described by Anet and co-workers. This work, which represents the first direct determination of *K* for the axial–equatorial equilibrium of **1**, provided a conformational free energy ($-\Delta G^\circ$) of 1.6 kcal/mol. See: Anet, F. A. L.; Bradley, C. H.; Buchanan, G. W. *J. Am. Chem. Soc.* **1971**, *93*, 258. (b) A minimum value of 1.8 kcal/mol for the conformational free energy of a methyl group was reported by Subbotin and Sergeev from a low-temperature NMR study of **1**; see: Subbotin, O. A.; Sergeev, N. M. *J. Chem. Soc., Chem. Commun.* **1976**, 141.

(13) Eliel and Wilen (ref 4, p 702) note that the energy difference between *cis*- and *trans*-1,3-dimethylcyclohexane should be close to that of the conformational energy of a methyl group. The experimental energy difference for the former pair is 1.7 ± 0.6 kcal/mol in the liquid phase and 1.9 ± 0.6 kcal/mol in the gas phase (Osborne, N. S.; Giddings, D. C. *J. Res. Natl. Bur. Stand.* **1947**, *39*, 453). It is well recognized that the energy difference between conformational isomers is often phase dependent (cf. ref 4, pp 600 and 710). The origin of the solvent effect on conformational energy differences has been interpreted in terms of the von Auwers–Skita rule which states that the isomer of higher enthalpy content has the smaller molecular volume; see: Allinger, N. L. *J. Am. Chem. Soc.* **1957**, *79*, 3443. Since the isomer of smaller molecular volume will have the higher heat of vaporization, there is no a priori reason to expect conformational energies determined in solution to be identical in magnitude to those observed in the vapor phase.

(14) Equilibrium constants (equatorial/axial) reported in ref 11, p 259, for methylcyclohexane (**1**) and isopropylcyclohexane (**3**) are as follows [K (temperature, absolute)]: 1 K = 426.7 (149), 222.5 (160), 183.0 (167), 164.2 (172); 3 K = 723 (149), 617 (155), 629 (162), 561 (169), 323 (175).

(15) Sergeev, N. M. *Org. Magn. Reson.* **1978**, *11*, 127.

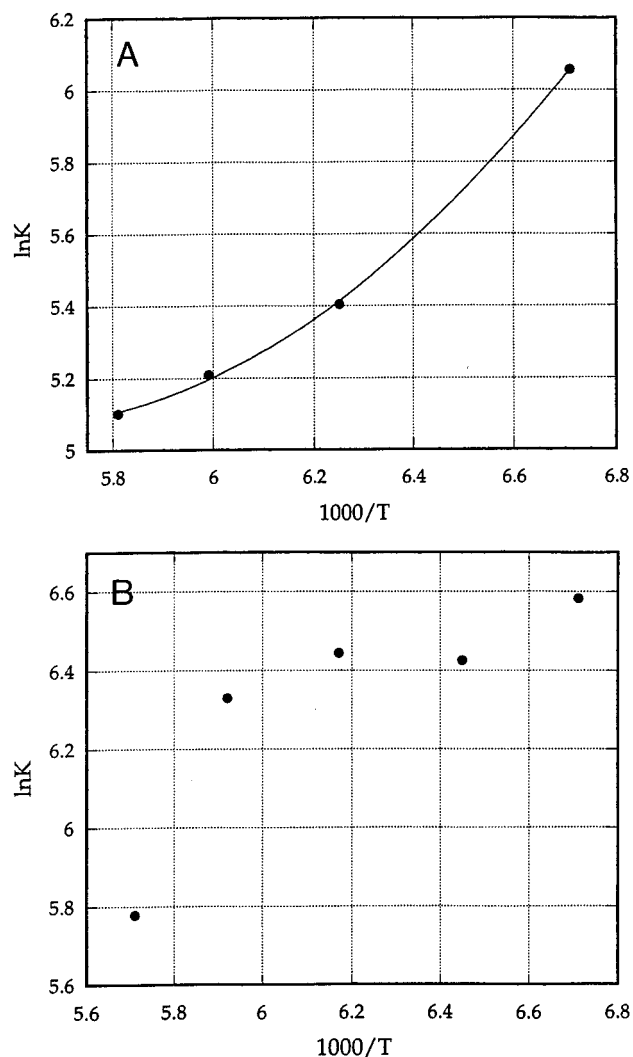


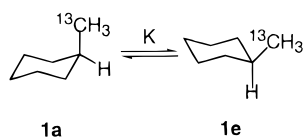
Figure 1. van't Hoff plots of the equilibrium data for (a) methylcyclohexane (**1**) and (b) isopropylcyclohexane (**3**) as reported by Booth and Everett (ref 11).

A van't Hoff plot, $\ln K$ vs T^{-1} , of the equilibrium data¹⁴ reported by Booth and Everett¹¹ for methylcyclohexane (**1**) is shown in Figure 1a: it represents a curve rather than a linear relationship. Nonetheless, a “best” line through the data leads to $\Delta H^\circ = -2.1$ kcal/mol, and it is difficult to see how the reported value ($\Delta H^\circ = -1.75 \pm 0.05$ kcal/mol)¹¹ could be derived from these data. The corresponding plot for the isopropylcyclohexane (**3**) data of Booth and Everett¹⁴ is shown in Figure 1b; here again, it is not clear how the reported conformational enthalpy ($\Delta H^\circ = -1.35 \pm 0.49$ kcal/mol)¹¹ could be determined from this nonlinear plot. In light of the uncertainty in the accuracy of the reported conformational energies of the methyl, ethyl,¹⁶ and isopropyl groups, we have reexamined the conformational behavior of the alkylcyclohexanes in CBrF₃–CD₂Cl₂ (5:1 by volume) solvent by low-temperature ¹³C NMR.

The approach used in this report to evaluate the highly biased equilibria of alkyl-substituted cyclohexanes, which appears not to have been used in any prior study of a

(16) The conformational enthalpy and entropy of the ethyl group in ethylcyclohexane (**2**) reported in ref 11 ($\Delta H^\circ = -1.60 \pm 0.06$ kcal/mol, $\Delta S^\circ = 0.64 \pm 0.35$ eu) were determined by the counterpoise technique using *cis*-1-ethyl-4-methylcyclohexane.

conformational equilibrium, is best appreciated by reference to the conformational equilibrium for $^{13}\text{C}_3$ -methylcyclohexane (99 atom % ^{13}C) illustrated below. Determination of the equilibrium constant for this process by low-temperature ^{13}C NMR spectroscopy requires evaluation of the area ratio [$^{13}\text{C}_3$ -**1e**/ $^{13}\text{C}_3$ -**1a**]. Fortunately, it is not necessary to measure this very large equatorial/axial ratio directly in order to obtain K for the equilibrium.



The ^{13}C resonance for the C(2,6) carbons of the equatorial isomer (**1e**), at δ 36.1 in CBrF_3 - CD_2Cl_2 (5:1 by volume), is well separated from other resonances and may serve as an internal reference. At a temperature low enough to allow observation of the conformational isomers by NMR, the intensity of the small signal for the ^{13}C -enriched axial methyl in **1a** at δ 17.63 is comparable in magnitude to the intensity of the natural abundance (i.e., 1.11 atom % ^{13}C) signal for the C(2,6) resonance of the equatorial conformer (**1e**). In the natural abundance ^{13}C NMR spectrum of methylcyclohexane, the relative areas of the CH_3 and C(2,6) resonances are in the statistical ratio of 1:2 provided that there is no differential enhancement due to differences in relaxation times and/or the nuclear Overhauser effect.¹⁷ In view of the possibility of differential enhancement of the relevant signals, the relative areas of the methyl and C(2,6) carbons in natural abundance methylcyclohexane were measured over a range of temperatures using the acquisition parameters employed in the conformational study described below: the intensity ratio was found to be temperature independent and in the statistical ratio of 0.5 within the experimental uncertainty.

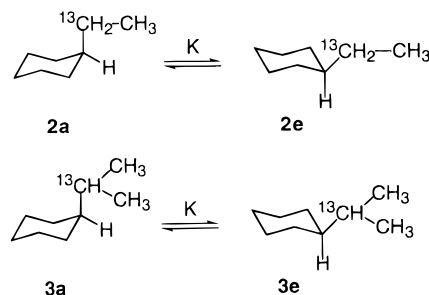
Given these preliminaries, the equilibrium constant for the **1a** \rightleftharpoons **1e** equilibrium is easily evaluated. Thus, one need simply measure the area of the C(2,6) resonance in **1e** relative to the area of the enriched $^{13}\text{C}_3$ nucleus in **1a** [$K' = (\text{C}(2,6)\text{-1e}/^{13}\text{C}_3\text{-1a})$] and make the appropriate corrections to account for the both statistical difference (0.5) and the differing ^{13}C -content of the carbons being monitored (i.e., 99%/1.11% = 89.2). In this way, the equilibrium constant for the **1a** \rightleftharpoons **1e** conformational equilibrium is given by eq 1.

$$K = K'(0.5 \times 89.2) = 44.6K' \quad (1)$$

In short, a highly one-sided equilibrium ($K \approx 200$ to 500) may be characterized by measurement of a ratio on the order of $K' \approx 4$ –10. An entirely analogous approach allows determination of K for the conformational equilibrium of ^{13}C -enriched (99 atom % ^{13}C) samples of **2** and **3**.

The relevant ^{13}C area ratios were obtained by fitting each signal to a Lorentzian line shape and allowing the center of the band, the band height, and the width at half-height to be adjusted to give a best fit; the area of the Lorentzian was derived from these parameters via

(17) (a) Slichter, C. P. *Principles of Magnetic Resonance*, 3rd ed.; Springer-Verlag: Berlin, 1992; pp 254–64. (b) Harris, R. K. *Nuclear Magnetic Resonance Spectroscopy*; Wiley: New York, 1986; pp 108–111.



an analytical expression.¹⁸ In some cases, the bands were not strictly Lorentzian due to slight asymmetry, and in these instances the band areas were corrected as described in the Experimental Section. The area ratios (K') obtained in this way from the low-temperature ^{13}C NMR spectra of **1–3** in CBrF_3 - CD_2Cl_2 (5:1 by volume) solution are small and relatively easy to measure. The equilibrium constants, K , derived from these experiments (eq 1) are reported in Table 1. It should be noted that experimental data were obtained both at Holy Cross, using a 300 MHz spectrometer, and at Yale, using a 500 MHz spectrometer. Studies using different NMR spectrometers at different laboratories should minimize systematic error in the measurements. The results obtained at the two sites are in good agreement (Table 1), and this suggests that the error in the relative band areas is less than 5%.

A major contributor to errors in measurement of the temperature dependence of equilibrium constants via low-temperature NMR is the temperature measurement itself.^{19,20} The commonly used methanol thermometer²¹ does not cover the full range of temperatures used in the current study, and since it involves two measurements, one of the sample tube containing methanol and the other of the experimental sample, there is no guarantee that the temperature of the NMR probe did not change between the two measurements. For this reason, we used neat 2-chlorobutane, contained in a capillary, as an internal thermometer. It has been found that the ^{13}C chemical shifts of 2-chlorobutane are temperature sensitive,²² and the variation in chemical shift of C(3) relative to C(4) with temperature [$\Delta\delta = \delta\text{C}(3) - \delta\text{C}(4)$] has been used as a thermometer.²³ The use of neat 2-chlorobutane to monitor temperature has the advantage that it is an internal thermometer and responds to the temperature present during the measurement of interest. The 2-chlorobutane thermometer has been calibrated by Kates,²⁴ and a fit to his data from -51 to -127 $^\circ\text{C}$, shown in Figure 2, is linear ($r = 0.999$). The temperature is given by eq 2, where $\Delta\delta = \delta\text{C}(3) - \delta\text{C}(4)$. For the range of temperatures of interest, there was good agreement between the 2-chlorobutane and methanol thermometers. Although the absolute error of the former thermometer may be 1 – 2 $^\circ$, it seems reasonable to believe that the relative error over a small temperature range would be

(18) NMR bands should have a Lorentzian line shape. The area of a Lorentzian is given by (height $\times \pi$)/ Γ , where Γ is 2/width at half-height.

(19) Binsch, G. *Top. Stereochem.* **1968**, *3*, 97.

(20) Ammann, C.; Meier, P.; Merbach, A. E. *J. Magn. Reson.* **1982**, *46*, 319.

(21) Van Geet, A. L. *Anal. Chem.* **1970**, *42*, 679.

(22) Schneider, H.-J.; Freitag, W. *J. Am. Chem. Soc.* **1976**, *98*, 478.

(23) Siehl, H.-U.; Fuss, M.; Gauss, J. *J. Am. Chem. Soc.* **1995**, *117*, 5983.

(24) Kates, M. R. Ph.D. Dissertation, Yale University, New Haven, CT, 1978.

Table 1. Experimental Equilibrium Data for Alkylcyclohexanes (Axial \rightarrow Equatorial)^a

Yale data				Holy Cross data			
$\Delta\delta$ (ppm)	T (K)	K'	K	$\Delta\delta$ (ppm)	T (K)	K'	K
Methylcyclohexane (1)							
21.711	165.7	4.96	221	21.716	166.3	5.44	243
21.658	159.9	6.61	295	21.667	160.9	6.36	284
21.604	153.0	8.16	364	21.600	153.4	8.99	401
21.560	149.0	9.05	404				
21.557	148.6	9.78	436				
Ethylcyclohexane (2)							
21.677	162.0	5.29	236	21.689	163.3	5.24	234
21.661	160.2	5.32	237	21.653	159.3	5.96	266
21.588	152.1	6.81	304	21.612	154.7	6.93	309
21.541	146.9	8.16	364	21.566	149.6	8.02	358
Isopropylcyclohexane (3)							
21.695	164.0	9.73	434	21.700	164.5	9.56	426
21.688	163.2	9.58	427	21.652	159.2	11.41	509
21.649	158.9	11.81	527				
21.648	158.7	10.73	479				
21.595	152.9	11.77	525				
21.591	152.4	13.96	623				

^a $\delta\Delta = \delta C(3) - \delta C(4)$ for the neat 2-chlorobutane thermometer (eq 2); K' is the observed ratio of band areas [viz., intensity of the C(2,6) resonance at natural abundance for the equatorial conformer/intensity of the ¹³C-labeled resonance of the axial conformer]; $K = 44.6K'$ (eq 1, see text).

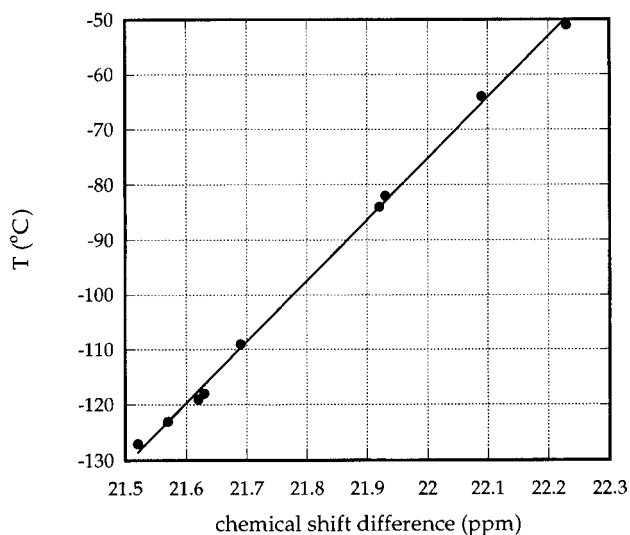


Figure 2. Calibration of the 2-chlorobutane thermometer using the data of ref 24; $\Delta\delta = \delta C(3) - \delta C(4)$.

on the order of 0.5°.

$$T(^{\circ}\text{C}) = 111.07\Delta\delta - 2518.8 \quad (2)$$

A typical ¹³C NMR spectrum of methylcyclohexane (**1**) in CBrF₃-CD₂Cl₂ (5:1 by volume) at -120 °C is shown in Figure 3. The signals for the 2-chlorobutane thermometer are well separated from the relevant resonances of **1**, and equilibrium constants at temperatures from -107.5 to -124.6 °C were easily extracted from measurement of the areas of C(2,6)-**1e** and ¹³CH₃-**1a** using eq 1. The data are summarized in Table 1. It would be desirable to carry out the measurement of K over a wider range of temperatures. However, the methyl signal begins to broaden at higher temperatures, while the melting point of the solvents, the decreased solubility of **1**, and slow equilibration times restrict the use of lower temperatures.

Be that as it may, a van't Hoff plot of the equilibrium data, shown in Figure 4, demonstrates that the Yale and Holy Cross results are in good agreement. The slope of

the plot is $-\Delta H^{\circ}/R$, where ΔH° is the conformational enthalpy difference between the axial and equatorial conformers and the intercept is $\Delta S^{\circ}/R$, where ΔS° is the conformational entropy difference. The slope of the plot leads to $\Delta H^{\circ} = -1.74 \pm 0.06$ kcal/mol, and the intercept gives $\Delta S^{\circ} = 0.4 \pm 0.4$ eu.²⁵ The calculations described below suggest that the entropy difference should be 0.2 eu. Since the calculated entropy difference depends only on computation of geometry (i.e., moments of inertia) and vibrational frequencies, it is usually more accurately determined by calculation than are energy differences, and this accuracy often exceeds that of an experimental determination of ΔS° due to uncertainty in the measurement of temperature.¹⁹ If the calculated conformational entropy is included as a constraint in the van't Hoff plot, the slope then corresponds to an enthalpy difference of -1.78 kcal/mol. It seems reasonable to choose the average of these values, $\Delta H^{\circ} = -1.76$ kcal/mol, as the conformational enthalpy of a methyl group, and we estimate an uncertainty of 0.10 kcal/mol.

The conformational equilibrium of ethylcyclohexane (**2a** \rightleftharpoons **2e**) was studied in the same fashion as for the methyl compound. The data are summarized in Table 1: a van't Hoff plot leads to $\Delta H^{\circ} = -1.42 \pm 0.04$ kcal/mol and the intercept corresponds to $\Delta S^{\circ} = 2.1 \pm 0.2$ eu.²⁵ The calculated entropy difference (vide infra) was 0.5 eu, and if this is included as a constraint to the van't Hoff plot the slope then gives $\Delta H^{\circ} = -1.66$ kcal/mol. Again, the true enthalpy difference is most likely bracketed by these values, and it seems appropriate to take the average, giving $\Delta H^{\circ} = -1.54$ kcal/mol as the conformational enthalpy of an ethyl group in cyclohexane, with an estimated uncertainty of 0.12 kcal/mol.

Isopropylcyclohexane (**3**) was studied in the same way, giving the data presented in Table 1. This compound presented an additional experimental difficulty in that one of its NMR bands overlapped a 2-chlorobutane resonance at lower temperatures, thus limiting the temperature range that could be used. A van't Hoff plot

(25) The uncertainties in the slope and intercept were estimated using the Marquardt algorithm and correspond to one standard deviation: Marquardt, D. W. *J. Soc. Indust. Appl. Math.* **1963**, *11*, 431.

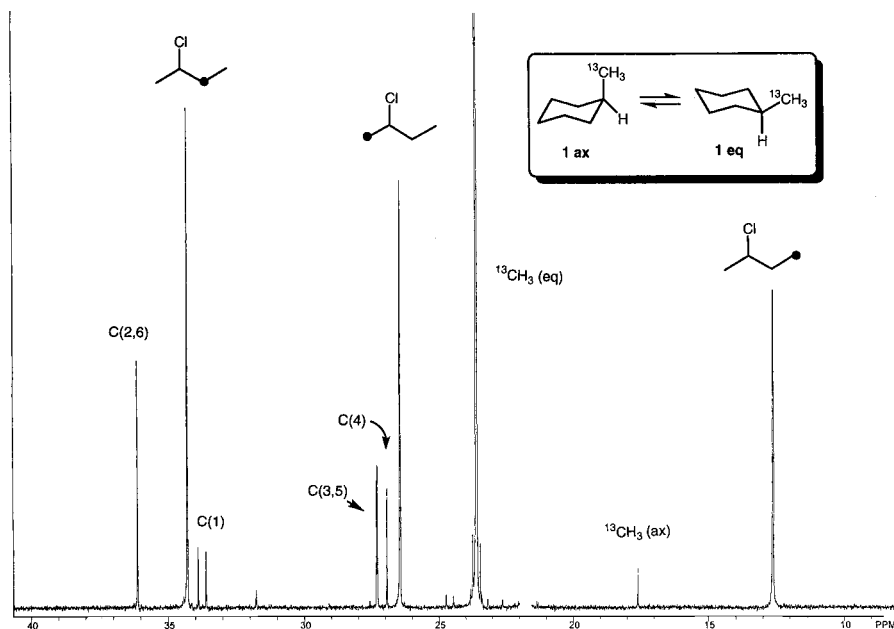


Figure 3. ^{13}C NMR spectrum of methylcyclohexane (**1**) at $-120\text{ }^\circ\text{C}$ in $\text{CBrF}_3 - \text{CD}_2\text{Cl}_2$ (5:1 by vol).

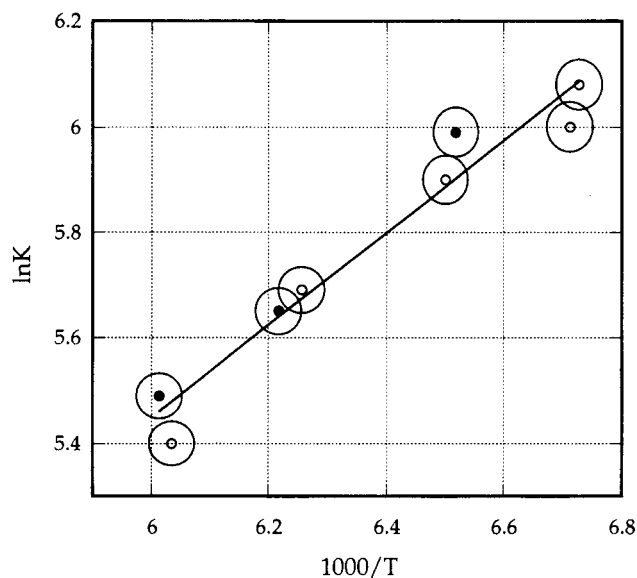


Figure 4. van't Hoff plot of the equilibrium data for methylcyclohexane (**1**) summarized in Table 1. The open circles correspond to data obtained at Yale and the closed circles represent the data obtained at Holy Cross; the circles represent an estimated error in K and $1/T$.

of the equilibrium data leads to $\Delta H^\circ = -1.25 \pm 0.10$ kcal/mol, and the intercept corresponds to $\Delta S^\circ = 4.4 \pm 0.6$ eu.²⁵ The calculated entropy change (vide infra) is 2.6 eu, and if this is included as a constraint, the slope of the van't Hoff plot corresponds to $\Delta H^\circ = -1.55$ kcal/mol. Taking the average of these values gives $\Delta H^\circ = -1.40$ kcal/mol, with an estimated uncertainty of 0.15 kcal/mol, as the conformational enthalpy of an isopropyl group in cyclohexane.

The conformational enthalpy, entropy, and free energy of methyl, ethyl, and isopropyl groups in cyclohexane determined in this study are summarized in Table 2. These values do not differ appreciably from those reported by Booth and Everett,¹¹ but they do stand on a more secure experimental foundation. With these data in hand, we may now examine the computational results.

Table 2. Experimental Conformational Enthalpy (ΔH°), Entropy (ΔS°), and Free Energy (ΔG°) for Alkyl-Substituted Cyclohexanes at 157K^a

compound	$-\Delta H^\circ$, kcal/mol	ΔS° , eu	$-\Delta G^\circ$, ^b kcal/mol
methylcyclohexane (1)	1.76 ± 0.10	0.2 ± 0.2	1.80 ± 0.02
ethylcyclohexane (2)	1.54 ± 0.12	1.3 ± 0.8	1.75 ± 0.02
isopropylcyclohexane (3)	1.40 ± 0.15	3.5 ± 0.9	1.96 ± 0.02

^a Data for axial \rightarrow equatorial equilibrium. ^b Derived directly from the equilibrium constants.

Computational Studies. Methylcyclohexane (1). Geometry optimizations were carried out for the two conformers of **1** using the HF, B3LYP, and MP2 theoretical levels with several basis sets.²⁶ The HF and B3LYP calculations gave a classical energy difference of 2.1–2.2 kcal/mol favoring the equatorial isomer, **1e**. This is clearly significantly larger than the experimentally measured energy difference. It has, however, recently been found that the B3LYP theoretical model often overestimates conformational energy differences, whereas MP2 appears to give values in better agreement with experiment.²⁷ The energy difference was calculated using MP2 with several different basis sets (Table 3), and with the larger basis sets, values close to the experimental energy difference were obtained. Thus, it appears that, in the present case, B3LYP also overestimates conformational energy differences. In the subsequent examination of the dimethylcyclohexanes (see below) it was found that B3LYP was in error with respect to the observed relative energies in one direction, while MP2 was in error in the opposite direction.

QCISD provides a superior method for correcting for the effects of electron correlation, and with the dimethylcyclohexane calculations described below, it gave relative energies in very good agreement with the experimental values. Therefore, the QCISD/6-311+G** energies for the **1a** and **1e** were obtained using the MP2/6-

(26) Additional theoretical levels and details of the thermal corrections to 298 K are given in the Supporting Information.

(27) Karpfen, A.; Choi, C. H.; Kertesz, M. *J. Phys. Chem. A* **1997**, *101*, 7426.

Table 3. Calculated Energies for Methylcyclohexane (1)

basis set	conformer energies ^a		ΔE (kcal/mol) ^b
	axial-CH ₃	equatorial-CH ₃	
MP2/6-311+G**	-274.367 91	-274.370 62	1.70
MP2/6-311+G (3df,2p)	-274.531 58	-274.534 21	1.65
QCISD/6-311+G**	-274.451 54	-274.454 42	1.81
QCISD/6-311+G(3df,2p)	-274.615 21	-274.618 01	1.76
energies (kcal/mol)			
CH ₃ rotational barrier	2.42	3.01	
ZPE ^c	119.15	118.97	0.18
($H^{\ddagger}_{298} - H^{\ddagger}_0$)	5.26	5.28	-0.02
($G^{\ddagger}_{298} - G^{\ddagger}_0$)	-19.28	-19.32	0.04
S^{\ddagger} (cal/mol-deg)	82.30	82.52	-0.22

^a Total energies, calculated using the MP2/6-311G* geometries, are given in hartrees (H); other energies are in kcal/mol (1 H = 627.51 kcal/mol). ^b Axial-CH₃ - equatorial-CH₃. ^c Zero point energies; HF/6-31G* frequencies were scaled by 0.893. The internal rotor modes were treated separately and their zero point energies are included.

311+G** geometries giving an energy difference of 1.81 kcal/mol (Table 3). Pople, in developing his G1 and G2 model chemistries, found that the effects of polarization functions were additive.²⁸ Thus, the QCISD/6-311+G(3df,2p) energies were estimated as follows: QCISD/6-311+G(3df,2p) = QCISD/6-311+G** + MP2/6-311+G(3df,2p) - MP2/6-311+G**. This procedure led to an energy difference of 1.76 kcal/mol as our best estimate of ΔE for the axial-equatorial equilibrium of **1**.

To compare the calculated energy difference with the experimental results, ΔE must first be corrected for the difference in zero-point energy (ZPE) between the two conformers, the change in ΔH^{\ddagger} on going from 0 K to the higher temperatures must be computed, and the enthalpy difference must then be converted to ΔG^{\ddagger} using the calculated entropy difference. These computations required estimates of the vibrational frequencies, and they were calculated at the HF/6-31G* level and scaled by the usual factor, 0.893. One of the modes corresponds to methyl rotation, and it was treated separately as previously described.²⁹ The rotational barriers were calculated at the B3LYP/6-311G* level and are included in Table 3.

The final calculated relative energies (ΔH^{\ddagger} , ΔS^{\ddagger} , and ΔG^{\ddagger}) of the axial and equatorial isomers of methylcyclohexane (**1a** and **1e**) at 157 and 298 K are given in Table 4. The data for 157 K correspond to the average temperature used in the experimental study (Table 1). The calculated enthalpy difference at 157 K, $\Delta H^{\ddagger} = -1.93$ kcal/mol, is in good agreement with the experimental value of -1.76 ± 0.10 kcal/mol.

It is of interest to note that the calculated rotational barriers for the axial and equatorial methyl rotamers (Table 3) are close to that for ethane and the changes in geometry on rotation parallel those found for rotation about the C-C bond in ethane. With the equatorial methyl conformer (**1e**), the MP2/6-311+G* calculated CH₃-C length increases from 1.527 to 1.542 Å on rotation and other structural changes were small. Thus, the origin of this methyl rotational barrier is the same as that for ethane, where the only significant structural change on rotation is found in the C-C bond length.²⁹

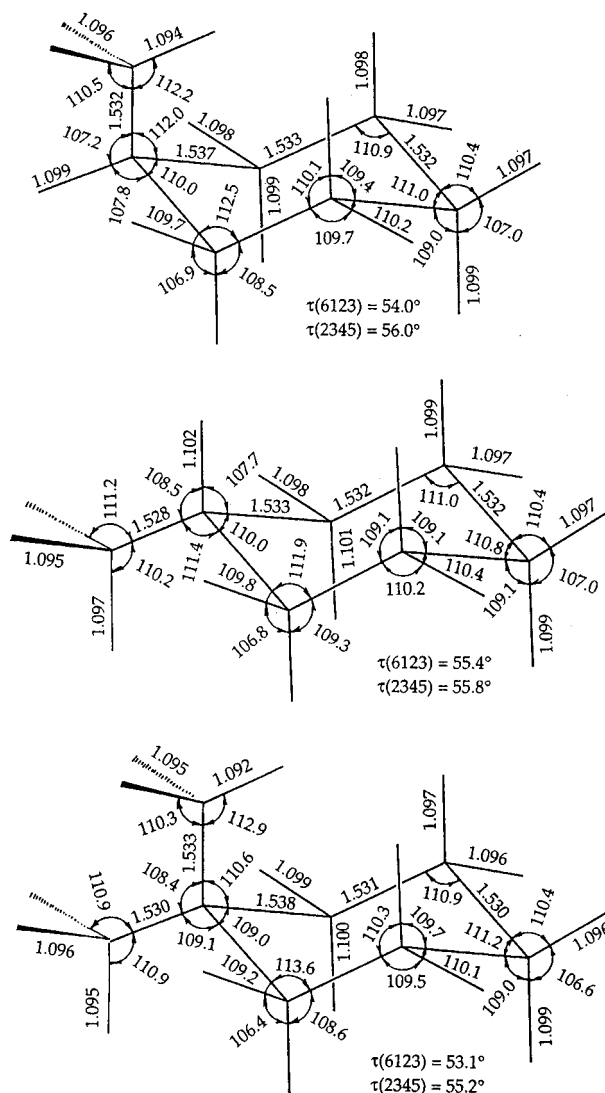


Figure 5. Calculated (MP2/6-311G**) structural data for the axial (**1a**) and equatorial (**1e**) conformers of methylcyclohexane and for 1,1-dimethylcyclohexane.

The difference in energy between the axial (**1a**) and the equatorial (**1e**) conformations of methylcyclohexane is often attributed to 1,3-synaxial interactions between the axial methyl group and the axial hydrogens at C(3,5),³⁻⁸ although the two gauche-butane interactions present in the axial conformer, but absent in the equatorial isomer, must also be important.³⁻⁸ One would think that such steric interactions should lead to some characteristic changes in geometry of the cyclohexane ring at positions remote from the axial substituent. Structural parameters for **1e** and **1a** derived from MP2/6-311+G** calculations are summarized in Figure 5.³⁰ In both conformational isomers, the calculated structural parameters at the C(3,5) and C(4) positions are quite close to those found in cyclohexane itself (bond angles: C-C-C = 111.28°, H-C-H = 106.65°, C-C-H_a = 108.83°, C-C-H_e = 110.55°).³¹ The C(2)-C(3)-H_a angle in **1a**

(28) Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys.* **1991**, *94*, 7221.

(29) Murcko, M. A.; Castejon, H.; Wiberg, K. B. *J. Phys. Chem.* **1996**, *100*, 16162.

(30) A previous study of methylcyclohexane at the HF/6-31G* level (Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8029) found slightly larger C-C(3,5)-H_a angular distortions for **1a**. The structural data obtained in the present study (Figure 5) should be more satisfactory.

(31) Dommen, J.; Brupbacher, T.; Grassi, G.; Bauder, A. *J. Am. Chem. Soc.* **1990**, *112*, 953 and references therein.

Table 4. Calculated Conformational Enthalpy (ΔH°), Entropy (ΔS°), and Free Energy (ΔG°) for Alkyl-Substituted Cyclohexanes^a

compound	$-\Delta H^\circ$, kcal/mol			ΔS° , eu		$-\Delta G^\circ$, kcal/mol	
	0 K	157 K	298 K	157 K	298 K	157 K	298 K
methylcyclohexane (1)	1.94	1.93	1.92	0.13	0.22	1.96	1.98
ethylcyclohexane (2)	1.82	1.77	1.67	0.55	0.99	1.86	1.96
isopropylcyclohexane (3)	1.60	1.53	1.46	2.56	2.92	1.94	2.33

^a Data for axial \rightarrow equatorial equilibrium; the energies are based on the corrected QCISD energy differences (see text).

(110.1°) is somewhat larger than the corresponding bond angle in **1e** (109.1°), but overall, these positions seem little affected by an axial methyl substituent. The fact that the axial hydrogens at C(3,5) in **1a** are not significantly splayed from their positions in **1e** by the presence of the axial methyl is significant: angle bending is not particularly costly in terms of energy, and one would expect larger than observed differences in the C(2)–C(3)–H_a angles of **1a** vis-à-vis **1e** if 1,3-synaxial interactions contributed in a major way to the conformational energy of the methyl substituent.

In contrast to the small changes in geometry at remote ring positions engendered by an axial methyl group, much larger structural perturbations are found at the substitution site. In the axial methyl conformer (**1a**), both the C(2)–C(1)–CH₃ bond angle (112.0°) and the C(1)–C(2)–C(3) angle (112.5°) are larger than those of the equatorial isomer (111.4 and 111.9°, respectively). Not surprisingly, the CH₃–C(1) bond length in **1a** (1.532 Å) is longer than that in **1e** (1.528 Å). In short, the structural data for **1e** and **1a** do not appear to be consistent with interpretations that attribute the conformational energy of a methyl group to 1,3-synaxial interactions. Rather, the data indicate that repulsive steric interaction between an axial methyl group and the ring carbons, including the gauche torsional interaction,^{3–8} is the major component responsible for destabilization of the axial methyl group.

Dimethylcyclohexanes. The 1,4- and 1,1-dimethylcyclohexanes are an important set of compounds for conformational studies. A comparison of the difference in energy between *cis*- and *trans*-1,4-dimethylcyclohexane with ΔH° for a methyl group provides a test of the assumption that the conformational energies of substituents at C(1) and C(4) are additive as assumed in the counterpoise method for obtaining $-\Delta G^\circ$ values.^{4,5,8,10} An examination of the structure of 1,1-dimethylcyclohexane would be useful in assessing the importance of the so-called “buttressing” effect in geminally disubstituted cyclohexanes.^{4,5} The energies of these compounds were calculated at several theoretical levels, and the results are summarized in Table 5 along with experimental heat of formation data for the 1,1- and 1,4-dimethylcyclohexanes.³²

The relative energies of the isomeric 1,4-dimethylcyclohexanes are reproduced by the B3LYP calculations and, to a lesser extent, by MP2. However, the B3LYP model does not reproduce the relative energy of 1,1-dimethylcyclohexane, and it might be noted that it also does not reproduce the relative energies of *n*-pentane and neopentane.³³ On the other hand, MP2 does better at reproducing the relative energy of 1,1-dimethylcyclohexane, although it appears to overcorrect at the highest

Table 5. Calculated Energies for the Dimethylcyclohexanes

	dimethylcyclohexane		
	<i>trans</i> -1,4-	<i>cis</i> -1,4-	1,1-
total energy ^a			
MP2/6-311G*	–313.447 82	–313.445 21	–313.447 79
MP2/6-311+G**	–313.570 18	–313.567 75	–313.570 25
QCISD/6-311+G*	–313.545 69	–313.542 73	–313.543 64
relative energies ^b			
MP2/6-311G*	0.00	1.63	0.02
MP2/6-311+G**	0.00	1.52	–0.04
QCISD/6-311+G*	0.00	1.86	1.29
ZPE ^c	135.70	135.89	135.80
$\Delta\Delta H^\circ_0$ ^d	0.00	2.04	1.39
$\Delta\Delta H^\circ_{298}$	0.00	1.98	1.24
experimental ΔH°_f ^e	–44.1 ± 0.4	–42.2 ± 0.4	–43.2 ± 0.5
$\Delta\Delta H^\circ_f$	0.0	1.9 ± 0.5	0.9 ± 0.6

^a Total energies are given in hartrees (H); 1 H = 627.51 kcal/mol. ^b Relative energies are in kcal/mol. ^c Zero point energies; HF/6-31G* frequencies were scaled by 0.893. ^d Based on QCISD calculated energies. ^e Experimental heat of formation (kcal/mol) at 298 K, taken from ref 31.

level (MP2/6-311+G*). The low relative energy of the 1,1-dimethyl compound presumably arises from the same interactions that stabilize neopentane relative to the other pentanes.³⁴

The deficiencies in the MP2 calculated energy differences led us to obtain the QCISD/6-311+G** energies using the MP2 geometries. After correcting for the differences in ZPE, and the change in energy on going from 0 to 298 K (Table 5), the calculated relative energies are in remarkably good agreement with the experimental ΔH°_f values.

The MP2/6-311+G* difference in energy between *cis*- and *trans*-1,4-dimethylcyclohexane is 2.04 kcal/mol after correcting for the difference in zero-point energy. The corresponding difference in energy between the axial and equatorial isomers of methylcyclohexane, **1a** and **1e** (Table 3), is 1.99 kcal/mol. The fact that these energy differences are virtually identical indicates that the C(4)–CH₃ in 1,4-dimethylcyclohexane does not affect the conformational energy of a methyl group in cyclohexane. This result lends strong support to the assumption that the counterpoise technique for obtaining conformational energies does not introduce large errors.

In 1,1-dimethylcyclohexane, with two methyl groups attached to the same carbon, one might expect that the axial methyl would be moved toward the cyclohexane ring, which should increase any 1,3-diaxial interactions that might be present (viz., the buttressing effect).^{4,5} Structural data for 1,1-dimethylcyclohexane, derived from MP2/6-311+G** calculations, are summarized in

(32) Pedley, J. B. *Thermochemical Data and Structures of Organic Compounds*; Thermodynamics Research Center, Texas A&M University: College Station, TX, 1994; Vol. 1.

(33) The B3LYP/6-311G* energies for *n*-pentane and neopentane are –197.813 79 and –197.815 34 H, respectively, giving a calculated energy difference of only 0.97 kcal/mol, or after correction for the difference in zero-point energy, 1.6 kcal/mol at 0 K. The experimental energy difference (ref 31) is 3.4 kcal/mol at 0 K.

(34) Laidig, K. E. *J. Phys. Chem.* **1991**, *95*, 7709.

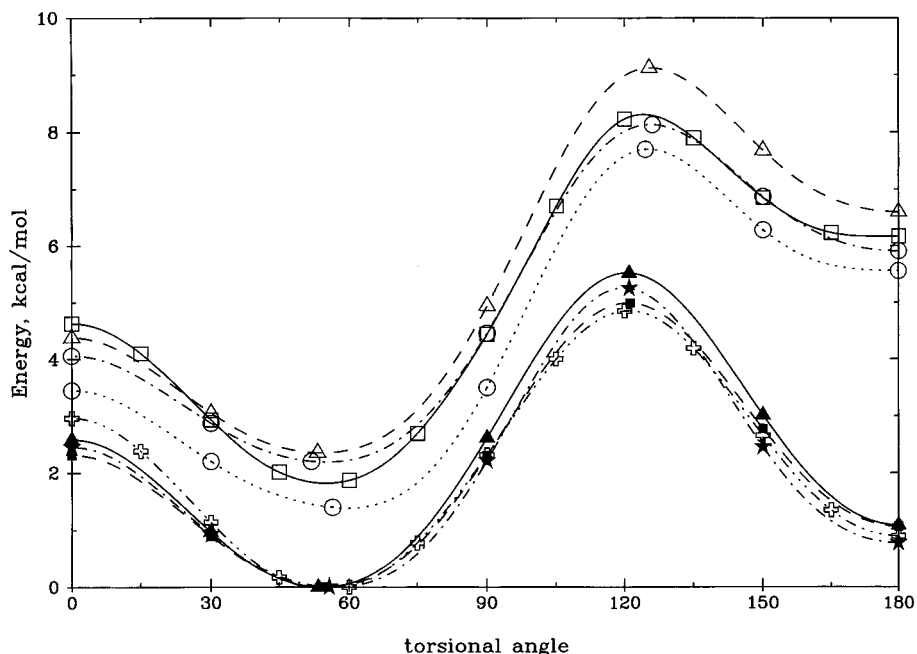


Figure 6. Potential energy change for rotation of the ethyl group in ethylcyclohexane; the torsional angle is defined by H(1)–C(1)–CH₂–CH₃. The upper curves are for the axial conformer (**2a**), and the lower curves are for the equatorial conformer (**2e**). Legend: axial (**2a**) = MM3, Δ = HF/6-31G*, \circ = B3LYP/6-311G*, \circ = MP2/6-311+G**; equatorial (**2e**) \square = MM3, \blacktriangle = HF/6-31G*, \blacksquare = B3LYP/6-311G*, \blackstar = MP2/6-311+G**.

Figure 5. The geometry at C(3), C(4), and C(5) is virtually unchanged on going from **1a** to 1,1-dimethylcyclohexane, despite the decrease in the C(2)–C(1)–CH₃ bond angle from 112.0° in **1a** to 110.6° in the geminally disubstituted cyclohexane. Thus, buttressing of the axial methyl by an equatorial group does not appear to have an effect on the geometry at remote ring positions when the axial groups at C(3,5) are hydrogen. This observation lends further support to the suggestion made above that interactions between an axial CH₃ and the synaxial hydrogens at C(3,5) are not an important factor in the determining the conformational preference of a methyl group.

Ethylcyclohexane (2). Whereas methylcyclohexane has a simple 3-fold rotational barrier for the methyl group, the rotational barrier for an ethyl group is more complex. The stationary points on the potential energy surface for ethyl rotation in the equatorial and axial isomers of **2** were located at the HF/6-31G*, B3LYP/6-311G*, MP2/6-31G*, and MP2/6-311+G** levels and are shown in Figure 6; the torsional angle (τ) is defined by H(1)–C(1)–CH₂–CH₃. As might be expected, the rotamer with a \sim 60 torsional angle (i.e., methyl gauche to H) had the lowest energy for both the axial (**2a**) and equatorial (**2e**) isomers. The general features of the torsional function for **2e** are the same for the several theoretical levels with a spread of less than 1 kcal/mol at the two maxima. Although the relative energies of **2a** and **2e** differ significantly on changing theoretical level, the general features are reproduced at all theoretical levels.

The MM3 molecular mechanics force field has been well optimized for hydrocarbons, and therefore, it was of interest to compare the rotational profile calculated above with that predicted by MM3; the results of these calculations are also shown in Figure 6. It can be seen that the MM3 force field gives fairly good agreement with the ab initio results.

The energies of the lower energy rotamers of axial and equatorial ethylcyclohexane were also calculated by

Table 6. Calculated Energies for Ethylcyclohexane (2)

basis set	conformer energies ^a		ΔE^b (kcal/mol)
	axial-CH ₃	equatorial-CH ₃	
MP2/6-311+G*	-313.445 06	-313.447 60	1.59
MP2/6-311+G (3df,2p)	-313.750 47	-313.752 68	1.39
QCISD/6-311+G*	-313.538 43	-313.541 33	1.82
QCISD/6-311+G (3df,2p) ^c	-313.843 84	-313.846 41	1.61
energies (kcal/mol)			
CH ₃ rotational barrier	2.58	2.62	
ZPE ^d	136.32	136.11	0.21
($H_{298}^{\circ} - H_0^{\circ}$)	6.16	6.31	-0.15
($G_{298}^{\circ} - G_0^{\circ}$)	-21.15	-21.29	0.14
S° (cal/mol-deg)	91.58	92.57	-0.99

^a Total energies are given in hartrees (H); other energies are in kcal/mol (1 H = 627.51 kcal/mol). ^b Axial-CH₃ – equatorial-CH₃. ^c Estimated energies as described in the text. ^d Zero point energies; HF/6-31G* frequencies were scaled by 0.893. The internal rotor modes were treated separately and their zero point energies are included.

geometry optimization at several theoretical levels. The results of these calculations are summarized in Table 6. Here again, the B3LYP model gave larger energy differences than did MP2. In view of the results described above, the energy difference between **2a** and **2e** also was calculated at the QCISD/6-311+G* level and corrected to the QCISD/6-311+G(3df,2p) using the MP2 data as described above, giving $\Delta E = 1.61$ kcal/mol. Thermochemical correction for internal rotation was made using the MP2/6-311+G** energy profile. The final calculated relative energies for **2** are summarized in Table 4. At 157 K, ΔH° for ethylcyclohexane is calculated to be -1.85 kcal/mol, which is in reasonable agreement with the experimental value of -1.54 ± 0.12 kcal/mol (Table 2).

Isopropylcyclohexane (3). The rotational profile for isopropylcyclohexane (**3**) was calculated at the HF/6-31G*, B3LYP/6-311G*, MP2/6-31G*, and MP2/6-311+G* levels, and they are compared with that predicted by MM3 in Figure 7 (τ is defined as the H(1)–C(1)–C–H

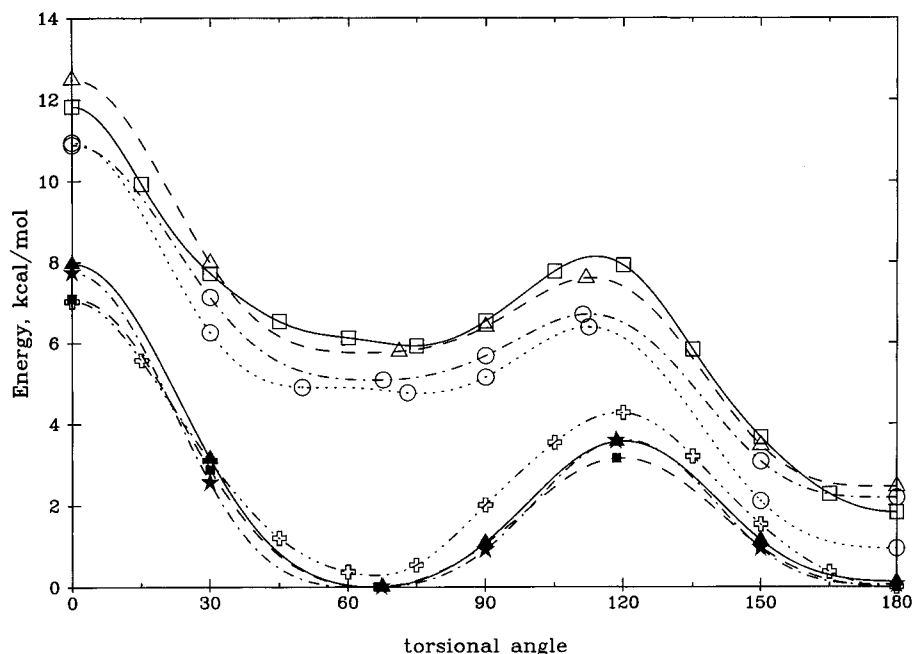


Figure 7. Potential energy change for rotation of the isopropyl group in isopropylcyclohexane; the torsional angle is defined by H(1)–C(1)–C–H. The legend is the same as for Figure 6.

Table 7. Calculated Energies for Isopropylcyclohexane (3)

basis set, torsional angle ^b (τ , °)	conformer energies ^a		ΔE^c (kcal/mol)
	axial-CH ₃	equatorial-CH ₃	
MP2/6-311G*, 180°	-352.622 05	-352.623 84	1.12
MP2/6-311G*, 60°	-352.615 88	-352.623 92	5.05
MP2/6-311+G**, ^d 180°	-352.760 71	-352.762 13	0.89
MP2/6-311+G**, ^d 60°	-352.754 62	-352.762 22	4.77
QCISD/6-311+G*, 180°	-352.731 56	-352.733 97	1.51
QCISD/6-311+G(3df,2p), 180°			1.31 ^e
energies (kcal/mol)			
CH ₃ rotational barrier ^d			
$\tau = 60^\circ$ (inner methyl)	3.74	2.83	
$\tau = 60^\circ$ (outer methyl)	2.99	2.96	
$\tau = 180^\circ$	2.43	2.75	
ZPE ^f ($\tau = 180^\circ$)	171.70	171.41	0.29
($H_{298}^\circ - H_0^\circ$)	6.88	7.02	-0.14
($G_{298}^\circ - G_0^\circ$)	-21.81	-22.54	0.73
S° (cal/mol-deg)	96.20	99.12	-2.92

^a Total energies are given in hartrees (H); other energies are in kcal/mol. ^b The torsional angle, τ , is defined as the H–C–C–H angle. ^c Axial-CH₃ – equatorial-CH₃. ^d Calculated using the MP2/6-311G* geometries. ^e Estimated value, see text. ^f Zero point energies; HF/6-31G* frequencies were scaled by 0.893. The internal rotor modes were treated separately, and their zero point energies are included.

angle). There are three low-energy rotamers for the equatorial conformer, **3e**, corresponding to torsional angles of $\sim 60^\circ$, 180° , and $\sim 300^\circ$. Although there are minima at the corresponding torsional angles for the axial conformer, only the 180° rotamer of **3a** has a low enough energy to be significantly populated. For the case of the **3e**, all theoretical levels give essentially the same potential energy curve, and that derived from MM3 is not very different. The spread of calculated potential energies for **3a** is greater, but this is mainly the result of differences in the relative energies of the axial and equatorial isomers.

The calculated energies for isopropylcyclohexane are summarized in Table 7. The QCISD/6-311+G* energies were calculated using the MP2 geometries, giving 1.51 kcal/mol as ΔE for the axial and equatorial isomers. Making the same correction for added polarization functions as found appropriate in the ethylcyclohexane case, the "best" estimate of the energy difference between **3a**

and **3e** becomes 1.31 kcal/mol. The thermochemical correction for internal rotation was made using the MP2/6-311+G** energy profile, and the final calculated relative energies at 157 and 298 K are given in Table 4. The calculated ΔH° for an isopropyl group at 157 K is -1.53 kcal/mol, in good agreement with the observed value of -1.40 ± 0.15 kcal/mol (Table 2).

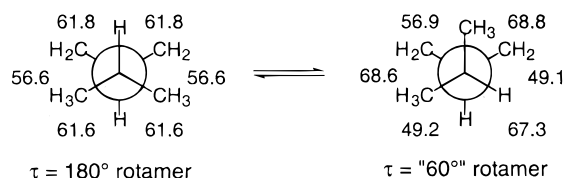
It is of some interest to note that the 180° and " 60° " rotamers of **3e**, depicted below with torsional angles derived from MP2/6-311G* calculations, have essentially the same energy (Figure 7) despite the fact that the latter conformation is subject to an additional gauche-butane interaction not present in the former. This seeming paradox is reminiscent of that in 2,3-dimethylbutane where the anti and gauche conformations are nearly equal in enthalpy.³⁵ As noted elsewhere,³⁵ this behavior arises from constraints on the torsional angles imposed by the larger than tetrahedral C–C–C bond angles found in congested molecular frameworks such as 2,3-dimeth-

Table 8. Calculated Energies for *tert*-Butylcyclohexane (4)

basis set	conformer energies ^a		
	equatorial	axial	twist-boat
MP2/6-31G*	-391.660 15	-391.651 22	-391.651 47
MP2/6-311G* ^b	-391.807 25	-391.798 58	-391.799 33
MP2/6-311+G** ^b	-391.961 16	-391.953 01	-391.953 22
relative energies			
MP2/6-31G*	0.00	5.60	5.45
MP2/6-311G*	0.00	5.44	4.97
MP2/6-311+G**	0.00	5.11	4.98
ZPE ^c	169.92	170.18	170.00

^a Total energies are given in hartrees (H); relative energies are in kcal/mol. ^b Calculated at the MP2/6-31G* geometries. ^c Zero point energies; HF/6-31G* frequencies were scaled by 0.893. The internal rotor modes were treated separately, and their zero point energies are included.

ylbutane and **3e**. Consequently, the anti rotamer has two small torsional angles ($\tau = 56.6^\circ$); moreover, if one of the small angles were to be increased so as to reduce steric interactions, the other would of necessity have to decrease. In sum, the 180° rotamer of **3e** is effectively destabilized via enhanced steric repulsion enforced by small torsional angles between the methyl groups and the C(2,6) positions.



***tert*-Butylcyclohexane (4).** A more limited computational study of the highly biased conformational equilibrium of *tert*-butylcyclohexane was conducted at several levels of theory (Table 8). The equatorial preference of *tert*-butyl is so large ($-\Delta G^\circ = 4.9$ kcal/mol)³⁶ that it has long been used as an anchoring substituent.⁶ Nonetheless, there are three conformational isomers that must be considered in an analysis of *tert*-butylcyclohexane. The lowest energy form of **4** clearly has an equatorial *tert*-butyl group.^{3,4,6,8,36} However, when the group is placed in the axial position, the molecule may escape the severe steric interactions by conversion to a twist-boat form that places the *tert*-butyl group in a pseudoequatorial position. The energies of the three relevant conformers of **4** were calculated, giving the data summarized in Table 8. The axial and twist-boat conformations were found to have virtually the same energy albeit with a slight preference for the nonchair conformation. After correction for differences in the zero point energies, the calculated conformational enthalpy of an axial *tert*-butyl group at the MP2/6-311+G* level ($\Delta H^\circ = -5.4$ kcal/mol) is in reasonable agreement with the accepted value ($-\Delta G^\circ = 4.9$ kcal/mol)³⁶ for the conformational energy of a *tert*-butyl substituent in cyclohexane.

(35) (a) Bartell, L. S.; Boates, T. L. *J. Mol. Struct.* **1976**, *32*, 379. (b) Heinrich, F.; Lüttke, W. *Chem Ber.* **1977**, *110*, 1246. (c) For a concise discussion of the conformational analysis of 2,3-dimethylbutane and related molecules, see ref 4, p 605–606 and references therein.

(36) (a) Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1984**, *25*, 3267. (b) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J.; Van-Catledge, F. A. *J. Am. Chem. Soc.* **1968**, *90*, 1199. (c) van de Graaf, B.; van Bekkum, H.; van Koningsveld, H.; Sinnema, A.; van Veen, A.; Wepster, B.; van Wijk, A. M. *Rec. Trav. Chim. Pays-Bas* **1974**, *93*, 135.

Conclusions

The results presented above demonstrate that it is possible to obtain a fairly accurate measurement of the conformational equilibrium constant for alkyl-substituted cyclohexanes by low-temperature ¹³C NMR of samples having ¹³C-enriched alkyl groups if one uses one of the cyclohexane ring resonances as an internal standard. The $-\Delta H^\circ$ values for methyl- (**1**), ethyl- (**2**), and isopropylcyclohexane (**3**) were found to be 1.76 ± 0.10 , 1.54 ± 0.12 , and 1.40 ± 0.15 kcal/mol, respectively. Ab initio calculations at the QCISD level reproduced the experimental values fairly satisfactorily, but B3LYP gave energy differences that were too large, whereas MP2 gave differences that were too small. It should be noted that, although the computed enthalpy differences are somewhat larger (by ~ 0.2 – 0.3 kcal/mol) than those observed in solution, this may well be a consequence of the fact that the experimental conformational enthalpies were determined in solution whereas the computational results are referred to the gas phase.¹³ An analysis of the structural data derived from the calculations indicated that an axial substituent affected only the local geometry; consequently, 1,3-diaxial interactions between a methyl, ethyl, or isopropyl group and a synaxial hydrogen are apparently not an important contributor to the energy difference between axial and equatorial alkyl groups.

Experimental Section

Materials. Methylcyclohexane enriched to 99 atom % ¹³C at the methyl carbon (**1**) was prepared by the catalytic hydrogenation of ¹³CH₃-toluene (99 atom %; Cambridge Isotope Laboratories) using Adam's catalyst in acetic acid (room temperature, 30 psi hydrogen pressure).³⁷ Ethylcyclohexane- α -¹³C (**2**) was prepared by the catalytic hydrogenation of 1-phenylethanol. The alcohol was obtained by LiAlH₄ reduction of acetophenone, which was prepared by the reaction of acetyl-¹³C chloride (99-atom %; Cambridge Isotope Laboratories) with benzene and aluminum chloride. Isopropylcyclohexane- α -¹³C (**3**) was obtained by the catalytic hydrogenation of 2-phenyl-2-propanol prepared by the reaction of methylmagnesium bromide with acetophenone-¹³C=O.

NMR Measurements. NMR spectra were obtained at 11.8 T at Yale using a Bruker AM-500 spectrometer and a dual-channel ¹H/¹³C probe. A 4.0 μ s pulse width ($\sim 35^\circ$ tip angle) was used with a recycle delay of 6.0 s to ensure complete relaxation of the sample. The spectra were obtained using 64K of points and sweep widths of 12–15 kHz to give an acquisition time of ~ 2.4 s and a resolution of ~ 0.4 Hz per point. Approximately 200 scans gave sufficient signal-to-noise for each compound. At Holy Cross the spectra were obtained at 7.1 T using a Bruker AC-300 spectrometer and a dual-channel ¹H/¹³C probe. The same parameters as noted above were employed except that the sweep width was ~ 7 kHz and 32K of points were collected to give the same acquisition time and spectral resolution.

Dilute solutions, approximately 10% by volume, of **1–3** in CBrF₃-CD₂Cl₂ (5:1 by volume) solvent were used in the low-temperature NMR studies; neat 2-chlorobutane contained in a capillary placed in the NMR tube was used as an internal thermometer (eq 2). It should be noted that the spectrometer temperature controllers were found to be in error by a considerable amount, and there were discrepancies of up to 13 °C between the internal temperature and the setting of the temperature control.

Following FT transformation, spectra were transferred in digital form to another computer. Relevant band areas were obtained in two independent ways. The first method consisted

(37) Adams, R.; Marshall, J. R. *J. Am. Chem. Soc.* **1928**, *50*, 1970.

of fitting the NMR bands to a Lorentzian curve. The area was then obtained from the height and width at half-height.¹⁸ In some instances, the bands were not precisely Lorentzian due to slight asymmetry; in these cases the small difference between the experimental and calculated curves was integrated using Simpson's rule, and the area was added to that of the Lorentzian curve. The second procedure for obtaining band areas involved the venerable "cut-and-weigh" method: the appropriate bands were adjusted to the same size using a known scaling factor and printed. Areas were then determined by cutting out the bands, weighing them, and correcting for the scaling factor. The two methods gave essentially the same relative areas in every instance. The areas obtained by integration were used for the van't Hoff plots; errors were determined using the Marquardt algorithm.²⁵

Calculations. The ab initio calculations were carried out using Gaussian 95.³⁸ The thermochemical corrections were

(38) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Sefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 95, Development Version (Rev. D)*; Gaussian, Inc.: Pittsburgh, PA, 1995.

carried out using locally developed programs. The rotational barriers were treated by calculating the energy and the reduced moment of inertia as a function of the torsional angle and then calculating the energy levels.²⁹ The partition function was obtained from the energy levels and the other terms were obtained using the usual statistical mechanics formalism.³⁹

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Supporting Information Available: Summary of the calculations, including additional theoretical levels and details of the thermal corrections to 298 K, and calibration of the 2-chlorobutane thermometer. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(39) Cf. Janz, G. J. *Estimation of Thermodynamic Properties of Organic Compounds*; Academic Press: New York, 1958.