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Article

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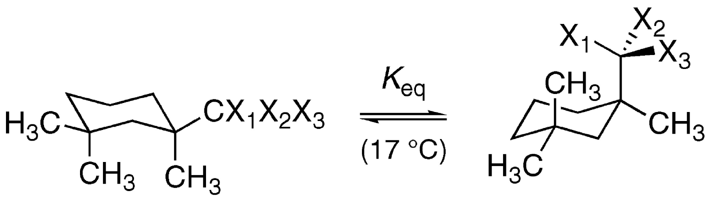

$\boldsymbol{K_{eq}}$(exp) = **1.042** for X_1=X_2=X_3=D
$\boldsymbol{K_{eq}}$(calc) = **1.0417** for X_1=X_2=X_3=D
$\boldsymbol{K_{eq}}$(calc) = **1.0370** for X_1= D, X_2=X_3=H
$\boldsymbol{K_{eq}}$(calc) = **1.0017** for X_2=D, X_1=X_3=H or X_3=D, X_1=X_2=H

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ARTICLES

A Steric Deuterium Isotope Effect in 1,1,3,3-Tetramethylcyclohexane

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Abstract: The equilibrium isotope effect (EIE) for the interconversion of the two chair isotopomers of 1-trideutero-1,3,3-trimethylcyclohexane was predicted using geometry and vibrational force constants derived from electronic structure theory at HF, B3LYP, and MP2 levels as input for the program THERMISTP. Agreement between theory and previously reported NMR results is very good (experimental $K_{eq} = 1.042 \pm 0.001$ vs $K_{eq} = 1.0409$ at MP2/6-311G* level, $K_{eq} = 1.0503$ at HF/6-311G*, and $K_{eq} = 1.0417$ at B3LYP/6-311G* level, all at 17 °C). In order to investigate the origin of this isotope effect, the calculated EIEs for the monodeuterated isotopomers were analyzed. It has been shown that the hydrogen atom on an axial methyl group which is unusually close to its counterpart on the other axial methyl is responsible for the large (steric) isotope effect in the compound studied.

Introduction

Isotope effects yield valuable detailed information about many features of structures and chemical reactions.[1] Kinetic isotope effects (KIE) give us information about transition states for reactions. Equilibrium isotope effects (EIE) result from bonding and nonbonding interactions in structures which are minima on the energy surface. In most cases, equilibrium isotope effects are considerably smaller than kinetic isotope effects; nevertheless, there are many cases where they can be measured very accurately. Equilibrium isotope effects can be expressed theoretically as appropriate ratios of partition functions (or more specifically reduced isotopic partition function ratios). Comparison of results from calculations with experimental results is useful in testing the accuracy of the theoretical methods used and also for gaining detailed information about a variety of qualitative effects on chemical structures and reaction mechanisms.

If we have a very rapid process which interconverts chemically equivalent structures (a degenerate equilibrium), the NMR spectrum shows peaks at the average of the frequencies because of nuclei being interchanged by this process. When an isotope is introduced which breaks the degeneracy, the equilibrium constant can be altered from unity because of an isotope effect.[2−4] The system is still going back and forth very rapidly. However, it spends more time on one side of the equilibrium than on the other. Frequencies which were averaged to single lines without the isotope are now split to give separate peaks. This is because each nucleus that we are looking at resides at the two sites a different fraction of the time. This is a true differential method because the splitting which appears when the isotope is introduced goes to zero if the isotope effect vanishes. Even if there were no equilibrium isotope effect, there might be a very small frequency difference because of an intrinsic isotope shift. Frequency differences can be measured accurately using NMR. We do need to know the chemical shifts that the nuclei which are exchanging would have in the absence of the fast reaction in order to calculate the equilibrium isotope effect. These frequencies often can be obtained by going to low enough temperatures so that the reaction slows down. In some cases, the shifts in analogous substances can be used. This method has been referred to as the isotopic perturbation method.[2−4] Even nondegenerate cases can be examined if the equilibrium constants are not too far from unity.[5]

In this report, we reexamine the steric deuterium equilibrium isotope effect in 1,1,3,3-tetramethylcyclohexane theoretically by means of a new program THERMISTP derived from QUIVER.[6] No new experimental data are reported. The improvement of the new program over Quiver is that it correctly tests the Teller−

[†] Yale University.

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(1) For general treatment of isotope effects see: (a) Bigeleisen, J.; Wolfsberg, M. *Adv. Chem. Phys.* **1958**, *1*, 15−76. (b) Melander, L. In *Isotope Effects on Reaction Rates*; Ronald Press: New York, 1960. (c) Collins, C. I., Bowman, N. S., Eds. *Isotope Effects in Chemical Reactions*, ACS Monograph 167; Van Norstrand Reinhold: New York, 1970. (d) Wolfsberg, M. *Acc. Chem. Res.* **1972**, *7*, 225−233. (e) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980. (f) *Isotope Effects in Chemistry and Biology*; Kohen, A., Limbach, H. H., Eds.; Taylor & Francis: New York, 2006.

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Redlich product rule. Its output explicitly notes the values of the vibrational frequencies and the six translation and rotation frequencies. (The closeness to zero of the latter six frequencies serves as a test of the accuracy of the electronic structure calculation[7]). The program is more user-friendly. Input and output samples of the program are presented below. The importance of testing the Teller−Redlich product rule in these calculations has recently been emphasized again.[7]

1,1,3,3-Tetramethylcyclohexane has been chosen not only because reliable experimental data exist that could verify the calculated EIE by the new program, but also to demonstrate the scope of the method and examine some features of the effect that were not possible to establish experimentally.

A Steric Deuterium Isotope Effect in 1,1,3,3-Tetramethylcyclohexane. 1,1,3,3-Tetramethylcyclohexane is a compound where there is a rapid equilibrium at room temperature between two chemically equivalent structures due to chair−chair interconversion. In this process, the two methyls which have been axial become equatorial and the two that have been equatorial become axial. Therefore, there is a single averaged peak in the carbon nuclear magnetic resonance spectrum for all four methyls. Each methyl group spends half of its time axial and half of its time equatorial. However, when one of the methyl groups is replaced by a trideuteromethyl group, the spectrum is found to be altered. If the trideuteromethyl group is at C_1 of the cyclohexane, the two methyl groups at C_3 were found to give two separate peaks with CMR chemical shifts differing by $\delta = 0.184$ ppm at 17 °C.[8]

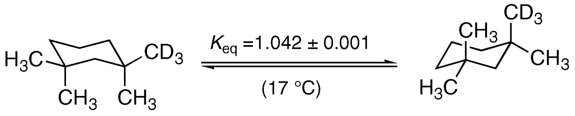
Axial and equatorial methyl carbons have different chemical shifts in 1,1,3,3-tetramethylcyclohexane. At low temperatures (−100 °C) the chair−chair interconversion slows down so that distinct unaveraged axial and equatorial ^{13}C NMR signals are seen, enabling measurement of the quantity called Δ ($\delta_{\text{equat}} - \delta_{\text{axial}} = \Delta = 9.03$ ppm). Δ measured for the tetramethyl compound in the previous work[8] was assumed to be temperature independent and applicable to the axial−equatorial difference between the two methyl groups on C3 in the 1-trideuteromethyl-1,3,3-trimethylcyclohexane. This will be discussed further in this report.

Let K_{eq} refer to the equilibrium constant between the molecule with the trideutero group axial and with the trideutero group equatorial

$$K_{\text{eq}} = \frac{X_{\text{axial}}}{X_{\text{equat}}} \tag{1}$$

where X denotes mole fraction. If K_{eq} differs from unity, it follows that the two methyl groups at C3 in the rapidly interconverting molecule at room temperature “see” different environments since the methyl partner on C3 which is axial when the trideutero methyl group on C1 is also axial becomes equatorial when the C1 trideutero methyl group becomes equatorial. Similar considerations apply to the other methyl group on C3 (Scheme 1).

Scheme 1



Thus, the averaged chemical shifts for the two methyls at C3 in the deuterated compound are related to the equilibrium constant according to the following equations:

$$\delta_1 = \frac{\delta_{\text{equat}} + K_{\text{eq}} \times \delta_{\text{axial}}}{1 + K_{\text{eq}}}; \quad \delta_2 = \frac{\delta_{\text{axial}} + K_{\text{eq}} \times \delta_{\text{equat}}}{1 + K_{\text{eq}}} \tag{2}$$

Since the observed splitting of the C3 methyls is $\delta = \delta_1 - \delta_2$, and the chemical shift difference between equatorial and axial carbon atoms is $\Delta = \delta_{\text{equat}} - \delta_{\text{axial}}$, one can straightforwardly derive the relation:

$$K_{\text{eq}} = \frac{\Delta + \delta}{\Delta - \delta} \tag{3}$$

With the use of the experimentally observed δ and Δ values, $K_{\text{eq}} = 1.042 \pm 0.001$ at 17 °C.

Why would the equilibrium constant be affected by introducing deuterium? Hydrogens on the two axial methyls are forced to be close together. This would be expected to raise some vibrational frequencies and increase the zero-point energy. Substitution of deuterium on one of these methyls will then decrease the zero-point energy more than it would in non-crowded positions. The isotopomer with deuterium in a crowded position of an axial methyl is therefore expected to be favored at equilibrium. This is the standard qualitative explanation of what has been described as a steric isotope effect.[9] A number of kinetic isotope effects have been interpreted as steric in nature, e.g., the inverse isotope effect obtained in racemization of the hexadeuterated (two deuteromethyl groups) 9,10-dihydro-4,5-dimethylphenanthrene.[10]

If we imagine starting from chair cyclohexane and make an “ideal” methylated structure by replacing a pair of axial hydrogens with methyls directed along the former CH bond directions and with exactly staggered torsion angles, we would get a structure where two of the axial methyl hydrogens are very close together. There would be a strong repulsive force pushing them apart. How can the structure respond to this force? There are two simple ways. The methyls can move apart by bending a series of bonds and distorting the ring or the methyls can rotate so as to move the close hydrogens further apart. As both of these distortions proceed, the repulsive force between the hydrogens becomes smaller. However, there is a counterforce which results from moving the methyls further apart and from twisting the methyls away from the preferred staggered torsion angle. This distortion stops when these forces balance. We can readily see in the side view of the theoretically predicted structure (Figure 1b) that the methyls have moved apart considerably. The top view (Figure 1a) shows no obvious torsional rotation of the methyls; however, the torsion angles listed in the output involving the interacting hydrogens show that there is a rotation of from 5−6° from the ideal staggered torsion angles.

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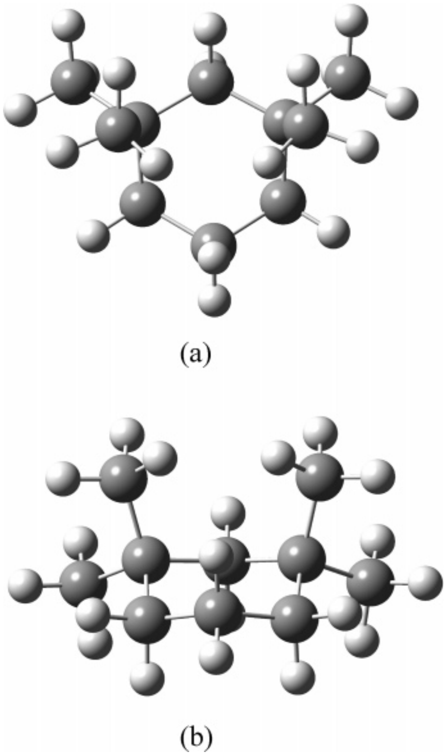

Figure 1. Top view (a) and side view (b) of the optimized structure of 1,1,3,3-tetramethylcyclohexane at B3LYP/6-31G(d) level made from the output using the *Gaussview* program.

It is important to calculate theoretical values for this isotope effect to compare with the experimental value.[7,11−13] Although very early theoretical estimates of deuterium (and also other) isotope effects were often based on the use of estimated values of a few CH stretching and/or corresponding bending frequencies, it has been known for some time[13,14] that all of the $3N - 6$ vibration frequencies of a molecule are affected by the introduction of a deuterium (or any other isotopic atom) and that they all should be included in a complete calculation of the thermodynamic isotope effects.

A theoretical calculation of K_{eq} requires the calculation of the reduced isotopic partition function ratio $(s_2/s_1)f$ of the axial 1-trideuteromethyl-1,3,3-trimethylcyclohexane and the corresponding equatorial trideuteromethyl compound. We make the assumption that the isotope effect is independent of solvent. Many such calculations have been discussed in the literature.[7] The quantum calculation (using Gaussian 03[15]) of geometry of the stable molecule and corresponding force constants was started with a chair structure and a single energy minimum was found in each calculation. Two different basis sets were used in these calculations (6-311G* and 6-31G*). With these two basis sets, which are fairly large, the results were not strongly dependent on basis set. One reason for doing the present calculations is to see how agreement with experiment varies with the level of the calculation. Calculations were therefore carried out at the HF level, at the MP2 level which is a traditional level of including correlation, and at the B3LYP level which is a density functional level of calculation. It is well-known that obtaining vibrational frequencies of isotopomers that satisfy the Teller−Redlich product "rule" requires special care in finding the energy minimum of a stable molecule. Optimization was done using the "verytight" qualifier. In some cases, convergence to the VERYTIGHT criteria did not occur because of oscillations. The use of CALCFC or CALCALL frequently helped achieve convergence. In the B3LYP calculation, the modifier GRID=ULTRAFINE was used. The six final (minimum energy) structures are quite similar, and they all have C_s symmetry.

Table 1. Calculated Equilibrium Isotope Effects (K_{eq}) and Calculated Chemical Shift Differences (Δ) and Splittings (δ) of the Methyl Carbons for Trideuteromethyl-1,3,3-trimethylcyclohexane

	K_{eq}				
level	290 K	300 K	closest HH distance (Å)	calcd Δ (ppm)	calcd δ at 290 K (ppm)
HF/6-31G*	1.0461	1.0447	2.0682	7.81	0.176
MP2/6-31G*	1.0384	1.0372	2.0036	8.18[a]	0.154
B3LYP/6-31G*	1.0385	1.0373	2.0334	8.64[b]	0.163
HF/6-311G*	1.0503	1.0488	2.0675	7.78	0.191
MP2/6-311G*	1.0409	1.0397	1.9993	8.15[a]	0.163
B3LYP/6-311G*	1.0417	1.0404	2.0334	8.67[b]	0.177

[a] Calculated at GIAO-MP2/6-311G* level using the geometry optimized at indicated level. [b] Calculated at GIAO-B3LYP/6-311G* level using the geometry optimized at indicated level.

After convergence, Gaussian was requested to produce an output file containing the structural coordinates and the Cartesian force constant matrix in each case by including the text "punch=(Title, Coor, Derivatives)" in the Gaussian input. The file is written to the Scratch directory. This file is then read by the new fortran program THERMISTP together with an input file that indicates how many isotopomers are to be considered and where the isotopes are in each. The temperatures and the isotopomers to be compared complete this file. The use of THERMISTP for the 1,1,3,3-tetramethylcyclohexane case is straightforward. The two isotopomers which are in equilibrium have the same total isotopic composition but one has three deuteriums on an axial methyl group and the other has three deuteriums on an equatorial methyl. Chart 1 shows an input file for the trideuterated isotopomer of 1,1,3,3-tetetramethylcyclohexane, while Chart 2 shows the corresponding output file.

The series of calculations for this molecule used Gaussian 03W at the levels indicated in Table 1 were carried out, followed by applying the program THERMISTP producing the results indicated in the Table for the equilibrium constants at 290 K (experimental temperature). Calculations of EIE were also done at 300 K in order to predict the temperature dependence and see whether the reported uncertainty in temperature could affect the agreement between experiment and theory.

Outputs of the program THERMISTP (Charts 2 and 3), in which both the six lowest frequencies which correspond to translations and rotations and the Teller−Redlich product ratios (which should be unity) are indications of closeness to the minimum of the energy surface.

In order to find out whether the theoretical splitting of the C3 methyl signals in the spectrum of 1-deuteromethyl-1,3,3-tetramethylcyclohexane can be predicted with reasonable accuracy, quantum chemical ^{13}C chemical shifts were calculated using GIAO method implemented in Gaussian 03.[15] Chemical shifts were calculated at MP2/6-311G* level using the geom-

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Chart 1. Input File for Program THERMISTP for the 1-Trideuteromethyl-1,3,3-trimethylcyclohexane Case

```
30              Number of atoms
3              Number of isotopomers
3              Number of relations between isotopomers
1,  2           Isotopomers which are related
1,  3           Isotopomers which are related
2,  3           Isotopomers which are related
C10H20                     First Isotopomer
12,12,12,12,12,12,12,12,12,12,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1    Masses of
atoms
2                     Number of temperatures
290.,   300.               values of temperature
C10H17D3                   Second Isotopomer eq
12,12,12,12,12,12,12,12,12,12,1,1,1,1,1,1,1,1,1,1,1,1,1,1,2,2,2,1,1,1    Masses of
atoms
C10D3H17                   Third Isotopomer  ax
12,12,12,12,12,12,12,12,12,12,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,2,2,2    Masses of
atoms
```

Chart 2. Output of Program THERMISTP for the 1-Trideuteromethyl-1,3,3-trimethylcyclohexane (Trideuterated Case)

```
           tetramethylcyclohexane B3LYP/6-311G*

         Temperatures:   290.  300.

        C10H17D3      Deuteriums on an axial methyl
        The Low Frequencies are: -1.8  .0  .0  .0  6.9  12.4

        C10D3H17     Deuteriums on an equatorial methyl
        The Low Frequencies are: -1.8  .0  .0  .0  6.9  12.2
         ==================================================

        RELATIONSHIPS of ISOTOPOMERS with D on Axial and Equatorial Methyls

         TEMPERATURE                     290.0       300.0
         TELLER-REDLICH PRODUCT RATIO   .99968519   .99968519
         (S2/S1)F                       1.0416786   1.0403813
```

etries obtained at MP2/6-31G* and MP2/6-311G* levels (GIAO-MP2/6-311G*//MP2/6-31G* and GIAO-MP2/6-311G*//MP2/6-311G*), at HF/6-311G* level using the geometries obtained at HF/6-31G* and HF/6-311G* levels (GIAO-HF/6-311G*//HF/6-31G* and GIAO-HF/6-311G*//HF/6-311G*), and at B3LYP/6-311G* level using the geometries obtained at B3LYP/6-31G* and B3LYP/6-311G* levels (GIAO-B3LYP/6-311G*//B3LYP/6-31G* and GIAO-B3LYP/6-311G*//B3LYP/6-311G*). At all levels, the axial methyl carbon is shifted upfield from the equatorial methyl carbon. The values of the calculated chemical shift differences (Δ) between the axial and equatorial methyl carbons are given in Table 1. The theoretical splittings of the C3 methyl carbons in the deuterated compound (δ) derived from the eq 3, using the theoretically predicted Ks at indicated level, are also presented in Table 1.

The agreement between the experimental EIE (1.042 ± 0.001) and the calculated values is quite good. Also, the theoretically predicted splitting (δ) in the spectrum is in good agreement with the experimental data (e.g., 0.184 ppm vs 0.177 ppm at B3LYP level). A number of factors could be considered which might have caused discrepancies. The calculations might not have been done with a large enough basis set or with an inadequate treatment of correlation. It is reassuring and perhaps significant that the agreement with the experimental value is best using the two highest QM levels. Gaussian uses the Born−Oppenheimer approximation, and no relativistic correction was made. Harmonic vibration frequencies were derived from the calculated second derivatives and no anharmonic corrections were undertaken. The torsional motions were also approximated as harmonic.

Robinson et al.[16] suggested that the introduced deuterium might directly cause chemical shift changes in the C3 methyls observed (an intrinsic isotope shift) producing an error in the reported experimental equilibrium isotope effect. If this intrinsic shift were the same for both distant methyls, it would not affect the reported result. Only a different effect on these two methyls would cause an error. As in the case of remote chemical effects due to charged groups (inductive effects), one could imagine intrinsic isotope shifts being transmitted through bonds or through space. One might guess that the through-bond part would be the same for both methyls but that the though-space part might be greater to the closer methyl. A recent reference[17] reported a great number of experimental intrinsic deuterium isotope effects on CMR shifts. There are some through-space effects reported, but they are much smaller than through-bond

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Chart 3. Output of Program THERMISTP for the 1-Deuteromethyl-1,3,3-trimethylcyclohexane (Monodeuterated Case)

```
tetramethylcyclohexane B3LYP/6-311G*  T = 290 K

22,23 and 24 are hydrogens on axial methyls - 24 is the crowded H
19,20 and 21 are hydrogens on equatorial methyls
 ==========================================================
 Calculated ratio of ISOTOPOMERS 22 and 19
 TELLER-REDLICH PRODUCT RATIO   .99996725
 (S2/S1)F             .988230
 -----------------------------------------------
           ISOTOPOMERS 22 and 20
 TELLER-REDLICH PRODUCT RATIO   .99992543
 (S2/S1)F             1.00285
 ----------------------------------------------
           ISOTOPOMERS 22 and 21
 TELLER-REDLICH PRODUCT RATIO   .99984235
 (S2/S1)F             .997957
 =============================== ===========================
           ISOTOPOMERS 23 and 19
 TELLER-REDLICH PRODUCT RATIO   .99992190
 (S2/S1)F             .998983
 ----------------------------------------------
           ISOTOPOMERS 23 and 20
 TELLER-REDLICH PRODUCT RATIO   .99988008
 (S2/S1)F             1.01376
 ----------------------------------------------
           ISOTOPOMERS 23 and 21
 TELLER-REDLICH PRODUCT RATIO   .99979700
 (S2/S1)F             1.00882
 ==========================================================
           ISOTOPOMERS 24 and 19
 TELLER-REDLICH PRODUCT RATIO   .99993345
 (S2/S1)F             1.02860
 -----------------------------------------------
           ISOTOPOMERS 24 and 20
 TELLER-REDLICH PRODUCT RATIO   .99989164
 (S2/S1)F             1.04381
 -----------------------------------------------
           ISOTOPOMERS 24 and 21
 TELLER-REDLICH PRODUCT RATIO   .99980856
 (S2/S1)F             1.03872
```

effects. Again, one might expect that an error due to differential intrinsic isotope shifts would upset the agreement between experiment and theory.

One might terminate the study at this point. Experiment and theory agree within the experimental error. This agreement is satisfying, but it also suggests the possibility of asking further detailed questions with the help of additional theoretical calculations. What is the origin of the substantial equilibrium isotope effect here? It has been recognized by many organic chemists that 1,3 diaxial groups on chair cyclohexane are close together and that there is repulsive interaction between them. Indeed, we chose this case to study experimentally, expecting that this interaction might result in a steric isotope effect. However, we can now ask whether this is the only possible explanation of the result. Conceivably, there might be an isotope effect as a result of preference for the deuterated methyl group to be axial or equatorial from factors unrelated to the steric effect but due to some intrinsic difference between hydrogens on axial and equatorial methyls.

A close look at the optimized structures suggests a further question. Only one hydrogen atom on each axial methyl group is close to its (symmetry related) counterpart on the other axial methyl. The distances between these pairs of hydrogen atoms are similar at all the levels of calculation. The other two hydrogens on each axial methyl group do not have any close interactions. Is the isotope effect due to this close pair of hydrogen atoms? One could measure the isotope effect experimentally for the monodeuterated compound. However, the extremely rapid rotation of the methyl groups would give a single averaged equilibrium isotope effect and make it very difficult or impossible to distinguish the effects of deuterium on the three nonequivalent positions. There will be an isotopic perturbation effect on the rotation of partially deuterated methyl groups.

It is easy to focus on this question using theoretical calculations on the monodeuterated system. The deuterium can be put, in turn, on each of the three different positions on the axial methyl and (for completeness) on each of the nonequivalent equatorial positions. There are therefore nine equilibrium isotope effects (but only six independent parameters). The results of these nine calculations are given in Chart 3. It may be seen immediately that the predicted equilibrium constants when the deuterium is at the crowded position are much larger than the effects when it is not. The average of the three equilibrium constants when D is in a crowded position is 1.0370. The other six equilibrium constants have an average value of 1.00175. The results thus imply that the crowded axial position is responsible for the large isotope effect in the compound studied. Furthermore, there does not appear to be an appreciable predicted isotope effect due only to differences between noncrowded axial and equatorial hydrogens.

Since CMR was used in the experimental study, one might ask about whether a $^{12}C-^{13}C$ isotope effect might come into play. There very well might be such an isotope effect. However, since only the ^{13}C can be observed in the NMR, shifts due to this effect would move all of the CMR peaks in the same direction and cancel out in the frequency differences used in this study. In order to look for this isotope effect specifically, one might consider preparing the compound where three of the four methyls contain 100% ^{13}C. Splitting should then occur in the CMR which should yield this isotope effect. Theoretical prediction could be done employing the same QM results as used here by just changing the input for THEMISTP.

Acknowledgment. We gratefully acknowledge the financial support of this research by the National Science Foundation (Grant No. 0120505) and the Ministry of Science and Technology of the Republic of Croatia (Grant No. 006-0982933-2963).

Supporting Information Available: Cartesian coordinates of 1,1,3,3-tetramethylcyclohexane optimized at HF/6-31G(d), MP2/6-31G(d), and B3LYP/6-31G(d) levels of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

JA072375R