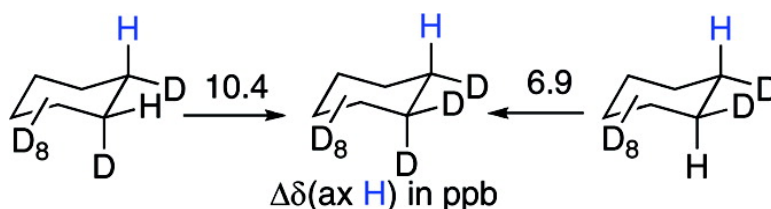


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J. Am. Chem. Soc., **2008**, 130 (41), 13659-13663 • DOI: 10.1021/ja802903a • Publication Date (Web): 18 September 2008

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Vicinal Deuterium Perturbations on Hydrogen NMR Chemical Shifts in Cyclohexanes

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Abstract: The substitution of a deuterium for a hydrogen is known to perturb the NMR chemical shift of a neighboring hydrogen atom. The magnitude of such a perturbation may depend on the specifics of bonding and stereochemical relationships within a molecule. For deuterium-labeled cyclohexanes held in a chair conformation at $-80\text{ }^\circ\text{C}$ or lower, all four possible perturbations of H by D as H–C–C–H is changed to D–C–C–H have been determined experimentally, and the variations seen, ranging from 6.9 to 10.4 ppb, have been calculated from theory and computational methods. The predominant physical origins of the NMR chemical shift perturbations in deuterium-labeled cyclohexanes have been identified and quantified. The trends defined by the $\Delta\delta$ perturbation values obtained through spectroscopic experiments and by theory agree satisfactorily. They do not match the variations typically observed in vicinal $J_{\text{H-H}}$ coupling constants as a function of dihedral angles.

Introduction

Deuterium labeling and NMR spectroscopy have served well to define the conformational inversions of cyclohexane leading from one chair form to another¹ and to facilitate determinations of chemical shifts and coupling constants^{2–4} characteristic of this archetypical cycloalkane. But they have not yet provided full data for cyclohexanes or led to clear theoretically solid insights on deuterium-induced perturbations of hydrogen chemical shifts. These gaps have now been closed. All four possible upfield perturbations of a ¹H NMR chemical shift, $\Delta\delta$, induced within a vicinal H–C–C–H unit when it is changed to the corresponding D–C–C–H structure in suitable deuterium-labeled cyclohexanes have been determined. The magnitudes of these $\Delta\delta$ values do not parallel trends seen for J coupling constants as functions of dihedral angles. And, most significantly, a theory-based computational approach has been developed to model the four possible $\Delta\delta$ perturbations, and the calculations, without recourse to any adjustable parameters or scale factors, account well for the experimentally observed values. The physical origins of such isotopic perturbations of

chemical shifts are now better understood, and $\Delta\delta$ can be computationally predicted in molecules of some complexity.

Results and Discussion

The $\Delta\delta$ phenomenon, known for more than 40 years,^{5–7} leads to perturbations demonstrated to be essentially linear with increasing deuterium substitution at equivalent positions.⁸ The stereochemical aspects of such perturbations for ¹³C chemical shifts in D–C–C–¹³C systems have received much attention,^{9–11} but D–C–C–H fragments have been relatively neglected. Various deuterium-induced chemical shift perturbations for vicinal hydrogens in selectively labeled *tert*-butylcyclohexanes and cyclohexanes have been reported.¹² The $\Delta\delta$ shifts for cyclohexane were then estimated through regression analysis calculations utilizing 12 equations and selected data.¹³ Values for three of the four possible deuterium isotope effects on a vicinal hydrogen were reported: $\Delta\delta$ (eqH, eqH \rightarrow D) = 7 ± 2 ppb, $\Delta\delta$ (axH, eqH \rightarrow D) = 7 ± 2 , and $\Delta\delta$ (axH, axH \rightarrow D) = 14 ± 1 , while $\Delta\delta$ (eqH, axH \rightarrow D) was not noted. These indirectly derived values appeared to parallel trends in vicinal ¹H–¹H spin–spin coupling constants.¹³

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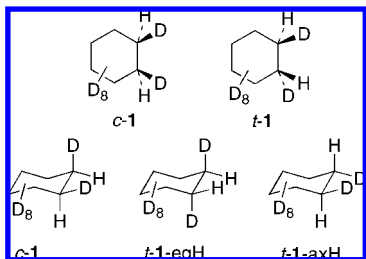
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Prompted by curiosity as to why $\Delta\delta$ (axH, axH \rightarrow D) in a cyclohexane might be so much larger than $\Delta\delta$ (eqH, eqH \rightarrow D) and $\Delta\delta$ (axH, eqH \rightarrow D), all four possible vicinal D–C–C–H perturbations of hydrogen chemical shifts have been recorded for appropriate deuterium-labeled cyclohexanes. Our values for $\Delta\delta$ (eqH, eqH \rightarrow D) and $\Delta\delta$ (axH, eqH \rightarrow D) agree well with the earlier parameters, but do not corroborate the larger $\Delta\delta$ (axH, axH \rightarrow D) effect reported.¹³ The magnitudes of the deuterium-induced upfield shifts do not parallel stereochemically sensitive J coupling constants between analogously positioned vicinal protons in cyclohexanes.

Through $^1\text{H}\{^2\text{H}\}$ spectral measurements on the cis and trans isomers of 1,2,3,3,4,4,5,5,6,6- d_{10} -cyclohexane, *c*-1 and *t*-1,^{14–16} isotopic perturbations on chemical shifts were readily seen. At -86°C the chair conformation of the cis isomer showed as expected two doublets arising from vicinal ^1H – ^1H coupling ($J = 3.55 \pm 0.015$ Hz), centered at 1.5846 ppm (equatorial) and 1.1092 ppm (axial). A 50:50 mixture of *c*-1 and *t*-1 had a singlet for the equatorial H of the *t*-1-**eqH** conformer of *t*-1 at 1.5846 ppm. The resonance for axial H in *t*-1-**axH**, at 1.1057 ppm, overlapped and obscured the upfield component of the axH doublet of *c*-1, calculated to be just 1.0 ppb further upfield, a difference of only 0.4 Hz.



The disposition of a vicinal D is of no net consequence for the chemical shift of an eqH, but the chemical shifts for the axH in *c*-1 and in *t*-1-**axH** differ by 3.5 ppb, a significant disparity. Whether the vicinal axD or the vicinal eqH provides the dominant upfield shielding effect on the axH cannot be inferred without further data. Hence $^1\text{H}\{^2\text{H}\}$ spectra for the mixture of cis and trans isomers of d_{10} -cyclohexanes, and increasing amounts of d_{11} -cyclohexane, were secured. The new absorptions seen for eqH and axH of the d_{11} -sample were recorded at 1.5771 and 1.0988 ppm (Figure 1).

These data give all four possible chemical shift perturbations induced by a deuterium replacing a vicinal hydrogen atom in a cyclohexane, defined here for an equatorial or axial H experiencing an upfield ^1H NMR chemical shift when a specific vicinal H is replaced by a D: $\Delta\delta$ (eqH, eqH \rightarrow D) = 7.5 ppb, $\Delta\delta$ (eqH, axH \rightarrow D) = 7.5, $\Delta\delta$ (axH, eqH \rightarrow D) = 10.4, and $\Delta\delta$ (axH, axH \rightarrow D) = 6.9 ppb. The replacement of a vicinal axH or eqH by D shifts an eqH by 7.5 ppb. In both cases the pairs of vicinal atoms are gauche to one another. But anti and gauche placements of a vicinal H with D alter chemical shifts of an axial H to different extents. The larger $\Delta\delta$ upfield shift is associated with

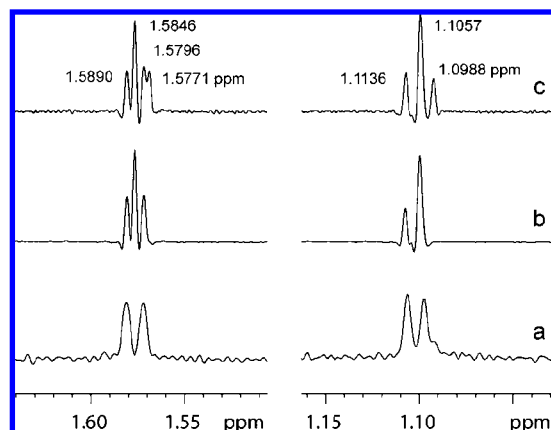
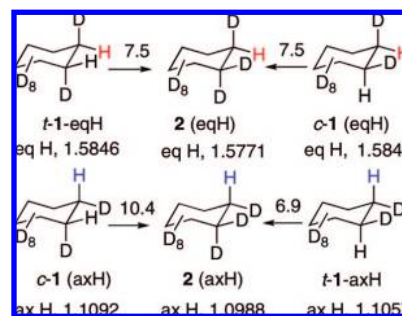


Figure 1. (a–c) $^1\text{H}\{^2\text{H}\}$ 400.13 MHz NMR spectra of deuterium labeled cyclohexanes **1** and **2** dissolved in CS_2 and recorded at a temperature of -80°C or colder using a Bruker DPX-400 spectrometer operating in an unlocked mode. The low-field resonances arise from eqHs and the high-field resonances from axHs. Each data set employed a single scan acquisition and the spectra were transformed with Gaussian resolution enhancement. (a) *cis*- d_{10} -cyclohexane (*c*-1) at -96°C ; equatorial and axial resonances are each doublets with $^3J = 3.55 \pm 0.15$ Hz; (b) a mixture of *c*-1 and *t*-1 at -81°C ; equatorial and axial resonances for *t*-1 are singlets, and the upfield singlet is superimposed on the most upfield resonances for *c*-1; (c) same conditions as (b), only with the sample spiked with a small quantity of d_{11} -cyclohexane (**2**) exhibiting equatorial and axial ^1H resonances at higher fields than those arising from *c*-1 and *t*-1. Chemical shifts (ppm) are listed for each peak.

Scheme 1. Deuterium Labeled Cyclohexanes, Observed ^1H NMR Chemical Shifts (in ppm), and Upfield Chemical Shift Perturbations (in ppb) Through D for H Replacements



the gauche, not the trans stereochemical relationship defined by the substitution (Scheme 1).

A theory-based understanding of these perturbations has not been fully developed, though progress toward this goal has been made.^{17,18} Current computational means for calculating molecular geometries, vibrational characteristics, and chemical shifts are well developed and have been applied with success to cyclohexane.^{19–24} These studies and related work on certain

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Table 1. Calculational Components Leading to Theory-Based Values of Isotopic Perturbations of NMR Chemical Shifts for Deuterium-Labeled Cyclohexanes

row	position of D substitution:	axD		eqD	
a	$\Delta_{DH} = \langle R \rangle_D - \langle R \rangle_H$ (Å)	−0.0046		−0.0049	
b	$C_{DH} = \langle R^2 \rangle_D - \langle R^2 \rangle_H$ (Å ²)	−0.0122		−0.0122	
row	Position of H δ value perturbed:	axH	eqH	axH	eqH
c	$d\delta_H/dR_D$ (ppb/Å)	−287.9	−738.1	−1244	−840.2
d	$(d^2\delta_H/dR_D^2)/2$ (ppb/Å ²)	−205.0	−554.4	−667.9	−607.3
e	$\Delta_{DH} \times (d\delta_H/dR_D)$ (ppb)	1.33	3.40	6.07	4.10
f	$C_{DH} \times (d^2\delta_H/dR_D^2)/2$ (ppb)	2.5	6.75	8.15	7.41
g	Sym. bend contraction (ppb)	1.11	−0.57	0.59	−0.56
	Total calculated $\Delta\delta$ perturbation (ppb)	4.9	9.6	14.8	10.9
	Experimental $\Delta\delta$ perturbation (ppb)	6.9	7.5	10.4	7.5

equilibrium NMR isotope effects²⁵ have not led to calculations able to account for intrinsic isotopic perturbations on H chemical shifts for cyclohexane or other hydrocarbons of comparable size.

The calculation of the effect of replacement of an H by a D atom on the chemical shift of an H on an adjacent C atom must involve differences in the range of positions sampled by the D compared to H.⁹ In the harmonic approximation the mean positions of the H and D are the same. The C–H or C–D stretch is anharmonic in general and in cyclohexane specifically.²⁰ This results in a small change in the bond length. Excursions of the atoms from the mean position result in larger contributions to the $\Delta\delta$ perturbation. These can be computed by displacement of the H atom that is to be replaced by D along a bending or stretching vibrational mode, calculating the chemical shift of a neighboring H for that displaced geometry and weighing each position by its probability.^{26–29}

Considering the theoretical factors at play in more detail starts with the recognition that a D at the same position as an H has exactly the same interaction with the molecular electrons. The effect of the D for H substitution arises from the difference in sampling of positions of the D compared to the H.⁹ This sampling difference results from the effect of the mass on the distribution of nuclear positions sampled. Here we consider only the ground vibrational state, i.e., the zero-point level. The D zero-point energy is lower than that for H and the probability distribution function is more sharply peaked and results in an average that is closer to the minimum of the anharmonic vibrational potential energy function.²⁰ In the case of harmonic potentials the average value would, of course, be independent of particle mass, but the width of the distribution would be different. Any contributions to the chemical shift at a neighboring H that are odd in a displacement will average to zero for a symmetric potential (including a harmonic oscillator) but terms that are even will not average to zero. The procedure used to compute the effect of isotopic substitution on the chemical shift of a neighboring H is to first compute the response of the chemical shift of this H, δ_H , to changes in the position of the H atom to be substituted by D, and then to average this effect using the weighting provided by the distribution, in this case the square of the ground-state nuclear wave function.

The variation of the chemical shift of a particular H atom as a function of the position of a nearby H atom is designated $\delta_H(\xi_S)$. The variable ξ_S may be either a stretch or a bend degree of freedom of the H atom at the substituted position (either axial or equatorial in this case). The variation of the chemical shift with ξ_S is separated into terms that are linear in ξ_S and those that are quadratic in ξ_S or, in general, terms that are odd and even. The odd terms give rise to a finite effect if an asymmetric anharmonic potential results in a shift in the position of the average. The quantity $\Delta\delta_H = \langle P_D(\xi_S)\delta_H(\xi_S) \rangle - \langle P_H(\xi_S)\delta_H(\xi_S) \rangle$ is the isotope shift of interest. Here the brackets $\langle \rangle$ indicate integration over the displacement variable. The subscript D or H refers to the atom at the site of substitution. In the usual approximation the functions $P_D(\xi_S)$ and $P_H(\xi_S)$ are replaced by delta functions at the equilibrium (minimum energy) value of the stretch or bend degree of freedom in question. In this case, the isotope effect vanishes.

The H atom at the position to be substituted has three degrees of freedom: a stretch in which the CH bond length changes and two bending motions, one in the plane of symmetry that contains the HCH bonds and the other perpendicular to that plane. The procedure used in detail for the CH stretch degree of freedom. The C–H (or C–D) stretch motion is anharmonic. This has been analyzed specifically for the axial and equatorial CH bonds of cyclohexane.²⁰ The resulting Morse functions deduced from overtone spectroscopy experiments can be used to compute the difference in the mean bond length of the CH and CD and the change in rms deviation. These calculations are most easily performed using the 1D Schrödinger solving program FGH.²⁶ For the Morse oscillator the average value of the bond length is larger than the minimum of the potential energy because the potential and thus the wave function are not symmetric around the minimum. This extension is decreased when H is replaced by D and so the CD bond length is slightly shorter than the CH bond length. This result and the change in the second moments of the distribution are given in the a and b rows of the Table 1 above. The notation used is that $\langle R \rangle_D$ is the average value of the bond length for a D atom for the CH Morse potential:²⁰ $\langle R \rangle_D = \langle R \times P_D(R) \rangle$ where $P_D(R)$ is the square of the zero-point wave function. The corresponding value for $\langle R \rangle_H$ is slightly larger so that their difference, Δ_{DH} , is negative. This shift vanishes for a symmetric potential. The width of the H and D distributions are determined by the average of the square of the corresponding variable, e.g., $\langle R^2 \rangle_D = \langle R^2 \times P_D(R) \rangle$. The difference in this value for the D and H cases, the “contraction” contribution, C_{DH} , is also negative since D has a narrower distribution than H.

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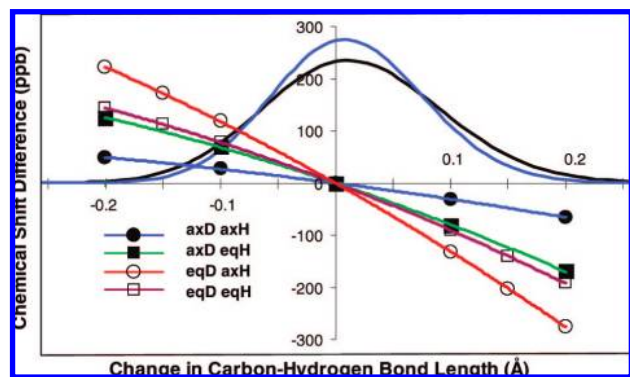


Figure 2. Variations in chemical shifts of axial and equatorial vicinal hydrogens when axial and equatorial CH bond lengths are extended or contracted relative to their values at the equilibrium geometries, and normalized and scaled distribution function $P_H(R)$ and $P_D(R)$.

The sensitivity of the chemical shift at a neighboring H to displacement of the H atom that is to be replaced by D can be determined by displacement of that atom along a bend or stretch direction and calculation of the chemical shift of the neighboring H for that displaced geometry. In this work GIAO calculations²⁷ were performed using Gaussian03²⁸ with the 6-31++G(2d,2p) basis set with the Hartree–Fock method. The HF method was used in order to permit evaluation of multiple individual contributions to be discussed. The CH bond stretching effect on the H atoms on neighboring C plotted as the chemical shift difference relative to that for the undisplaced, equilibrium position is shown in Figure 2. This is found to be fit exactly with a two-term polynomial. This polynomial interpolation is a smoothing operation. The subsequent integration removes any error the polynomial interpolation may introduce. The resulting linear and quadratic coefficients are given in rows c and d of Table 1 for these HF calculations.

The four functions in Figure 2 are for chemical shift differences as a function of bond extension depending on stereochemical relationships between two vicinally related CH bond in chair cyclohexane; they are designated by whether an axial or an equatorial CH bond is the one substituted by D. The solid symbols and blue and green lines are for variations of an axial R_{CH} ; the open symbols and red and plum lines represent equatorial R_{CH} variations. The circles are for the axial vicinal H atoms; the squares are for the equatorial vicinal H atoms. The order of entries in the Figure 2 legend parallels the data in Table 1. The four curves are $\Delta\delta = aR + bR^2$ polynomials fit to the data. The values of (a,b) with units of ppb/Å and ppb/Å², are, in the same order, axD, axH (−287.9, −205.0); axD, eqH (−738.1, −554.4); eqD, axH (−1244, −667.9); eqD, eqH (−840.2, −607.3). These form the entries in rows c and d of Table 1. The blue and black curves at the top of Figure 2 are scaled squares of the zero-point energy wave functions for H or for D in a Morse potential for an axial CH bond²⁰ obtained from FGH.²⁶ Blue is for D; black is for H. On the scale shown, the squares of the wave functions for the Morse potentials for equatorial CH and CD bonds are indistinguishable.

The values of the linear term in the fit for the effect resulting from variation of an axial bond of −287.9 and −738.1 ppb/Å may be compared to MP2 values using the same basis set of −264.3 and −744.8 ppb/Å. The quadratic terms −205.0 and −554.4 ppb/Å² for HF are −185 and −597.6 ppb/Å² with MP2. The correlation treatment does not seem to be crucial here. It has also been found that basis set changes result in only very small differences in the final quantities.

Table 2. Vicinal Deuterium Perturbations on Vicinal Hydrogen NMR Chemical Shifts in Cyclohexanes, in ppb

H	D for H	$\Delta\delta_{\text{expt}}$	$\Delta\delta_{\text{calc}}$	calc – expt
eqH	eqH → D	7.5	10.9	3.4
eqH	axH → D	7.5	9.6	2.1
axH	eqH → D	10.4	14.8	4.4
axH	axH → D	6.9	4.9	−2.0

The problem has been divided into one part that prescribes the probability distribution function for variation of D and for H for stretching and bending displacements and another part that uses the GIAO method to determine the response of a hydrogen atom to alterations of a vicinal CH bond. The quantity of interest is then the difference in the weighted values for the D and H distributions. Illustrating this with the case of CH bond length variations designated R, $P_H(R)$ is the probability distribution of H. The normalized distribution function for a D is $P_D(R)$. These are, in turn, the squares of the normalized nuclear wave functions for R for the zero-point level, for D and for H. When the variation of the chemical shift with R, $\delta_H(R)$, is expressed as a polynomial and integrated over the distribution function, and $\Delta_{DH} = \langle R \rangle_D - \langle R \rangle_H$ and $C_{DH} = \langle R^2 \rangle_D - \langle R^2 \rangle_H$, we have:

$$\langle \Delta\delta \rangle_R = \langle P_D(R)\delta_H(R) \rangle_R - \langle P_H(R)\delta_H(R) \rangle_R = \Delta_{DH} \times (d\delta_H/dR)_D + C_{DH} \times (d^2\delta_H/dR^2)_D/2 \quad (1)$$

The first term on the right results from the bond length change and a linear variation of the chemical shift. These are given in row (e) of Table 1. The contribution to the shift quadratic in the displacement is sampled over the H and D probabilities along that displacement. The resulting difference in the chemical shift is then given by the difference in the mean square amplitude of the H and D distributions times the coefficient of the quadratic variation of the chemical shift, as listed in row (f) of Table 1. The effect of the bending degree of freedom in the symmetry plane is treated as being harmonic. While that may not be the case it is probably a good approximation. This degree of freedom has both linear and quadratic terms of which only the quadratic terms contribute a net effect. The contribution from the bend displacement is smaller than that for the stretch and is negative in some cases. The bending degree of freedom transverse to the symmetry plane has only odd terms and thus does not contribute a net effect in the harmonic (or any symmetric) approximation. This is a general result for any non-totally symmetric local or normal mode of motion. This has been discussed within a normal mode treatment.²⁹

The implicit assumption has been made that the bond length and angular terms are additive, i.e., $\Delta\delta(R,\theta) = \Delta\delta(R) + \Delta\delta(\theta)$. This ignores any cross terms in the variation. Similarly, in this analysis the sensing H atom is constrained to be at its mean position. The response of the sensing H atom to the mean position and excursions of the H that is replaced by D presumably also depends on the position of the sensing H atom. The net contribution from this two-particle variation is currently being evaluated. Anharmonicity in the bending degrees of freedom and motions of other atoms may also make minor contributions. It appears, however, that the predominant effects have been identified. The results, in abbreviated form, are given in Table 2.

The root-mean-square (rms) deviation between the calculated and observed values for the above data set is 3.1 ppb. Previous treatment of a similar problem²⁹ involving heavy atom chemical shifts associated with perdeuteration was based on the harmonic

approximation. If the harmonic approximation is made for the problem at hand then the displacements in row a of Table 1 become zero because of the symmetry of the potential. Imposing this harmonic approximation results in an rms deviation between the computed and observed values of 2 ppb. However, the anharmonicity of the CH bonds in cyclohexane is real and cannot be ignored.

A local mode treatment has been applied in this treatment with the stretch and angular coordinates of a single atom being the only displacements considered. This is justified since, in the case of $C_6H_{11}D$ (or $C_6D_{11}H$) the motions of the unique nucleus is highly localized. More generally, if a normal mode approximation were used, the effect due to each normal mode would be added together, simulating the local mode result. The use of a local mode model facilitates explicit treatment of the anharmonicity.

Conclusions

The shift in R_{CD} relative to R_{CH} from the anharmonicity and the linear part of the variation of the chemical shift result in a contribution of 1–6 ppb to the deuterium perturbation (row e of Table 1). The change in the width of the D distribution compared to that for H results in a contribution of 2.5–8 ppb (row f of Table 1). In all cases the “width” effect dominates over the “shift” effect. The in-plane bending mode contribution is relatively small, -0.57 to 1.11 ppb (row g of Table 1). The other bending degree of freedom makes no contribution.

The results computed according to this theory-based computational model are remarkably insensitive to basis set or method (HF, DFT, MP2). No adjustable parameters or scale factors are used in these calculations, and some conceivably important theoretical considerations have yet to be included. Specifically, in this analysis the sensing H atom is constrained to be at its mean position and any cross terms in $\Delta\delta(R,\theta)$ have been neglected. The net contribution from the two-particle and two displacement variations have yet to be evaluated. Anharmonicity in the in-plane bending degree of freedom, if it has a large enough value, may be expected to have a significant effect. Motions of other atoms may also make minor contributions. Yet even at this stage, it appears that the predominant physical origins of the phenomenon in question have been identified; they model the new experimental findings, summarized in Scheme 1, quite satisfactorily.

Acknowledgment. We thank the Pomona College Chemistry Department and the National Science Foundation (CHE-0240104 and CHE-0514376) for financial support of this work.

Supporting Information Available: Selected high resolution NMR spectra and the full citation for ref 28. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA802903A