Theoretical and NMR Studies of Deuterium Isotopic Perturbation of Hydrogen Bonding in Symmetrical Dihydroxy Compounds

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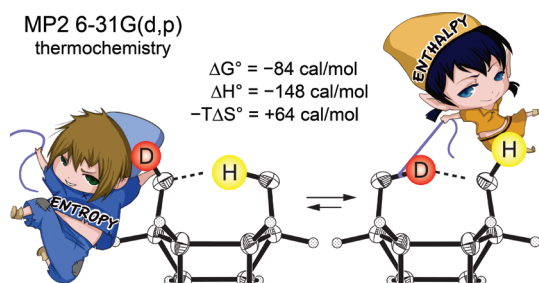
Deuterium equilibrium isotope effects (EIEs) for a cage diol and 2,6-dihydroxyacylaromatics and complexes thereof containing intra- or intermolecular hydrogen bonds have been calculated using harmonic and anharmonic vibrational frequencies using Gaussian '03 and the HF, B3LYP, and MP2 levels of theory. The predicted isotope effects have been compared with experimental NMR data, and the origins of the isotope effects have been characterized in terms of zero-point vibrational energy differences and enthalpic and entropic contributions to the free energy difference between labeled species. Reliable free energy predictions based upon harmonic frequencies were found for systems whose isotope effects are governed by bond stretching effects and for systems whose isotope effects are determined by low-frequency vibrational modes. In contrast, thermochemical predictions based upon anharmonic frequencies were found to be far less consistent. Vibrational entropy is predicted to play an important role in modulating and, in some cases, governing isotopic site preferences in hydroxyl-derived intra- and intermolecular hydrogen bonds.

Introduction

Substitution of a proton with a deuteron is a small perturbation, but often enough to perturb an equilibrium in a measurable way. Isotopic perturbation of equilibrium has been used to predict the preferential position of deuteriation in a number of cases.[1] This method has also proved very useful in nuclear magnetic resonance (NMR) studies of degenerate systems,[2] and a particularly useful application of the NMR isotopic perturbation methodology is for the detection and characterization of intramolecular OH/OH hydrogen bonds.[3−5]
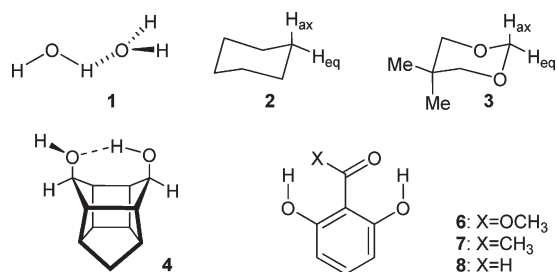
For example, isotopic perturbation of equilibrium has been studied in conformationally rigid 1,3- and 1,4-diols

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such as cage diol **4**.[6,7] With the intramolecular OH/OH hydrogen bond geometry fixed by the rigid nature of the hydrocarbon backbone, the cage 1,4-diol mimics the water dimer (**1**) and is a convenient model for hydrogen bonding in carbohydrates and other natural products. The cage diols have served as a useful model for calibrating the sign and magnitude of deuterium isotope effects on proton chemical shifts of hydroxyl substituents and revealed other features of OH/OH hydrogen bonding such as scalar coupling between hydroxyl resonances.[8,9] The substances may also be helpful in finally deciding the origin of hydrogen-bond-derived isotope effects obtained in carbohydrates.[10] Although intrinsic isotope effects have been proposed[11] as an explanation for the isotope shifts, we have provided evidence supporting the idea[12] that the shifts are due to an equilibrium isotope effect. For example, monodeuteriation of symmetric diol **4** dissolved in an apolar solvent such as CD_2Cl_2 resulted in an upfield shift[13] of the OH/OD resonance (relative to the OH/OH isotopologue). This suggests deuterium has a preference for the bridging position and the partner OH group averages more to the exterior and more shielded site. The interpretation of the NMR data is in agreement with experimental[14] and theoretical[15] studies of the monodeuterated water dimer (**1**), a prototypical hydrogen-bonded complex in which the bridging OD group is preferred.

A series of 2,6-dihydroxyacylaromatics (**6**−**8**) have previously been investigated by variable-temperature NMR to determine the barrier to rotation and for deuterated species to determine the preferred position of deuteriation and indirectly to determine the strength of the hydrogen bond. The analysis was done using isotopic perturbation of equilibrium.[16−18] It was found, for example, that deuterium preferred the non-intramolecularly hydrogen-bonded position in diol **7**. The 2,6-dihydroxyacylaromatics are so-called resonance-assisted hydrogen bond (RAHB) type (the intervening double bonds allow electron redistribution), whereas the cage compounds are not.

A principal motivation for this study is the experimental observation that the isotopic site preference in **7** is opposite
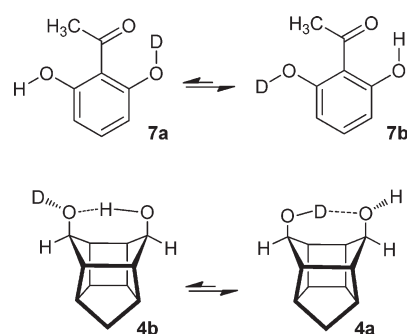

FIGURE 1. Convention for designating isotopomers of 2,6-dihydroxyacetophenone **7** and cage diol **4**.

to that in **4** (Figure 1). Both the 2,6-dihydroxyacylaromatics and the cage diols are good testing grounds for theoretical predictions of the preferred position of deuteration, as both molecules are reasonably rigid and are of a size amenable for computation. Given a choice between two or more bonding sites, deuterium is known to prefer the stiffest bond as this leads to the greatest lowering of the zero-point energy. In many cases, the site preference is determined by the high-frequency stretching frequencies. In the compounds discussed here, however, it is the low-frequency motions that determine isotopic site preferences. Low-frequency motions are more susceptible to thermal excitation, and this means that calculations of isotope effects in intra- and intermolecular hydrogen bonds are dependent upon accurate estimates of low-frequency vibrational modes. These lower energy modes are also expected to be more anharmonic than the high-energy stretching modes,[19] and so we therefore sought to compute and compare the isotope effects in a number of systems using the more accurately computed anharmonic frequencies and with coupling corrections to the rigid rotor−harmonic oscillator model.

Results and Discussion

Use of Harmonic/Anharmonic Frequency Calculations for Estimating Equilibrium Isotope Effects: An Examination of Four Test Cases. Because we were interested in comparing thermochemical predictions based upon harmonic and anharmonic frequency calculations, we wanted to better understand the origin of the thermochemical output accompanying Gaussian frequency calculations done in the context of studies of equilibrium isotope effects.[20] For calculations based upon harmonic vibrational frequencies, the program utilizes the harmonic oscillator−rigid rotor model assuming complete separation of internal energy modes. For example, the entropy is computed as a sum of contributions arising from translational, rotational, and vibrational modes, and the enthalpy is computed using a function of the characteristic vibrational temperatures.[21]

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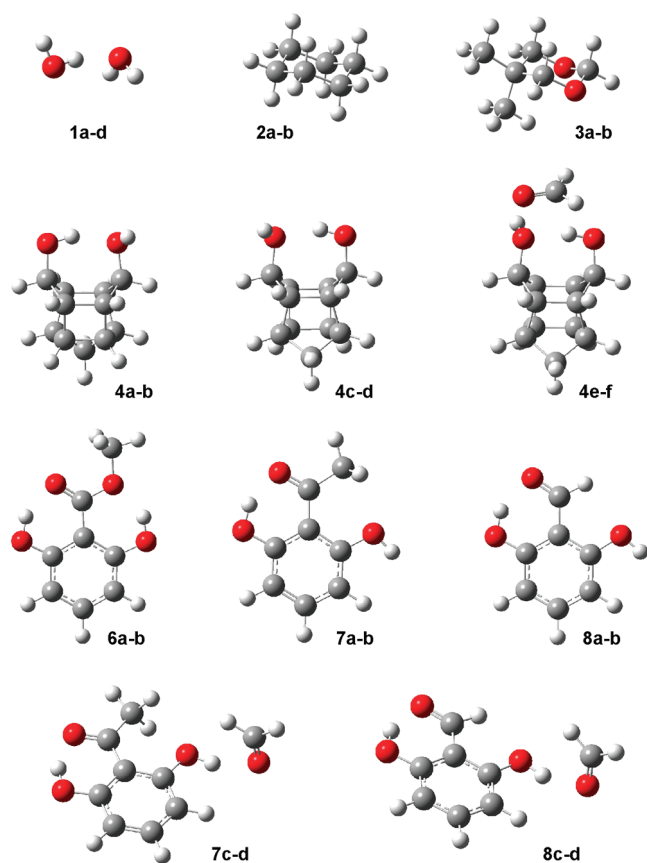
FIGURE 2. MP2 6-31G(d,p) optimized electronic structures for water dimer **1a−d**, cyclohexane **2a,b**, 5,5-dimethyl-1,3-dioxane **3a**, **b**, cage diol structures **4a,b/4c,d** and formaldehyde complex **4e,f**, 2,6-dihydroxymethylbenzoate **6a,b**, 2,6-dihydroxyacetophenone **7a,b** and formaldehyde complex **7c,d**, and 2,6-dihydroxybenzaldehyde **8a,b** and formaldehyde complex **8c,d**.

We noted that Gaussian does not use the correct rotational symmetry number in thermochemical calculations of systems whose symmetry is broken by the addition of isotopes. This only has a consequence for the calculation of the rotational contribution to the entropy. For example, the rotational entropy contribution for HOD ($\sigma = 1$) is computed using $\sigma = 2$, which is the symmetry number for H_2O. Of course, this discrepancy only affects the magnitude of the calculated entropy and does not affect the entropy difference between labeled species, provided they in fact do have the same symmetry number.[22]

We next explored the use of anharmonic frequency calculations to gauge isotopic preferences in the water dimer. A prior experimental study of the water dimer in a Kr matrix at 20−35 K revealed that deuterium prefers the bridging position in this system by 172 cal/mol.[23] This behavior was

(22) To calibrate the reader on the consequence of this issue for H_2O, HOD, and D_2O, the computed entropies using unscaled MP2 6-31G(d,p) frequencies were found to be 45.086, 46.262, and 47.357 cal mol^{-1} K^{-1}, respectively. The JANAF values, which are based upon spectroscopic data, are 45.132, 47.684, and 47.404 cal mol^{-1} K^{-1} (Chase, M.W., Jr. NIST-JANAF Tables. In *J. Phys. Chem. Ref. Data, Monograph 9*; American Institute of Physics, American Chemical Society: New York, 1998). The MP2 6-31G(d,p) HOD entropy was recomputed, using the standard equations and with $\sigma = 1$ for the rotational contribution and was determined to be 47.641 mol^{-1} K^{-1}.

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TABLE 1.   Comparison of Computed Thermodynamic Parameters for the Water Dimer at 298.15 K and 1 atm (C_s Structure Was Optimized with Very Tight Convergence Criteria (opt = vtight) and Used As the Input File for Frequency/Thermochemical Calculations)
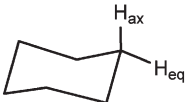

parameter	1a	1b	1c or 1d
	MP2 6-31G(d,p) unscaled harmonic frequencies		
H° (kcal/mol)	31.931	32.110	32.079
S° (cal/mol K)	71.049	71.331	71.291
G° (kcal/mol)	10.748	10.843	10.824
ΔG° (kcal/mol)	0.000	0.095	0.076
ZPE (kcal/mol)	27.569	27.780	27.758
ΔZPE (kcal/mol)	0.000	0.210	0.189
	MP2 6-31G(d,p) scaled (0.96) harmonic frequencies		
H°	30.995	31.165	31.135
S°	71.426[a]	71.699[b]	71.658
G°	9.699	9.787	9.770
ΔG°	0.000	0.088	0.071
ZPE	26.594	26.796	26.777
ΔZPE	0.000	0.202	0.183
	MP2 6-31G(d,p) anharmonic frequencies		
H°	31.661	31.821	31.783
S°	73.865	74.869	73.948
G°	9.638	9.499	9.735
ΔG°	0.139	0.000	0.236
ZPE	27.141	27.290	27.285
ΔZPE	0.000	0.148	0.143

[a]71.426 cal mol^{-1} K^{-1} (S_{tot}) = 36.757 (S_{tr}) + 21.171 (S_{rot}) + 13.499 (S_{vib}). [b]71.699 cal mol^{-1} K^{-1} (S_{tot}) = 36.757 (S_{tr}) + 21.463 (S_{rot}) + 13.479 (S_{vib}).

confirmed with ab initio calculations of zero-point vibrational energy (ZPVE) differences among isotopomers. Both experimental and theoretical studies pointed to a low-frequency wagging mode involving the bridging hydrogen isotope as the driving force for the isotope effect. In the water dimer, deuterium prefers the bridging position because it gains zero-point energy stabilization by occupying the site having the *higher* low-frequency wagging mode. This low-frequency wagging more than counteracts the effects of high-frequency stretching modes, which serve to reverse the preference because the bridging OH stretching frequency is weakened relative to the nonbridging positions.

Harmonic and anharmonic frequency calculations were performed on the isotopically substituted water dimer structures **1a−1d** at 298 K using a structure optimized with C_s symmetry (Figure 2, Table 1). Using harmonic frequencies, deuterium is predicted to prefer the bridging site in terms of both ΔG° at 298 K and ΔZPVE. On the other hand, while D is predicted to favor the bridging position on the basis of ZPVE in the anharmonic approximation, it is predicted to occupy the nonbridging position of the hydrogen bond donor water molecule by ca. 139 cal/mol in terms of ΔG°. The source of this preference change is due to a rather large (and presumably incorrect) difference in the computed entropy for the nonbridging position of the donor compared

TABLE 2. Comparison of Computed Thermodynamic Parameters for Monodeuterated Cyclohexane (2) at 298.15 K and 1 atm[a] (D_{3d} Structure Was Optimized with Very Tight Convergence Criteria (opt = vtight) and Used As the Input File for Frequency/Thermochemical Calculations)

H_{ax}

H_{eq}

2a: eq=D
2b: ax=D

parameter	2a	2b	2a	2b
	harmonic[b]		anharmonic[c]	
	MP2 6-31G(d,p)		MP2 6-31G(d,p)	
H° (kcal/mol)	108.072	108.075	110.894	110.882
S° (cal/mol K)	71.702	71.708	71.114	71.121
G° (kcal/mol)	86.694	86.695	89.691	89.677
ΔG° (kcal/mol)	0.000	0.001	0.000	−0.014
ZPE (kcal/mol)	108.774	108.775	106.701	106.687
ΔZPE (kcal/mol)	0.000	0.001	0.000	−0.014
	B3LYP 6-31G(d,p)		B3LYP 6-31G(d,p)	
H° (kcal/mol)	106.146	106.150	329.732	313.217
S° (cal/mol K)	72.188	72.070	62.132	62.113
G° (kcal/mol)	84.660	84.662	311.208	294.698
ΔG° (kcal/mol)	0.000	0.003	0.000	−16.510
ZPE (kcal/mol)	101.791	101.794	327.366	310.851
ΔZPE (kcal/mol)	0.000	0.003	0.000	−16.515
	HF 6-31G(d,p)		HF 6-31G(d,p)	
H° (kcal/mol)	104.812	104.816	114.486	114.491
S° (cal/mol K)	72.188	72.194	72.660	72.670
G° (kcal/mol)	83.289	83.292	92.823	92.824
ΔG° (kcal/mol)	0.000	0.003	0	0.002
ZPE (kcal/mol)	100.433	100.435	110.428	110.428
ΔZPE (kcal/mol)	0.000	0.002	0.000	0.000
	MP2 6-311G(d,p)			
H° (kcal/mol)	106.877	106.884		
S° (cal/mol K)	71.999, 75.560[d]	72.007, 75.568[d]		
G° (kcal/mol)	85.412	85.413		
ΔG° (kcal/mol)	0.000	0.003		
ZPE (kcal/mol)	102.529	102.533		
ΔZPE (kcal/mol)	0	0.004		

[a]Experimental ΔG° (298 K) = +0.0061 ± 0.0021 kcal/mol = $-RT\ln([2b]/[2a])$; refs 24−26. [b]Scaled harmonic frequencies (HF 6-31G(d,p) = 0.90, B3LYP 6-31G(d,p) = 0.97, MP2 6-31G(d,p) = 0.96). [c]Anharmonic frequencies. [d]Entropy computed with $\sigma = 1$ (C_s); all other values in this table are taken from the default Gaussian output and have been computed with $\sigma = 6$ (D_{3d}).

with the other positions (**1b** 74.869 vs **1a** 73.865 and **1c/d** 73.948 cal mol^{-1} K^{-1}, Table 1).

While the accuracy of one of the entropy values computed using the anharmonic approach remains in question for the water dimer, the harmonic calculations suggest that entropy plays a role in determining isotopic preferences in hydrogen-bonded systems. For example, if we compare the results from scaled harmonic MP2 6-31G(d,p) frequency calculations, the computed enthalpies follow the same trend as the ZPVEs, which is expected as both terms are a function of the vibrational frequencies. The computed entropies all serve to decrease the importance of the enthalpic contribution to the free energy difference by significant amounts for each of the isotopomers. The entropy for the isotopomer with deuterium at the bridging position is lower than that of the other two isotopomers by ca. 0.2 cal mol^{-1} K^{-1}. Scheiner and Čuma found a similar result in their calculations of the water dimer and discussed these entropic differences as vibrational in origin.[15] We find the difference arises primarily from the rotational contribution to the entropy (Table 1).

S_{rot} has an inverse dependence upon the rotational temperatures, and the D-bridged isotopomer has larger computed rotational temperatures and accordingly has a smaller computed entropy. It is worthwhile noting that none of these entropy differences are due to the aforementioned issue with Gaussian not properly handling symmetry number differences, as the deuterated water dimers **1a**−**1d** are either C_s or C_1 and thus all structures have $\sigma = 1$.

The results obtained for the water dimer prompted us to investigate two additional systems in order to validate EIE predictions based upon harmonic and anharmonic frequency calculations. The systems, cyclohexane-*d* (**2**) and 5,5-dimethyl-1,3-dioxane-2-*d* (**3**), were selected on the basis of their having accurately determined equilibrium isotope effects of different orders of magnitude. These are also molecules in which the equilibrium isotope effect is largely governed by high-frequency bond stretching effects. Accordingly, the inclusion of anharmonicity should not be as important and either computational approach should, in principle, provide reasonable predictions. Experimental studies

TABLE 3. Comparison of Computed Thermodynamic Parameters for Monodeuterated Dioxane 3 at 298.15 K and 1 atm[a] (C_s Structure Was Optimized with Very Tight Convergence Criteria (opt = vtight) and Used As the Input File for Frequency/Thermochemical Calculations)

3a: eq=D
3b: ax=D

parameter	3a	3b	3a	3b
	harmonic[b]		anharmonic[c]	
	MP2 6-31G(d,p)		MP2 6-31G(d,p)	
H° (kcal/mol)	114.296	114.356	117.266	117.285
S° (cal/mol K)	85.688	85.692	84.933	84.940
G° (kcal/mol)	88.749	88.808	91.943	91.960
ΔG° (kcal/mol)	0.000	0.059	0.000	0.017
ZPE (kcal/mol)	108.619	108.678	111.711	111.728
ΔZPE (kcal/mol)	0.000	0.058	0.000	0.017
	B3LYP 6-31G(d,p)		B3LYP 6-31G(d,p)	
H° (kcal/mol)	112.363	112.429	114.201	114.216
S° (cal/mol K)	86.411	86.417	85.062	85.069
G° (kcal/mol)	86.600	86.664	88.840	88.853
ΔG° (kcal/mol)	0.000	0.064	0.000	0.012
ZPE (kcal/mol)	106.585	106.649	108.611	108.626
ΔZPE (kcal/mol)	0.000	0.064	0.000	0.014
	HF 6-31G(d,p)		HF 6-31G(d,p)	
H° (kcal/mol)	111.801	111.849	121.785	121.876
S° (cal/mol K)	86.411	86.417	83.886	83.903
G° (kcal/mol)	86.079	86.127	96.775	96.861
ΔG° (kcal/mol)	0.000	0.048	0.000	0.086
ZPE (kcal/mol)	106.045	106.092	116.434	116.520
ΔZPE (kcal/mol)	0.000	0.048	0.000	0.086

[a]Experimental $\Delta G°$ (298 K) = +0.049 ± 0.003 kcal/mol = $-RT\ln([3b]/[3a])$; ref 27. [b]Computed using scaled harmonic frequencies (HF 6-31G(d,p) = 0.90, B3LYP 6-31G(d,p) = 0.97, MP2 6-31G(d,p) = 0.96). [c]Computed using anharmonic frequencies.

of cyclohexane-*d* in the liquid phase have revealed that deuterium prefers the equatorial position by 6.1 ± 2.1 cal/mol at room temperature.[24−26] The origin of the EIE is mainly due to the larger stretching force constant associated with the equatorial bond. In the liquid phase, the equatorial preference in 5,5-dimethyl-1,3-dioxane-2-*d* is larger, 49 ± 3 cal/mol. This is because the axial bond is weakened as a result of n−σ* donation by the adjacent oxygen lone pairs.[27]

The computational results for cyclohexane-*d* are compiled in Table 2, and a representative optimized geometry is shown in Figure 2. The equatorial preference for deuterium in **2** is correctly predicted by each of the harmonic calculations (HF, DFT, and MP2), with the free energy differences falling in the range of 1−3 cal/mol.[28] The anharmonic predictions are far less consistent. The anharmonic MP2 6-31G(d,p)

calculation predicts that deuterium prefers the axial bond in terms of both $\Delta G°$ and ΔZPVE by 14 cal/mol. There is something very wrong with the B3LYP free energy and zero-point energy calculations, both of which predict an axial preference by 16 kcal/mol! This result, clearly spurious, was replicated with several independent calculations. The source of this large difference is the computed enthalpy. Of the three anharmonic calculations, only the HF 6-31G(d,p) $\Delta G°$ calculation gave a result in nominal agreement with experiment, although this calculation also incorrectly predicts no ZPVE difference between the axial and equatorial isotopomers. Because unlabeled cyclohexane has high symmetry (D_{3d}, $\sigma = 6$), the Gaussian entropy calculation for the mono-deuterated species (C_s, $\sigma = 1$) is in error. The magnitude of this discrepancy, which is about 3.5 cal mol^{-1} K^{-1}, was determined by an independent calculation, and the correct values are shown for the harmonic MP2 6-311G(d,p) calculation in Table 2. Of course, the entropy difference between **2a** and **2b** is unaffected by this error.

Predictions of the equilibrium isotope effect in 5,5-dimethyl-1,3-dioxane-2-*d* (**3**, Table 3, Figure 2) followed the same general pattern as that observed for cyclohexane. The scaled harmonic calculations gave the correct sign and magnitude for the free energy differences (59, 64, and 48 cal/mol for the

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(28) For previous ab initio computational studies of cyclohexane-*d*, see: (a) Williams, I. H. *J. Chem. Soc., Chem. Commun.* **1986**, 627. (b) Kopelevich, M. Ph.D. Dissertation. University of California at Los Angeles, **1989**. (c) O'Leary, D. J. Ph.D. Dissertation. University of California at Los Angeles, **1991**.

MP2, B3LYP, and HF approaches, respectively). These values were in fairly good agreement with the experimental value, 49 ± 5 cal/mol.[27] Because of the small entropy differences between isotopomers, the free energy differences closely mirror the ZPVE differences. The anharmonic predictions of 17, 12, and 86 cal/mol (MP2, B3LYP, and HF) were consistent with the experimental measurement in terms of the sign, but two of the three approaches (MP2 and B3LYP) underestimated the isotope effect while HF overestimated the effect.

Studies of Isotope Effects in a Rigid 1,4-Diol. As was mentioned earlier, previous experimental studies have qualitatively established that deuterium prefers the bridging hydrogen bond position in 1,3- and 1,4-diols dissolved in apolar solvents such as CD_2Cl_2 and benzene-d_6.[6,7] Here, we report a quantitative estimate of the isotope effect for diol **4** dissolved in dry CD_2Cl_2 at room temperature. Estimates in a solvent such as this are amenable for comparison with theoretical predictions, as CD_2Cl_2 is a relatively noninteracting solvent and should be a reasonable approximation of the gas phase. Quantitative isotopic perturbation measurements rely upon being able to access accurate values of the limiting parameters (chemical shifts or coupling constants) whose average is perturbed by the presence of isotopes. In the case of isotopic perturbation of proton chemical shifts of hydroxyl substituents in diols, these limiting chemical shifts are often difficult to determine because of the highly sensitive nature of hydroxyl resonances. Proton chemical shifts of hydroxyl substituents are notoriously dependent upon concentration, the presence of exchange catalysts, moisture, and temperature. To minimize these issues, we worked with a dilute solution of partially deuterated diol **4** and monobenzyl ether alcohol **5** in a J-Young NMR tube containing CD_2Cl_2, neutral alumina, and 3 Å molecular sieves. As shown in Figure 3, these conditions provided sharp hydroxyl resonances and a measurement of the isotope shift (−57 ppb) and a simultaneous estimate of the limiting chemical shifts for the interior and exterior OH groups. In alcohol **5**, the OH group has a vicinal ^3J coupling constant of 12.148 Hz, which suggests it resides preferentially in the interior conformation and antiperiplanar to the vicinal proton. Its chemical shift of 5.480 ppm is therefore taken as an estimate of the interior position. The chemical shift of the exterior position can be estimated on the basis of assuming the proton chemical shift of hydroxyl substituents of the OH/OH diol isotopologue is the average of the inside and outside chemical shifts. The perturbation of the equilibrium can be determined with the equation $K = (\Delta\delta' - \Delta)/(\Delta\delta' + \Delta)$, where Δ equals the isotope shift in parts per million and $\Delta\delta'$ equals one-half the chemical shift difference between the interior and exterior sites.[1] For diol **4**, this analysis provided $K = 1.091 \pm 0.001$ ($\Delta G° = -51.5 \pm 0.5$ cal/mol at 298 K). In analyzing the NMR data, we noticed the $^3J_{H-O-C-H}$ coupling constant in monodeuterated diol **4** was measurably smaller (7.233 Hz) than that in the OH/OH isotopologue (7.441 Hz). A decrease in the coupling constant for the OH/OD isotopologue is consistent with the OD group having a preference for the bridging position, as the OH group averages more to the site with the smaller three-bond coupling constant. The perturbation of equilibrium was therefore estimated in an independent manner using the equation $K = (\Delta J' - \Delta)/(\Delta J' + \Delta)$, where Δ equals the isotope shift in J (0.208 Hz) and $\Delta J'$
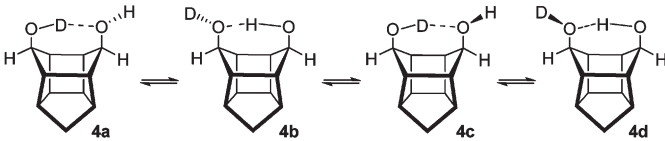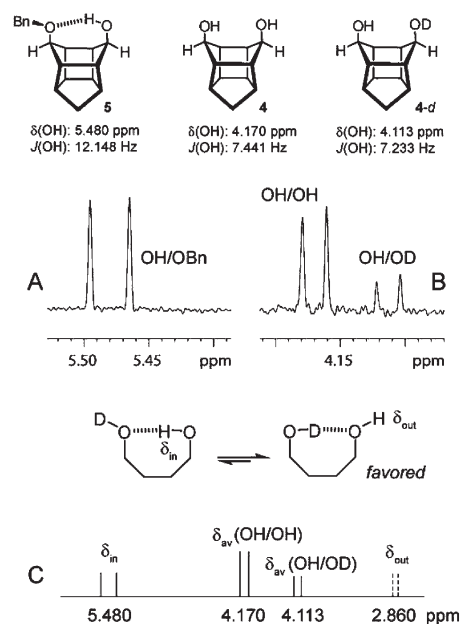

FIGURE 3. ^{1}H NMR spectra (400 MHz) for the hydroxyl resonances of (A) monobenzylated cage alcohol **5** and (B) hydroxyl resonances arising from the OH/OH and OH/OD isotopologues of cage diol **4**. The sample consisted of the two partially deuterated components (0.5 mg/mL) dissolved in an NMR tube containing dry CD_2Cl_2 and 3 Å molecular sieves. The data (256 scans, 0.02 Hz/pt digital resolution) have been processed with Gaussian resolution enhancement (LB = −1.8 Hz, GB = 0.18). The isotope shift in the sample is −57 ppb and arises as a consequence of deuterium having a preference for the bridging position, causing the proton to shift upfield. As shown in (C), monobenzylated cage alcohol **5** provides an estimate of the limiting chemical shift for the interior OH group (5.480 ppm). The limiting chemical shift for the exterior site (2.860 ppm) is estimated by assuming the OH/OH chemical shift for cage diol **4** is the average of the two sites. The isotope shift and the limiting chemical shifts were used to determine the equilibrium isotope effect, which is $K = 1.091 \pm 0.001$ ($\Delta G° = -51.5 \pm 0.5$ cal/mol at 298 K). In a similar manner, the isotopically perturbed coupling constant (7.233 Hz) and the limiting coupling constants were used to provide an independent estimation of the isotope effect, which is $K = 1.092 \pm 0.001$ ($\Delta G° = -52.3 \pm 0.5$ cal/mol at 298 K).

equals one-half the coupling constant difference between the interior and exterior sites (4.707 Hz). These data provided an independent estimation of the isotope effect: $K = 1.092 \pm 0.001$ ($\Delta G° = -52.3 \pm 0.5$ cal/mol at 298 K).

While the two estimates of $\Delta G°$ are in close agreement, it is important to note the difficulty associated with the accuracy of these measurements. There is the obvious problem associated with achieving highly accurate NMR frequencies. This issue is particularly relevant for the value derived from the isotopically perturbed J value. To illustrate another point, the isotope shift shown in Figure 3 (−57 ppb) is larger than the value (−46 ppb) we reported earlier.[7] The difference is due to the amount of water or other hydroxylic solvents present in the samples. In related studies, we have found that residual amounts of hydrogen bonding solvents can serve to decrease isotope shifts in apolar solvents such as CD_2Cl_2, an effect arising from intermolecular hydrogen bonds, which serves to alter the limiting chemical shifts and/or the isotopic preferences.[29]

(29) Anderson, C. E.; Britt, D. K.; Sangji, S.; O'Leary, D. J.; Anderson, C. D.; Rychnovsky, S. D. *Org. Lett.* **2005**, 7, 5721–5723.

TABLE 4. Comparison of Computed Thermodynamic Parameters Using Scaled Harmonic Vibrational Frequencies For Monodeuterated Cage Diol 4 at 298.15 K and 1 atm[a]

parameter	4a	4b	4c	4d
	MP2 6-31G(d,p)[b]			
ΔZPE (kcal/mol)	0.000	0.138	0.017	0.157
$\Delta G°$ (kcal/mol)	0.000	0.084	0.019	0.104
x ($\Delta G°$)[c]	0.272	0.236	0.264	0.228
K, $\Delta G°$ (kcal/mol)[d]	1.153, −0.084			
	B3LYP 6-31G(d,p)[b]			
ΔZPE (kcal/mol)	0.000	0.129	0.023	0.155
$\Delta G°$ (kcal/mol)	0.000	0.073	0.019	0.094
x ($\Delta G°$)[c]	0.270	0.239	0.261	0.230
K, $\Delta G°$ (kcal/mol)[d]	1.134, −0.074			
	HF 6-31G(d,p)[b]			
ΔZPE (kcal/mol)	0.010	0.143	0.000	0.133
$\Delta G°$ (kcal/mol)	0.009	0.092	0.000	0.083
x ($\Delta G°$)[c]	0.276	0.220	0.280	0.224
K, $\Delta G°$ (kcal/mol)[d]	1.150, −0.083			

[a]Experimental $\Delta G°$ (298 K) = −52 ± 0.5 cal/mol for D at the bridging position; this work. [b]Structures optimized at indicated levels of theory and scaled harmonic frequencies (HF 6-31G(d,p) = 0.90, B3LYP 6-31G(d,p) = 0.97, MP2 6-31G(d,p) = 0.96) were used to compute thermodynamic parameters. [c]Mole fractions computed on the basis of $\Delta G°$ values. [d]Equilibrium constant (K) and $\Delta G°$ computed for K = [**4a**][**4c**]/[**4b**][**4d**] using the mole fractions shown.

In our hands, the largest isotope shift for diol **4** in CD$_2$Cl$_2$ is 59 ppb—this value was measured for an NMR tube prepared in a glovebox using a predeuterated sample of **4** dissolved in CD$_2$Cl$_2$ that had been distilled from CaH$_2$ and stored over sieves. In this sample, the J isotope shift was 0.199 Hz ($\Delta G°$ = 50.7 cal/mol). Further work is necessary to define the upper bound of $\Delta G°$ in this system. Until that time, we are content to say that the actual value is no smaller than 50 cal/mol.

A computational study was undertaken to further explore the isotope effect in diol **4**. Representative optimized structures are shown in Figure 2. As shown in Table 4, there are four possible monodeuterated conformers of diol **4** containing hydrogen bonds. The structural difference between **4a** with **4c** (and with **4b** and **4d**) is that the orientation of the acceptor OH group is syn to the five-membered ring in one case and syn to the four-membered ring in the other. The overall preference for deuterium occupying the bridging position can be determined by consideration of the predicted enthalpies, entropies, and zero-point vibrational energies for each isotopomer. The structures and vibrational frequencies were computed with HF, B3LYP, and MP2 theory utilizing 6-31G(d,p) basis sets, and the thermodynamic preferences for deuterium at each position are compiled in Table 4.[30] The values derived from scaled harmonic frequency calculations are found to be consistent across the theoretical approaches and basis set selection: deuterium is predicted to prefer the bridging position by 74−84 cal/mol in terms of $\Delta G°$ and
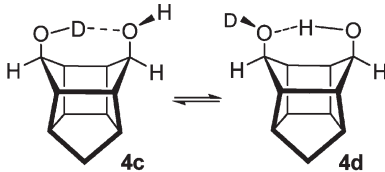
130 cal/mol or more in terms of ΔZPVE. The sign and general magnitude of the predicted values are in qualitative agreement with the two experimental estimates.

As discussed earlier in the context of the water dimer, when $\Delta G°$ < ΔZPVE it is usually a hallmark for entropic contributions which reduce the relative contribution of enthalpy to the free energy difference. A dissection of the translational, rotational, and vibrational contributions to the entropy reveals that the primary entropy difference in isotopomers of **4** can be traced to S_{vib}. For example, using the scaled MP2 6-31G(d,p) frequencies for **4a** (D inside), we find 89.946 cal mol^{-1} K^{-1} (S_{tot}) = 41.455 (S_{tr}) + 30.011 (S_{rot}) + 18.480 (S_{vib}), whereas for **4b** (D outside), it is 90.164 cal mol^{-1} K^{-1} (S_{tot}) = 41.455 (S_{tr}) + 30.026 (S_{rot}) + 18.682 (S_{vib}). The largest difference in entropy between the two conformers is in the S_{vib} term. This is in contrast to the water dimer, where the calculations identified S_{rot} as the primary contributor to entropic differences between isotopomers. This result is not surprising, as diol **4** is a much larger molecule in comparison with the water dimer. In a larger molecule, deuterium would not be expected to significantly alter the rotational moments of inertia, but the site it occupies does appear to significantly affect S_{vib}.

For diol 4, S_{vib} is predicted to be largest when deuterium occupies the nonbridging position. This prediction makes qualitative sense because S_{vib} increases as the number of low-frequency vibrational modes becomes larger. The torsional mode for the exterior OH bond is a significantly lower frequency mode in comparison with the interior position: ν_{in} = 707.8 cm^{-1}, ν_{out} = 349.9 cm^{-1} (unscaled MP2 6-31G(d,p) frequencies for the unlabeled compound). When deuterium occupies the exterior position, therefore, it provides

(30) Data using 6-311G+(d,p) basis sets with the HF, B3LYP, and MP2 levels of theory are very similar to those given in Table 4.

TABLE 5. Comparison of Computed Thermodynamic Parameters Utilizing Scaled Harmonic and Anharmonic Frequencies for Monodeuterated Cage Diol 4 at 298.15 K and 1 atm (C_1 Structure Was Optimized with Very Tight Convergence Criteria (opt = vtight) and Used As the Input File for Frequency/Thermochemical Calculations)
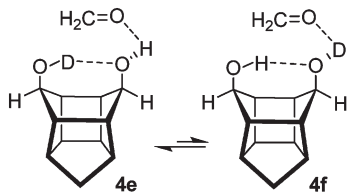

parameter	4c	4d	4c	4d
	harmonic MP2 6-31G(d,p)[a]		anharmonic MP2 6-31G(d,p)[b]	
$\Delta G°$ (kcal/mol)	0.000	0.085	0.000	0.117
ΔZPE (kcal/mol)	0.000	0.140	0.000	0.127
$\Delta G°$ (kcal/mol)[c]	0.000	0.085		
	B3LYP 6-31G(d,p)[a]		B3LYP 6-31G(d,p)[b]	
$\Delta G°$ (kcal/mol)	0.000	0.075	0.000	0.055
ΔZPE (kcal/mol)	0.000	0.133	0.000	0.127
	HF 6-31G(d,p)[a]		HF 6-31G(d,p)[b]	
$\Delta G°$ (kcal/mol)	0.000	0.083	0.000	0.078
ΔZPE (kcal/mol)	0.000	0.133	0.000	0.127

[a]Scaled harmonic frequency analysis (HF 6-31G(d,p) = 0.90, B3LYP 6-31G(d,p) = 0.97, MP2 6-31G(d,p) = 0.96). [b]Anharmonic frequency analysis. [c]Computed using scaled harmonic frequencies and the Bigeleisen−Mayer formalism. The contributions to $\Delta G°$ computed in this manner are $\Delta G°_{VP}$ = −5 cal/mol, $\Delta G°_{ZPVE}$ = 140 cal/mol, and $\Delta G°_{EXC}$ = −50 cal/mol.

an even lower vibrational frequency, which is thermally excited and makes a larger contribution to S_{vib} in comparison with isotopic substitution at the bridging position. The vibrational and rotational entropic effects, which at 298 K favor deuterium at the exterior position by 60 cal/mol ($T\Delta S_{vib}$) and 5 cal/mol ($T\Delta S_{rot}$), respectively, serve to counteract the computed enthalpic preference (148 cal/mol) of deuterium for the bridging position.

We have thus far analyzed and discussed diol **4** using results obtained with the thermochemistry subroutine in Gaussian, which uses the standard harmonic oscillator−rigid rotor approximation for computing thermodynamic quantities.[21,31] Many investigators prefer to use the Bigeleisen−Mayer formalism[32,33] and implementations of it such as the Saunders−Wolfsberg QUIVER program[34] to compute the separate components (K_{ODin}/K_{ODout} = VP × EXC × ZPE; symmetry term excluded) of the reduced partition function using computed vibrational frequencies. As shown in Table 5 for the **4c/4d** diol equilibrium, the Bigeleisen−Mayer equation using scaled MP2 6-31G(d,p) harmonic frequencies yields the same prediction as the Gaussian thermochemistry calculations: deuterium prefers the bridging position with $\Delta G°_{298}$ = 85 cal/mol, and Bigeleisen contributions $\Delta G°_{VP}$ = −5 cal/mol, $\Delta G°_{ZPVE}$ = 140 cal/mol, and $\Delta G°_{EXC}$ = −50 cal/mol. The

(31) Laurendeau, N. M. *Statistical Thermodynamics: Fundamentals and Applications*; Cambridge University Press: New York, 2005.
(32) Bigeleisen, J.; Wolfsberg, M. *Adv. Chem. Phys.* **1958**, *1*, 15.
(33) Bigeleisen, J.; Goeppert-Mayer, M. *J. Chem. Phys.* **1947**, *15*, 261.
(34) Saunders, M.; Ladig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989.

TABLE 6. Comparison of Computed Thermodynamic Parameters Utilizing Scaled Harmonic Frequencies for Monodeuterated Cage Diol−Formaldehyde Complex at 298.15 K and 1 atm (Structure Was Optimized with Very Tight Convergence Criteria (opt = vtight) and Used As the Input File for Frequency/Thermochemical Calculations)

parameter	4e	4f
	HF 6-31G(d,p)[a]	
$\Delta G°$ (kcal/mol)	0.000	0.038
ΔZPE (kcal/mol)	0.000	0.048
	B3LYP 6-31G(d,p)[a]	
$\Delta G°$ (kcal/mol)	0.000	0.018
ΔZPE (kcal/mol)	0.000	0.027
	MP2 6-31G(d,p)[a]	
$\Delta G°$ (kcal/mol)	0.000	0.016
ΔZPE (kcal/mol)	0.000	0.024

[a]Scaled harmonic frequency analysis (HF 6-31G(d,p) = 0.90, B3LYP 6-31G(d,p) = 0.97, MP2 6-31G(d,p) = 0.96).

agreement in the predicted $\Delta G°$ values between the two approaches is more than satisfactory, and the dissection of

TABLE 7.   Comparison of Computed Thermodynamic Parameters Utilizing Scaled Harmonic and Anharmonic Frequencies for Monodeuterated Methyl 2,6-Dihydroxybenzoate 6 at 298.15 K and 1 atm (Structure Was Optimized with Very Tight Convergence Criteria (opt = vtight) and Used As the Input File for Frequency/Thermochemical Calculations)

parameter	6a	6b	6a	6b
	harmonic B3LYP 6-31G(d)[a]		anharmonic B3LYP 6-31G(d)[b]	
H° (kcal/mol)	101.367	101.382	100.311	100.371
S° (cal/mol K)	100.633	100.748	98. 334	98. 432
ΔG° (kcal/mol)	0.000	−0.020	0.000	0.031
ΔZPE (kcal/mol)	0.000	0.000	0.000	0.048
MP2 6-31G(d,p)				
ΔG° (kcal/mol)	0.000	−0.013		
ΔZPE (kcal/mol)	0.000	0.008		
HF 6-31G(d,p)				
ΔG° (kcal/mol)	0.000	−0.002		
ΔZPE (kcal/mol)	0.000	0.017		

[a]Unscaled harmonic frequency analysis. [b]Anharmonic frequency analysis.

the contributions is as expected: The Bigeleisen−Mayer VP (vibrational product) term replaces the Bigeleisen−Mayer mass and moment of inertia (MMI) term after application of the Redlich−Teller product rule,[35] and its sign and magnitude is similar to $T\Delta S_{rot}$, which is itself dependent on the rotational constants. The size and sign of the Bigeleisen−Mayer EXC (excitation) term, −50 cal/mol, is fairly close to $T\Delta S_{vib}$ (−60 cal/mol). Both the EXC term and ΔS_{vib} account for thermally excited low-vibrational modes, so this outcome is to be expected. The Bigeleisen−Mayer ZPVE (zero-point vibrational energy) term is expected to closely mirror any enthalpy differences, and the calculations meet this expectation.

The correlation of the MMI/VP and EXC terms with entropic contributions and the ZPE term with enthalpic contributions has been previously pointed out by Parkin et al. in their studies of isotope effects in metal hydrides. Like intra- and intermolecular OH/OH hydrogen bonds, equilibrium isotope effects in these systems are also governed by low-frequency vibrational modes.[36] The interplay of the EXC and ZPE terms has been likewise discussed by Perrin, Houk, and Kresge[37,38] in their studies of kinetic isotope effects in C−N bond rotation, another case in which low-frequency vibrational frequencies make large contributions to the isotope effect.

A comparison of $\Delta G°$ and $\Delta ZPVE$ for the **4c/4d** equilibrium using scaled harmonic and anharmonic

Gaussian-derived thermochemistry is provided in Table 5. The anharmonic predictions for this system generally capture the correct sign and magnitude of the isotope effect, but it should be noted that anharmonic frequency calculations for even medium-sized molecules are time-intensive endeavors. For example, each isotopomer requires a separate and sometimes lengthy calculation. On a Hewlett-Packard BL2×220c G5 blade containing 8 Intel Xeon CPU cores running at 2.83 MHz with 16 GB of RAM, the run times were MP2/6-31G(d,p), 50.9 d using 7 processors; B3LYP/6-31G(d,p), 4.5 d using 4 processors; HF/6-31G(d,p), 0.9 d using 4 processors.

As was mentioned earlier, experiments have shown that deuterium isotope effects on ^{1}H chemical shifts for **4** are strongly influenced by solvent. For example, isotope shifts of −12 and 0 ppb were measured for **4** dissolved in DMSO-d_6 and pyridine-d_5, respectively.[7] This reduction in the isotope shift can be attributed to deuterium gaining a preference for the intermolecular solvent hydrogen bond and to the limiting chemical shifts changing their low-field and upfield character. We were interested to see if calculations would predict a change in preference of deuterium to the intermolecular hydrogen bond in a complex of diol **4** with formaldehyde, selected as a model hydrogen bond acceptor. The calculations, compiled in Table 6, do not predict a complete site preference change but instead find a reduced ($\Delta G° = 16−38$ cal/mol) preference for the intramolecular bridging position relative to the noncomplexed diol ($\Delta G° = 73−84$ cal/mol).

Studies of Isotope Effects in 2,6-Dihydroxyaromatics. Structures are calculated for diols **6−8** (Figure 2) using a variety of computational approaches. For diols **7** and **8**, these calculations have also been extended to formaldehyde

(35) McLennan, D. J. In *Isotopes in Organic Chemistry*; Buncel, E. E., Lee, C. C., Eds.; Elsevier: New York, 1987; Vol. 7, Chapter 6.

(36) Janak, K. E.; Shin, J. H.; Parkin, G. *J. Am. Chem. Soc.* **2004**, *126*, 13054.

(37) Perrin, C. L.; Thoburn, J. D.; Kresge, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 8800.

(38) Olson, L. P.; Li, Y.; Houk, K. N.; Kresge, A. J.; Schaad, L. J. *J. Am. Chem. Soc.* **1995**, *117*, 2992.

TABLE 8. Comparison of Computed Thermodynamic Parameters Utilizing Scaled Harmonic and Anharmonic Frequencies for Monodeuterated 2,6-Dihydroxyacetophenone 7 and Its Formaldehyde Complex at 298.15 K and 1 atm (Structures Were Optimized Using the Indicated Basis Sets and Used As the Input File for Frequency/Thermochemical Calculations)

7a: X = nothing
7c: X = H$_2$C=O
7b: X = nothing
7d: X = H$_2$C=O

parameter	7a	7b	7a	7b
	harmonic		anharmonic	
X = nothing	B3LYP 6-31G(d)[a]		B3LYP 6-31G(d)[b]	
H° (kcal/mol)	97.012	97.096	96.080	96.102
S° (cal/mol K)	95.012	95.337	95.253	95.554
ΔG°$_{298}$ (kcal/mol)	0.000	−0.013	0.000	−0.068
ΔZPE (kcal/mol)	0.000	0.052	0.000	−0.010
	MP2 6-31G(d,p)			
ΔG°$_{298}$ (kcal/mol)	0.000	0.011		
ΔZPE (kcal/mol)	0.000	0.083		
	HF 6-31G(d,p)			
ΔG°$_{298}$ (kcal/mol)	0.000	0.058		
ΔZPE (kcal/mol)	0.000	0.120		
parameter	7c	7d	7c	7d
X = H$_2$C=O	B3LYP 6-31G(d)[a]		B3LYP 6-31G(d)[b]	
H° (kcal/mol)	118.021	117.966	116.790	116.702
S° (cal/mol K)	119.787	119.857	120.509	120.488
ΔG°$_{298}$ (kcal/mol)	0.000	−0.076	0.000	−0.082
ΔZPE (kcal/mol)	0.000	−0.069	0.000	−0.096
	MP2 6-31G(d,p)			
ΔG°$_{298}$ (kcal/mol)	0.000	−0.058		
ΔZPE (kcal/mol)	0.000	−0.052		
	HF 6-31G(d,p)			
ΔG°$_{298}$ (kcal/mol)	0.000	−0.002		
ΔZPE (kcal/mol)	0.000	0.009		

[a]Unscaled harmonic frequency analysis. [b]Anharmonic frequency analysis.

complexes in a manner discussed earlier. Representative optimized geometries are shown in Figure 2. The computed EIEs are compiled in Tables 7, 8, and 9.

For **6**, the experimentally observed favored isotopomer (D bridged with the ether-type oxygen of the ester group)[18] is predicted to be slightly preferred in terms of ΔG° (2−20 cal/mol) in the harmonic approximation. In all cases, the entropic contributions are decisive (Table 7). The harmonic ZPVE differences predict the opposite site preference, although the energy differences are again quite small (0−17 cal/mol). The B3LYP anharmonic calculation predicts a reasonably strong preference (ΔG° = 31 cal/mol) for deuterium occupying the position bridging with the ester carbonyl group.

For diol **7**, we see a more complex pattern (Table 8). The harmonic and anharmonic B3LYP calculations predict that deuterium prefers the nonbridging position, in agreement with experiment.[17] However, this preference is not maintained in the harmonic MP2 or HF calculations. Again, the entropic contribution is decisive (Table 8). When diol **7** is complexed with formaldehyde, deuterium is predicted to prefer the intermolecular hydrogen bonding site in terms of ΔG° at all levels of theory. ΔH° and ΔS° point in this case in the same direction. ΔZPVE follows the same behavior with

the exception of the HF calculation, where the ΔG° prediction is small (9 cal/mol).

For diol **8** in the harmonic approximation, deuterium is predicted to prefer the intramolecular hydrogen bonding site at all levels of theory and in terms of both ΔG° and ΔZPVE (Table 9). The ΔG° values are found to be reduced in magnitude relative to ΔZPVE, indicative of entropic contributions. In this case, no experimental results are available. The anharmonic B3LYP calculation predicts a preference for the nonbridging position according to ΔG° and a small ΔZPVE preference for the intramolecular hydrogen bond. When diol **7** is complexed with formaldehyde, deuterium is preferred to occupy the intermolecular hydrogen bond in the harmonic B3LYP and MP2 calculations of ΔG° and ΔZPVE; the HF calculation predicts the opposite. The anharmonic B3LYP calculation gave a result that again seems questionable: that deuterium prefers the intramolecular hydrogen bond by 404 cal/mol in terms of ΔG°, whereas the intermolecular site is preferred (57 cal/mol) on the basis of ΔZPVE. Relative to the other calculations on this system, these values appear to be in error, and an inspection of the contributions to ΔG° reveals that the computed entropies are again in error (data not shown).

TABLE 9. Comparison of Computed Thermodynamic Parameters Utilizing Scaled Harmonic and Anharmonic Frequencies for Monodeuterated 2,6-Dihydroxybenzaldehyde 8 at 298.15 K and 1 atm (Structures Were Optimized Using the Indicated Basis Sets and Used As the Input File for Frequency/ Thermochemical Calculations)

8a: X = nothing
8c: X = H₂C=O

8b: X = nothing
8d: X = H₂C=O

parameter	8a	8b	8a	8b
		harmonic		anharmonic
X = nothing	B3LYP 6-31G(d)[a]		B3LYP 6-31G(d)[b]	
H° (kcal/mol)	78.564	78.674	77.866	77.909
S° (cal/mol K)	87.933	88.253	88.282	88.619
$\Delta G°_{298}$ (kcal/mol)	0.000	0.014	0.000	−0.057
ΔZPE (kcal/mol)	0.000	0.081	0.000	0.012
		MP2 6-31G(d,p)		
$\Delta G°_{298}$ (kcal/mol)	0.000	0.038		
ΔZPE (kcal/mol)	0.000	0.110		
		HF 6-31G(d,p)		
$\Delta G°_{298}$ (kcal/mol)	0.000	0.073		
ΔZPE (kcal/mol)	0.000	0.134		

parameter	8c	8d	8c	8d
X = H₂C=O	B3LYP 6-31G(d)[a]		B3LYP 6-31G(d)[b]	
H° (kcal/mol)	99.575	99.548	98.638	98.576
S° (cal/mol K)	112.648	112.703	120.079	118.516
$\Delta G°_{298}$ (kcal/mol)	0.000	-0.043	0.000	0.404
ΔZPE (kcal/mol)	0.000	-0.038	0.000	−0.057
		MP2 6-31G(d,p)		
$\Delta G°_{298}$ (kcal/mol)	0.000	−0.035		
ΔZPE (kcal/mol)	0.000	−0.032		
		HF 6-31G(d,p)		
$\Delta G°_{298}$ (kcal/mol)	0.000	0.014		
ΔZPE (kcal/mol)	0.000	0.024		

[a]Unscaled harmonic frequency analysis. [b]Anharmonic frequency analysis.

Conclusions

Four test molecules revealed several interesting features of the Gaussian thermochemical approach to computing EIEs. For example, the program produces an incorrect calculation of the rotational entropy in cases where isotopic substitution affects the rotational symmetry number. Thermochemical calculations using harmonic ab initio frequencies in the water dimer confirmed earlier theoretical and experimental predictions of a preferred D-bridged structure. The calculations presented here suggest that this preference has a strong enthalpic preference that is diminished by rotational entropic preferences for the nonbridging position. Anharmonic frequency calculations revealed a problem in the entropy calculation of the monodeuterated water dimer isotopomers. In particular, the entropy for the non-D-bridged isotopomer **1b** was predicted to be unusually high relative to the other forms. This large entropy resulted in a predicted free energy preference of D for the nonbridging position. We have not yet attempted to discover the origin of this discrepancy, but it is reasonable to suggest the problem is associated with the calculation of the rovibronic corrections to the rigid rotor/ harmonic oscillator model.

Comparative calculations such as these were extended to EIEs in cyclohexane-*d* and 5,5-dimethyl-1,3-dioxane-2-*d*. For both molecules, the harmonic calculation provided predictions in reasonable agreement with the experimental values. On the other hand, no improvement was realized by using the anharmonic approach. Instead, the anharmonic calculations tended to show less consistency in predicting the magnitude of the EIE, and one of the cyclohexane calculations was severely affected by an error in the enthalpy calculation.

For monodeuterated diol **4**, a harmonic computational study predicts a preferred D-bridged structure, in agreement with experiment. As in the case of the water dimer, entropic contributions were found to diminish the enthalpic preference of D for the bridging position. In diol **4**, however, these are primarily vibrational entropy effects arising from the low-frequency vibrational modes of the nonbridged position. Antagonistic interplays of entropy and enthalpy are well-known in other isotopically perturbed systems, especially those with isotope effects governed by low-frequency vibrational modes. The enthalpy, and translational, rotational, and vibrational entropy components are readily available from Gaussian calculations, and these values have correspondence with the VP, EXC, and ZPE terms computed with the Bigeleisen−Mayer

approach. The inclusion of anharmonicity for EIE calculations of diol **4** gave satisfactory results, although the free energy prediction spanned a larger range (55−117 cal/mol) than did the results obtained with the harmonic approach. Finally, calculations of an intermolecular hydrogen-bonded complex between diol **4** and formaldehyde showed a reduced preference of D for the intramolecular bridging position. This prediction is in qualitative agreement with experimental results.

For the compounds **6**−**8** with intramolecular hydrogen bonds for which the donor and acceptor are linked with a formal double bond, calculations in the harmonic approximation show for the former two that deuterium is preferably at the non-hydrogen bonding position in agreement with experimental findings. This preference is determined by the entropic contribution. Accordingly, use of zero-point energy calculations alone is not useful for predicting isotopic preferences in this type of molecule. For **8**, no experimental data are available, and the calculations predict a preference for deuterium at the intramolecular hydrogen bond position. Complexing **8** and **9** with formaldehyde as a mimick for an intermolecular hydrogen bond resulted in a calculated decrease of preference for deuterium at the intramolecularly hydrogen-bonded position.

In summary, our studies have identified the important and sometimes controlling role of vibrational entropy in intramolecular and intermolecular OH/OH and OH/O=C hydrogen bond isotope effects. The experimental preference of deuterium for the bridging position in diol **4** and the nonbridging position in diol **7** may be explained by considering the relative contributions of enthalpy and entropy in each system. In diol **4**, there is a computed strong enthalpic or ZPVE preference (130−160 cal/mol, harmonic data) of D for the bridging position. This relatively large enthalpic contribution is offset by an entropic preference for the nonbridging position. The D-bridging preference is maintained, and the computed free energy difference is on the order of 70−80 cal/mol. The computed range agrees reasonably well with the experimental estimates of 50 cal/mol. The same situation is computed to be operative in diol **7**, although in this case the enthalpic or ZPVE bridging preference (52−120 cal/mol) is smaller. In calculations predicting a small enthalpic contribution, therefore, the relative contribution of the entropic nonbridging preference can determine the site preference. The antagonistic interplay of entropy and enthalpy in hydrogen-bonded systems is evidenced by the computational studies presented here. It is clear that computational predictions of isotopic site preferences in hydrogen bonds need to be more detailed than simply comparing ZPVE differences. A harmonic approach to the calculation of equilibrium isotope effects remains a much more time-efficient and reliable method for estimating isotope effects in organic molecules.

Experimental Section

Calculations. The calculations reported here utilized Gaussian 03 and Gaussian 03W.[39] Gaussian 03 calculations utilized a grid network consisting of HP (Hewlett-Packard) BL2×220c G5 blades, each containing 8 Intel Xeon CPU cores running at 2.83 MHz with 16 GB of RAM, running the Centos 5.x Linux OS. Gaussian 03W calculations were performed on a Dell Precision PWS 370 workstation containing one Pentium 4 CPU core running at 3.6 GHz with 3 GB of RAM, running Windows XP Professional. To ensure accurate calculation of low frequencies, MP2 and HF geometries were optimized using the opt = tight or opt = vtight keyword. B3LYP geometries were optimized with the opt = vtight keyword and modified integration grids: int(grid = fine), int(grid = ultrafine), or, in some cases, int(grid = 199974).[40]

NMR Measurements. The preparation and characterization of diol **4** and alcohol **5** are reported elsewhere.[7] NMR spectra were recorded at 19 °C on a 400 MHz NMR spectrometer. Each spectrum consisted of 256 scans and was processed in a manner to provide a digital resolution of 0.02 Hz/pt. Partial deuteration of hydroxyl groups was accomplished by careful addition of microliter aliquots of CD_3OD to an NMR tube containing diol **4** dissolved in deuterated methylene chloride, 2−3 molecular sieve (3 Å) pellets, and 20−40 mg of neutral alumina. Isotope shifts were obtained via the spectrometer software peak-picking algorithm, which takes the observed maximum point and fits a parabola through it and its two nearest neighbors. Using the acquisition parameters described above, we estimate the uncertainty in any given measurement to be ±0.1 ppb or ±0.04 Hz at 400 MHz. This estimation was obtained by performing a statistical analysis of the peak-to-peak separation within the five-line ^1H multiplet arising from DMSO-d_5 in a sample of DMSO-d_6.

For the 4-methyl derivative of **8**, it was attempted to measure the isotopic perturbation of equilibrium at ^{13}C chemical shifts by investigating the deuterated compound. This turned out to be impossible as the barrier to rotation at room temperature and temperatures below was too high to allow rotation of the aldehyde group. At −50 °C, two sharp OH resonances were observed at 9.86 and 11.96 ppm.

Supporting Information Available: Optimized geometries for water dimer **1**, cyclohexane **2**, dioxane **3**, cage diol **4a**−**4d**, cage diol−formaldehyde complex **4e,f**, methyl 2,6-dihydroxybenzoate **6**, 2,6-dihydroxyacetophenone **7a,b**, 2,6-dihydroxyacetophenone formaldehyde complex **7c,d**, 2,6-dihydroxybenzaldehyde **8a,b**, 2,6-dihydroxybenzaldehyde formaldehyde complex **8c,d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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