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Unraveling the Electronic and Vibrational Contributions to Deuterium Isotope Effects on ^{13}C Chemical Shifts Using ab Initio Model Calculations. Analysis of the Observed Isotope Effects on Sterically Perturbed Intramolecular Hydrogen-Bonded *o*-Hydroxy Acyl Aromatics

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Abstract: Deuterium isotope effects on chemical shifts, $^{n}\Delta C(OD)$,have been measured in a series of *o*-hydroxy acyl aromatics of the type 2-hydroxyacetophenone (**1**) and 1,3,5-triacetyl-2,4,6-trihydroxybenzene (**3**). $^{2}\Delta C(OD)$ increase as the number of neighboring hydrogen-bonded moieties increase. The calculated molecular ab initio geometries with Density Functional Theory(BPW91/6-31G(d(p)) (5D) with p functions on the chelate protons only) show a large increase in R_{OH} in going from **1** to **3** and a large corresponding decrease in the $C{=}O\cdots H{-}O$ distance. $R_{O\cdots O}$, $A_{OH\cdots O}$, $R_{OH\cdots O}$, as well as R_{OH} and $R_{C=O}$ correlate linearly as do $^{2}\Delta C(OD)$ and $R_{O\cdots O}$. The nuclear shielding[1] and the first derivative of the ^{13}C nuclear shielding with respect to O-H bond stretching, ($d\sigma/dR_{OH}$), has been calculated with the 6-31G(d) (6D) basis set using the GIAO/B(PW91) method (exchange term only). (Chemical shift and nuclear shielding are used intermittently. It should be remembered that they lead to different signs.) The change in the R_{OH} distance upon deuteriation ($\Delta R_{OH(D)}$) was obtained from a potential scan of OH bond stretching and analyzing the data with a fitted Morse function. Isotope effects are calculated as the product of $d\sigma/dR_{OH}$ and $\Delta R_{OH(D)}$. The variations in the calculated $^{2}\Delta C(OD)$ are dominated by $\Delta R_{OH(D)}$. The calculated $^{n}\Delta C(OD)$ correlate well with experimental isotope effects. Three parameters, $^{2}\Delta C(OD)$, $\Delta R_{OH(D)}$, and $R_{O\cdots O}$ all show promise as gauges of hydrogen bond strength. Calculated O*H* and ^{1}H chemical shifts in general show good agreement with experimental values (RMSD = 0.40 ppm) as do the ^{13}C chemical shifts (RMSD = 1.9 ppm). The large experimental $^{2}\Delta C(OD)$ values can be understood in terms of a steric effect caused by the neighboring CH_3CO group leading to shorter $OH\cdots O$ and $O\cdots O$ distances and consequently stronger hydrogen bonds.

Introduction

Over the years much effort has been concentrated on characterization of hydrogen-bonded systems in order to provide parameters to describe hydrogen-bond strength and geometry.[1−6] Intramolecular hydrogen bonding of the resonance assisted (RAHB) type[1−4] as found in *o*-hydroxy acyl aromatics is a very common type of intramolecular hydrogen bond. NMR parameters often used to characterize hydrogen bonds are O*H* chemical shifts, primary isotope effects,[7−9] or secondary deuterium isotope effects on chemical shifts.[10−29] For ^{13}C the latter is defined as $^{n}\Delta C(OD) = \delta C(OH) - \delta C(OD)$. Deuterium isotope effects

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on ^{13}C chemical shifts, $^{n}\Delta$C(OD), have been studied extensively in intramolecular hydrogen-bonded systems[4,10−29] and are shown qualitatively to describe hydrogen-bond strength. The latter is described e.g. by the oxygen−oxygen distance ($R_{\mathrm{O}\cdots\mathrm{O}}$).[30] A weakness so far has been the relatively narrow range of deuterium isotope effect values except in the case of indandiones.[16,22] With the present set of compounds this is now changed. Deuterium isotope effects on chemical shifts have likewise been shown to distinguish "localized" and tautomeric hydrogen-bonded systems,[10,11,15,26,27] and some interesting isotope effects in *o*-hydroxy acyl aromatic compounds in which the acceptor group (RCO) is sterically perturbed previously have been described.[28]

In recent years ab initio methods to calculate nuclear shieldings[31−37] and deuterium isotope effects on nuclear shieldings[38,39] have been developed to a high degree of accuracy and have become generally accessible due to still faster computers and commercial software. Furthermore, the theoretical developments of Jameson[40,41] and Chesnut[42] have made it possible to identify the important contribution to the secondary isotope effect to a product of the first derivative of the nuclear shielding with respect to O−H(D) bond stretching, $d\sigma/dR_{\mathrm{OH}}$, and the change in the average O−H(D) bond length upon deuteriation, $\Delta R_{\mathrm{OH(D)}}$.

The main aim of the present study is to demonstrate that deuterium isotope effect on chemical shifts and especially $^{2}\Delta$C(OD) is a quantitative descriptor of hydrogen-bond strength and how these data are calculated theoretically. A further aim is showing that reliable structures can be obtained and very good ^{1}H and ^{13}C chemical shifts can be calculated in intramolecularly hydrogen-bonded cases.

Experimental Section

Compounds. Compound **2**[49] was synthesized as described but obtained only in a rather low yield from a chromatographic separation on silica gel (eluent: hexane/methylene chloride/methanol, 4:1:1). Compound **3** and its analogues[50] were prepared as described. An elemental analysis gave C: 57.34% and H 4.77% (theoretical C 57.14% and H 4.76%).

Table 1. BPW91/6-31G(d(P)) 5D Calculated Bond Lengths and Angles in **1**−**6**

	1	**2a**	**2b**	**3**	**4**	**5**	**6**
				Bond Length/Å			
$R_{\mathrm{C1-C2}}$	1.437	1.441	1.443	1.444	1.452	1.422	1.438
$R_{\mathrm{C2-O}}$	1.340	1.330	1.326	1.318	1.334	1.335	1.347
$R_{\mathrm{O-H}}$	1.019	1.050	1.045	1.086	1.024	1.022	1.012
$R_{\mathrm{H\cdots O}}$	1.577	1.461	1.467	1.360	1.562	1.566	1.607
$R_{\mathrm{O\cdots O}}$	2.523	2.459	2.452	2.400	2.518	2.515	2.541
$R_{\mathrm{C7=O}}$	1.258	1.268	1.265	1.274	1.259	1.258	1.255
$R_{\mathrm{C1-C7}}$	1.468	1.454	1.469	1.458	1.464	1.470	1.478
				Bond Angle (deg)			
$V_{\mathrm{C1-C2-O}}$	121.7	119.2	121.0	119.0	120.5	123.0	122.3
$V_{\mathrm{C2-O-H}}$	104.4	104.0	103.9	103.7	104.6	103.8	104.5
$V_{\mathrm{O-H\cdots O}}$	152.1	156.2	154.6	157.7	153.2	152.1	151.3
$V_{\mathrm{C7=O\cdots H}}$	102.3	101.1	103.3	102.3	102.0	102.5	102.9
$V_{\mathrm{C1-C7=O}}$	120.7	120.8	119.5	119.5	120.6	120.8	120.4
$V_{\mathrm{C2-C1-C7}}$	118.6	118.6	117.7	117.8	119.1	117.8	118.7
$V_{\mathrm{C1-C7-C8}}$	120.7	121.2	123.1	123.7	121.0	121.0	120.5

NMR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC250 MHz instrument using $CDCl_3$ as solvent except for low-temperature spectra for which CD_2Cl_2 was used. TMS was used as internal reference. ^{13}C NMR spectra were recorded with a spectral resolution of 0.55 Hz/point. COLOC[43] spectra were recorded as described earlier.[24]

Spectra of isotopologues were repeated with different deuterium contents.

Calculations. The molecular geometries were optimized using the Gaussian94 suite of programs[31] and BPW91 Density Functional Theory (DFT) (Beckes exchange[44] and Perdew−Wang correlation terms[45]), and a mix of the built-in Gaussian-type basis sets. The 6-31G(d) (5D) basis set was used at carbon, oxygen, and hydrogen bound to carbon. The 6-31G(d,p) basis set was used at hydrogens bound to oxygen (hydrogen-bonded chelate hydrogens). No symmetry constraints were used in the geometry optimizations, but all calculated structures were essentially flat with **3** converging toward C_{3h} symmetry, **4** and **5** towards C_{2v} symmetry, and **6** toward C_{2h} symmetry. The resulting geometries with some relevant bond lengths and angles are shown in Table 1 and in Scheme 1.

In addition to the compounds shown in Scheme 1, structures of compounds at the same level of calculations are given in Table 1S (Supporting Information): salicylaldehyde (**7**), 1-acetyl-2,4-dihydroxy-3-formylbenzene (**8**), 1-acetyl-2,6-dihydroxy-3-formylbenzene (**9**), 1,3-diformyl-2,4-dihydroxybenzene (**10**), 1,3-diacetyl-5-formyl-2,4-dihydroxybenznene (**11**), 1-acetyl-3,5-diformyl-2,4,6-trihydroxybenene (**12**), and 1,3,5-triformyl-2,4,6-trihydroxybenzene (**13**).

The NMR nuclear shieldings were calculated with the 6-31G(d) (6D) basis set using the GIAO[32,33] method and with the exchange term only on the fully converged molecular orbitals, B(PW91), recently shown to yield superior results relative to the RHF/GIAO method,[46] especially for nuclei other than carbon (Table 2). The correlation between the experimental chemical shifts and the calculated nuclear shielding is shown in Figure 1a,b for ^{1}H and ^{13}C signals, respectively.

The first derivative of the nuclear shielding with respect to the O−H bond lengths ($d^{13}C/dR_{\mathrm{O-H}}$) was calculated simply by shortening the O-H bond by 0.01 Å and recalculating the nuclear shielding. The derivatives of the nuclear shielding with respect to O-H bond length are shown in Scheme 2.

The amount of the O−H bond shortening due to hydroxy deuterium isotope substitution ($\Delta R_{\mathrm{OH(D)}}$) was calculated by scanning the O-H bond in the bond direction at the BPW91/6-31G(d(p)) level in eight increments of 0.05 Å around the equilibrium position, yielding a total

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Scheme 1. BPW91/6-31 G(d(p)) Optimized Structures with Some Relevant Geometric Features (Distances are in Å; $R_{O\cdots O}$ distances in bold.)

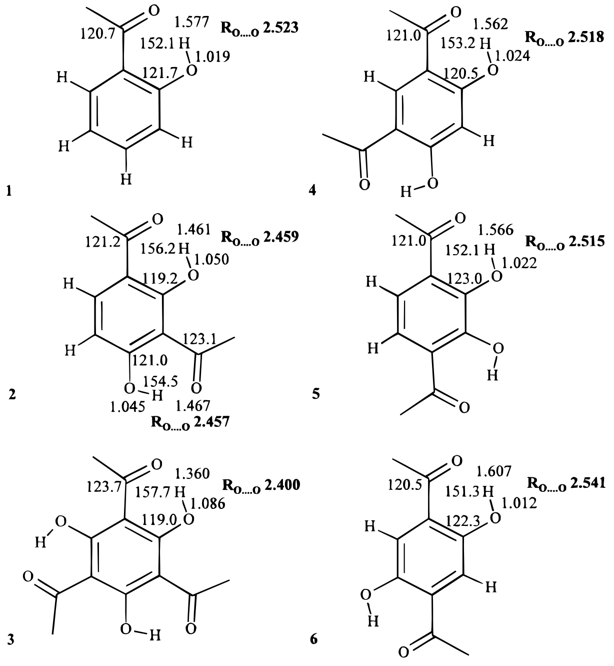

Table 2.

Experimental ^1H Chemical Shifts (δ^1H) (ppm)

	H1	H2	H3	H4	H5	H6
1	2.60	12.26	6.48	7.48	6.90	7.74
2	2.57	14.79	2.78	14.26	6.46	7.82
3	2.73	17.09				
4	2.64	13.09		6.36		8.22

GIAO B(PW91)/6-31G(d) Calculated ^1H Nuclear Shielding (σ^1H) (ppm)

	H1	H2	H3	H4	H5	H6
1	29.51	18.62	25.26	24.75	25.38	24.64
2	29.61	16.25	29.28	16.57	25.91	24.74
3	29.33	14.44				
4	29.58	18.47		26.06		24.46
5	29.51	18.20			25.29	
6	29.45	19.64		25.15		

Experimental Carbon Chemical Shifts ($\delta^{13}C$) (ppm)

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
1	119.6	162.4	118.2	136.3	118.8	130.6	204.5	26.5		
2	112.0	168.2	109.9	170.9	109.6	137.8	202.9	26.2	205.6	33.5
3	103.2	175.7					205.0	32.9		
4	113.6	168.9	105.0			136.2	202.4	26.0		

GIAO B(PW91)/6-31G(d) (6D) Calculated ^{13}C Nuclear Shielding ($\sigma^{13}C$) (ppm)

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
1	76.3	32.7	76.6	61.5	79.0	67.1	−2.8	163.0		
2	82.4	27.7	83.4	26.0	84.7	61.7	0.9	163.8	−3.4	155.8
3	87.8	23.0					−1.6	156.6		
4	81.6	28.8	89.7			63.0	−0.4	163.6		
5	74.6	38.0			79.9		−3.6	162.5		
6	72.0	41.6	76.8				−4.9	162.4		

of nine points. A Morse function was fitted to the points that were below three times the zero-point energy. The O-H bond length perturbation was calculated from the analytical solution to the Morse oscillator,[47,48] using the reduced masses, from a harmonic approximation normal mode analysis (IR frequency calculation). One example of such a potential energy scan is shown in Figure 2. The $\Delta R_{O-H(D)}$ values are

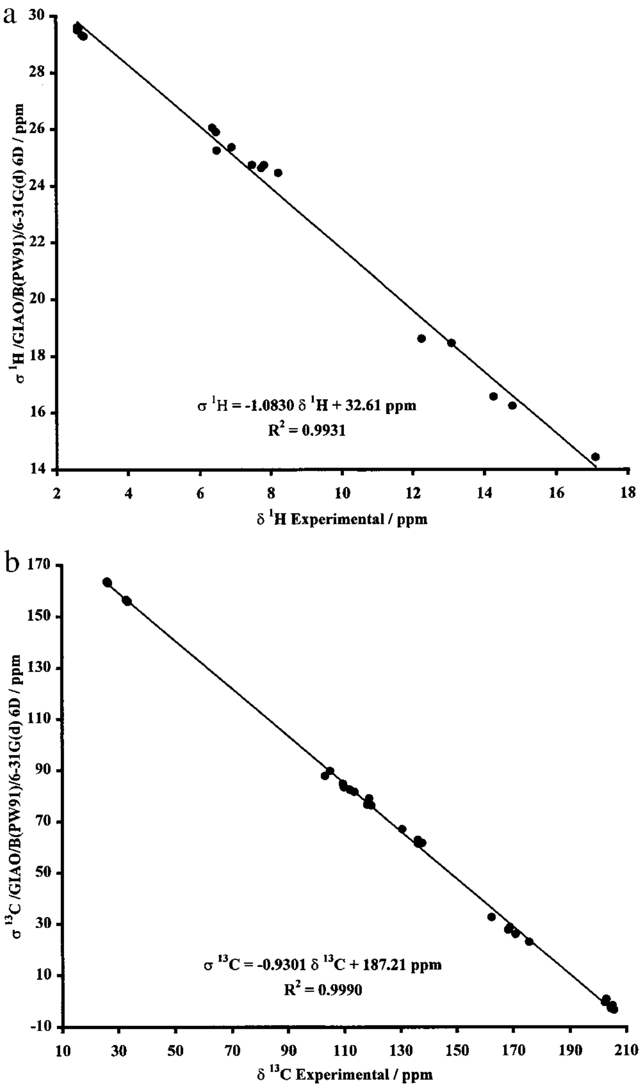

Figure 1. GIAO/B(PW91)/6-31G(d) (exchange term only) calculated nuclear shieldings vs experimental: (a) ^1H and (b) ^{13}C chemical shifts.

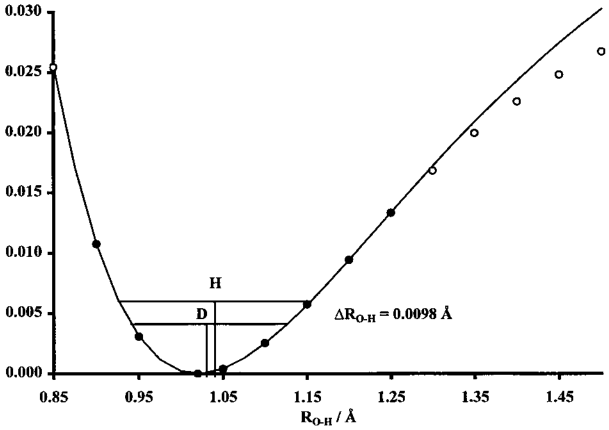

Figure 2. BPW91/6-31G(d(p)) calculated Morse function for O−H hydrogen displacements in the bond direction of **1**, including the average O−H(D) geometry and the zero-point energy for the two isotopologues. Open circles are calculated data not used in the fit.

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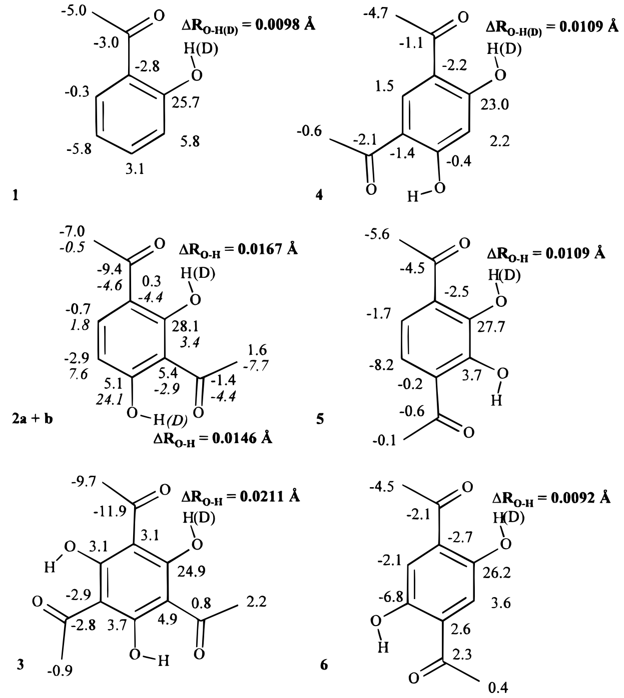
Scheme 2. GIAO/B(PW91)/6-31G(d) Calculated Nuclear Shielding Gradients for O-H ($d^{13}C/dR_{OH}$ are in units of ppm Å^{-1}; numbers in italics refer to **2b**; $\Delta R_{OH(D)}$, in bold.)



given in Scheme 2, and some of the results of the normal mode analysis and the Morse oscillator, in Table 3.

Assignments. The assignment of **2** was achieved by COLOC[43] experiments. ^{13}C chemical shifts are given in Table 2. The assignment of the isotope effects of compounds with more than one exchangeable OH proton was done in the following fashion. The isotope effects in *o*-hydroxy acyl aromatics were grouped into categories as described in refs 15 and 18 and are roughly similar to those of **1** (Scheme 3). As an example, at the methyl group of the *o*-acetyl group, a negative isotope effect proportional to δOH was observed. A very large and unusual four-bond isotope effect, $^4\Delta C(OD)$ is observed in compounds **2** and **3**. This is assigned to $^4\Delta C\text{-}4(OD\text{-}2)$.

Temperature Effects. The deuterium isotope effects on ^{13}C chemical shifts are measured in one-tube experiments with both the protio and the deuterio species present and in varying ratios. A prerequisite for this type of measurement is slow exchange of the OH proton at the NMR time scale.

For **3**, the O*H* resonance was observed at high frequency, 17.09 ppm, and the C-2,C-4,C-6 carbon resonances showed one very large isotope effect (0.72 ppm) and two medium ones (0.229 and 0.186 ppm). Cooling had no effect on the magnitude of the isotope effects, indicating that tautomerism is not at play.

Results

Theoretical calculations. The ab initio geometries show (Scheme 1) that all of the carbons of the structures are in one plane. Furthermore, a large gradual increase in the OH bond length (R_{OH}) and a corresponding large gradual decrease in the C=O···H distance occurred when going from **1** to **2** to **3** with **4** being similar to **1**. The decrease in C=O···H distance is followed by a decrease in $R_{O\cdots O}$ (**1**, 2.523 Å; **4**, 2.518 Å; **2a**, 2.459 Å (steric compression at oxygen), **2b**, 2.457 Å (steric compression at methyl group); **3**, 2.400 Å. Plots of R_{OH}, $R_{C=O}$, and $R_{(O)H\cdots O}$ vs $R_{O\cdots O}$ or $\Delta R_{OH(D)}$ showed good correlation (Figure 3a,b).

A comparison of the calculated structures of **4** and **6** with the low-resolution X-ray structures[53,54] yielded average (RMSD) absolute atomic coordinate differences of 0.027 (0.011) and 0.032Å (0.020), respectively between corresponding heavy atoms in the superimposed geometries. Furthermore, plotting the data of $R_{O\cdots O}$ vs R_{OH} onto the graph of Steiner and Saenger[55] gave data points on the correlation line of that plot.

^{1}H and ^{13}C Chemical Shifts and Derivatives. The ^{1}H and ^{13}C chemical shifts are calculated very well using GIAO B(PW91)/6-31G(d) DFT ab initio methods as seen from Figure 1, which indicates that the quality of the calculated structures including the hydrogen-bond geometry is very good.

The first derivative of the nuclear shielding $d\sigma/dR_{OH}$ was calculated ab initio using the above-mentioned geometries (see Experimental Section) simply by shortening the OH bond 0.01 Å and recalculating the nuclear shielding. The $d\sigma/dR_{OH}$ is nicely correlated to the isotope effects within each compound and is seen not to vary much from compound to compound (Scheme 2 and Figure 4a) except for C-7, for which the $d\sigma/dR_{OH}$ decreased in going from **1** to **2** to **3**. Furthermore, those data for C-7 fall outside the correlation line for all the four compounds (One illustration is given in Figure 4a).

Changes in the Average Bond Length upon Deuteriation. Deuteriation at the OH position will lead to a change in the average OH(D) bond length, and as this vibrational mode is very localized and does not involve significant movement of other atoms in the molecule (Table 3) this will likely be the dominant effect of deuteriation for all other species than **3**. A potential scan of the OH bond stretching as described in the experimental section and shown in Figure 2 is constructed (BPW91/6-31G(d(p)) data). These data are fitted with a Morse function,[47,48] leading to the changes in the OH bond length upon deuteriation $\Delta R_{OH(D)} = R_{OH} - R_{OD}$ as seen in Scheme 2. We have scanned the entire vibrational normal coordinate from a harmonic approximation normal mode analysis for several systems, but the differences between this more rigorous treatment and the values shown here are negligible. To calculate the hydrogen displacement one needs the reduced masses, and we have just used those calculated in the normal mode analysis for OH and OD isotopologues, but again the differences between using the correct value or just values of 1 for H and 2 for D are negligible, except for **3**. The values presented are calculated from the analytical solution to the Morse oscillator.[47,48]

A dramatic increase is found in $\Delta R_{OH(D)}$ in going from **1** to **2** to **3**. Again, values for **4**−**6** are very similar to those of compound **1**. The $\Delta R_{OH-4(D)}$ of O−H4 in **2b** is seen to fall in between the value of **1** and $\Delta R_{OH-2(D)}$ of **2a**. R_{OH} and $\Delta R_{OH(D)}$ correlated well ($R = 0.982$) (Figure 3b).

By knowing the change in the bond length upon deuteriation as just described and the first derivative of the shielding, the isotope effects can be calculated as $d\sigma/dR_{OH} \times \Delta R_{OH(D)}$ (see Discussion). Figure 4b has the derivatives of the nuclear shieldings plotted against the experimental $^n\Delta C(OD)$ values and a plot of the experimental vs calculated isotope effects reveals a very good correlation, which improves when using the normal mode related reduced masses. Although the calculated values are slightly too small it is readily apparent that the slopes for each compound have become much more alike (not shown).

Two-Bond Deuterium Isotope Effects on ^{13}C Chemical Shifts, $^2\Delta C(OD)$. The $R_{O\cdots O}$ are distances correlated with $^2\Delta C(OD)$ ($R = 0.977$).

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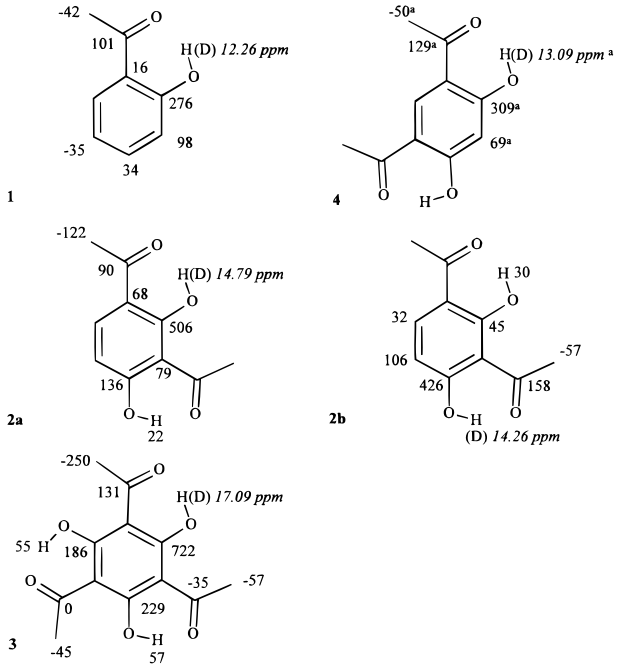
Table 3. O−H(D) Stretching Mode Morse Function Parameters and Normal Mode Analysis Calculated Reduced Masses and Vibrational Frequencies

	1	**2a**	**2b**	**3**	**4**	**5**	**6**
α^a (Å^{-1})	3.2	4.0	3.8	4.0	3.4	3.4	3.2
dissociation energy^a (kJ)	129.0	51.4	63.9	34.6	106.3	106.5	143.1
μ (O−H) reduced masses^b (amu)	1.0743	1.0995	1.0871	1.1385	1.0764	1.0748	1.0693
μ (O−D) reduced masses^b (amu)	2.3061	2.6591	2.5067	4.2013^c	2.3259	2.3137	2.2783
υ (O−H) vibrational frequency^b (cm^{-1})	2873	2420	2506	2049	2808	2838	3008
υ (O−D) vibrational frequency^b (cm^{-1})	2104	1811	1858	1639	2062	2080	2194

[a] From Morse function fitted to O−H bond stretching BPW91/6-3l G(d(p)) 5D potential. [b] BPW91/6-31G(d(p)) 5D harmonic approximation normal-mode analysis calculated values. [c] The higher reduced mass for **3** is caused by coupling of the OD stretch vibration in this compound to other vibrational modes in particular the C═O stretch mode.

Scheme 3. Experimentally Observed Deuterium Isotope Effects on ^{13}C and ^{1}H Chemical Shifts (^{1}H chemical shifts are in italics.)[a]



[a] 230 K in CD$_2$Cl$_2$. $^n\Delta$C(OD) for **2a** at 260 K in CDCl$_3$ C-1, 67 ppb; C-2, 416 ppb; C-4, 63 ppb; C-7, 104 ppb and C-8, −125 ppb. **2b** at 260 K in CDCl$_3$, C-2, 136 ppb; C-3, 86 ppb; C-4, 485 ppb; C-5, 124 ppb; C-6, 32 ppb; C-9, 159 ppb and C-10, −85 ppb. **3** at 250 K in CD$_2$Cl$_2$, C-2, 724 ppb.

A comparison of $^2\Delta$C-2(OD) of **1**−**4** revealed that **1** and **4** are very similar, but the values for **2** had increased dramatically and even more so for **3**. The increase from **1** to **2** to **3** can be ascribed to steric compression (see Discussion) leading to a shorter $R_{\mathrm{O\cdots O}}$ and hence to a long R_{OH} and short $R_{\mathrm{OH\cdots O}}$ distances. A small steric effect was found in 3,5-di-*tert*-butyl-2-hydroxyacetophenone,[10] and a large one also in the *tert*-butyl derivative, 2-pivaloyl-1,3-indandione.[16,22]

$^n\Delta$C(OD). A comparison of the long-range isotope effects showed a very large four-bond effect, $^4\Delta$C-2(OD-4) in **2** and **3**. Another significant observation is the rather small $^4\Delta$CO-(OD-2) observed parallel with $^5\Delta$CH$_3$(OD-2) became more and more negative.

Steric Effects. The decrease in $R_{\mathrm{O\cdots O}}$ is mainly coupled to a decrease in the C-1,C-2, O and C-2,C-1,C═O angles (see Scheme 1 and Figure 5a). This is seen from the following numbers: the angles (in degrees) (C-2,C-1,C═O and C-1,C-2,O): **1** (118.6; 121.7); **4** (119.0; 120.5); **2a** (118.6; 119.2); and for **2b** angles C-3,C-4,O; C-4,C-3,C═O, 121.0, 117.7; **3** (117.8; 119.0).

A comparison of calculated bond length of **3** and the corresponding molecules in which one, two, or three of the acetyl groups are replaced by formyl groups (**11**−**13**, for data see Table 1S) revealed that the $R_{\mathrm{O\cdots O}}$ distances for an intramolecular hydrogen bond of CH$_3$CO···HO type are similar for similar steric motifs (Figure 5b) irrespective of the number of acetyl or formyl groups on the benzene ring. The same is true for a HCO···HO type of hydrogen bonds. For a CH$_3$CO···HO motif with Y = OH and X = CH$_3$C═O, $R_{\mathrm{O\cdots O}} = 2.402 \mp 0.002$

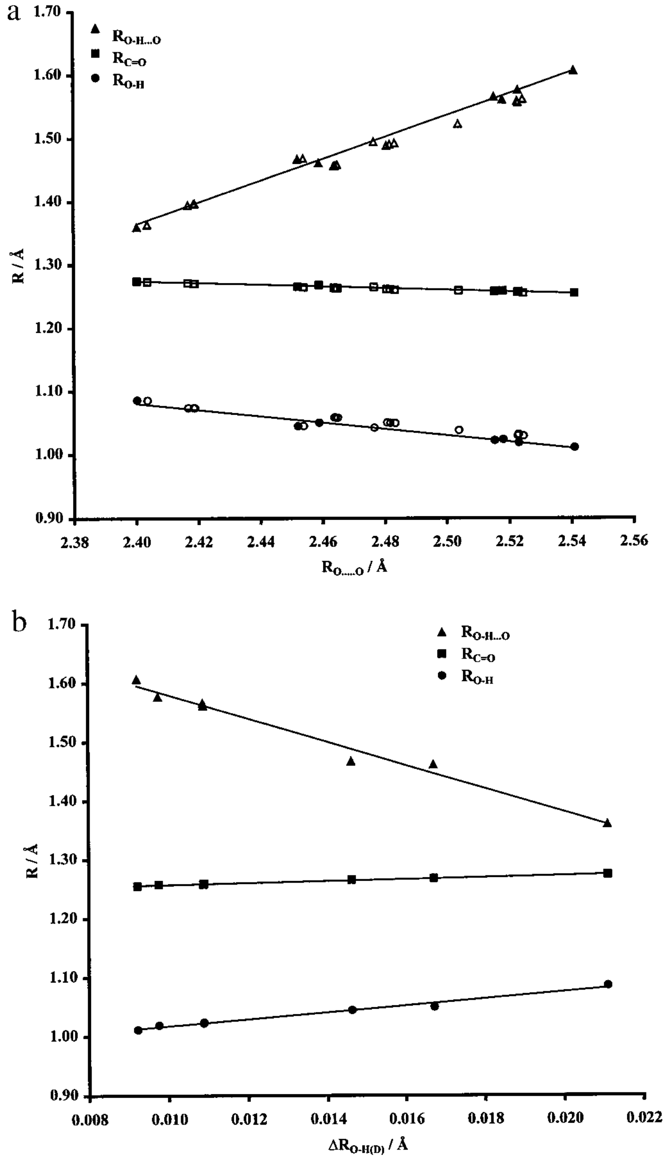


Figure 3. (a) Plot of $R_{\mathrm{(O)-H\cdots O}}$, $R_{\mathrm{C=O}}$, and R_{OH} distances vs $R_{\mathrm{O\cdots O}}$ distances and (b) plot of $R_{\mathrm{(O)-H\cdots O}}$, $R_{\mathrm{C=O}}$, and R_{OH} distances vs $\Delta R_{\mathrm{OH(D)}}$ distances. All data are from calculated structures. Open symbols are used for aldehyde analogues, compounds **7**−**13** (see Table s1); filled symbols, for compounds **1**−**6**. Regression line is based on data for compounds **1**−**6** only.

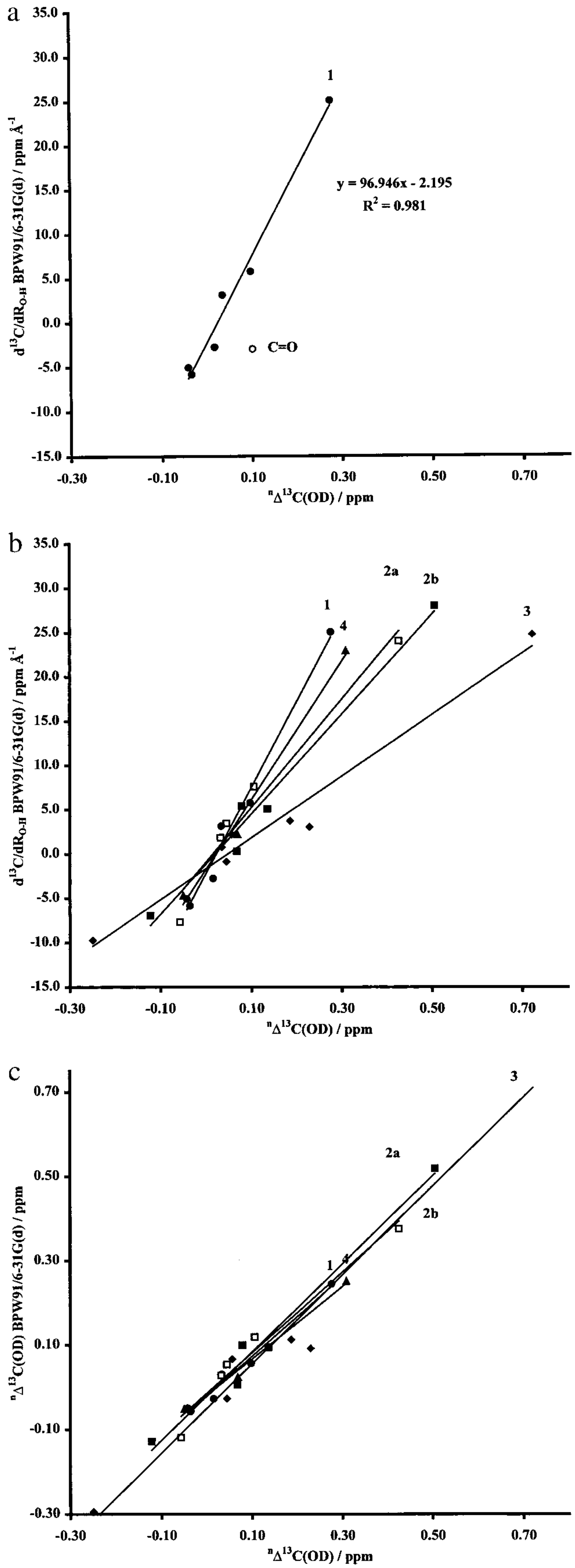


Figure 4. (a) Calculated ^{13}C Nuclear shielding gradients (d^{13}C/dR_{OH}) values plotted against the experimental isotope effects for **1** and (b) for **1**−**4**, and (c) calculated isotope effects using BPW91/6-31G(d(p)) 5D normal mode analysis calculated reduced masses in the average vibrational geometry calculation, plottet agains the experimental values.

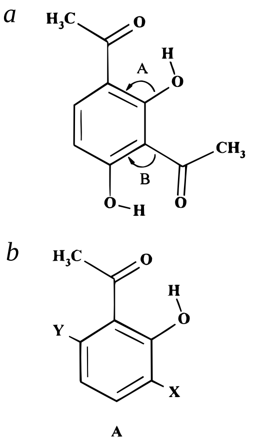


Figure 5. (a) Model for steric interactions and (b) steric motifs.

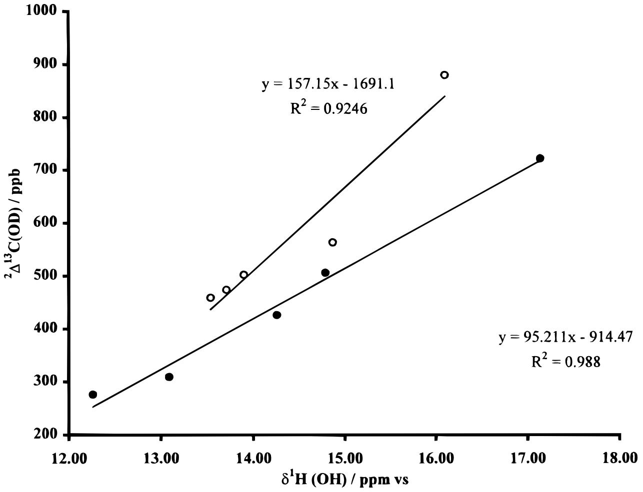


Figure 6. Plot of experimental δOH vs $^2\Delta$C(OD): (●) *o*-hydroxy acyl aromatics and (○) indandiones from refs 16 and 22.

Å; Y = OH and X = HC=O, $R_{O\cdots O} = 2.418 \mp 0.001$ Å and Y = OH and X = H. $R_{O\cdots O} = 2.456$ Å. For HC=O···HO with Y = OH and X = CH$_3$C=O, $R_{O\cdots O} = 2.464 \mp 0.001$ Å; Y = OH and X = HC=O, $R_{O\cdots O} = 2.482 \mp 0.001$ Å and Y = OH and X = H, $R_{O\cdots O} = 2.524$ Å. For **2** and **7**−**10** similar relations can be written. Combining these results, it is found that an acetyl group ortho to the OH group of an intramolecular hydrogen bond causes a decrease in $R_{O\cdots O}$ of 0.017 Å more than for a compounds with a formyl group in the ortho position.

δOH vs $^2\Delta$C(OD). The unusually large $^2\Delta$C(OD) isotope effects for benzene derivatives observed in this study allowed an extension of the range previously studied.[10,15,17,18] As seen from Figure 6 a reasonable correlation is found between δOH and $^2\Delta$C(OD)(R = 0.93). The data for the indandiones[22] show possibly a steeper slope (0.157) than those of the benzene derivatives (0.095) and larger $^2\Delta$C(OD) (Figure 6).

$^6\Delta$OH(OD). Relatively large deuterium isotope effects on O*H* chemical shifts are observed over six bonds, $^6\Delta$OH(OD) in **2** and **3**. For **2**, $^6\Delta$OH-2(OD-4) < $^6\Delta$OH-4(OD-2).

Discussion

The following discussion of deuterium isotope effects and their correlation to hydrogen bond strength is based on the assumption that the isotope effects to a large extent can be approximated by the term, dσ/dR_{OH} × ($\Delta r - \Delta r^*$). The former is termed, by Jameson, the electronic factor and tells how the effect is transmitted through the bonds. The latter is the change in the mean O-H distance upon deuteriation (called $\Delta R_{OH(D)}$ in this paper). A justification for leaving out terms involving bond angle deformations and second order terms are given by Jameson[40,41] and by the results on second-order derivatives by Chesnut.[42] Other important points are that the displacements are close to the equilibrium geometry and that the nuclear shielding is linear in this region.[39,41,56] A further basic assumption is that hydrogen bond strength can be described by the $R_{O\cdots O}$ distance.[30]

The study of *o*-hydroxy acyl aromatics and the corresponding aldehydes showed that the isotope effects of the two types of compounds were proportional, supporting the idea that the isotope effect depended on two factors, $d\sigma/dR_{OH}$ and $\Delta R_{OH(D)}$. The present study shows that the latter factor is very important (Scheme 2) as the former is more or less constant for all compounds (Scheme 2). It is also interesting to notice that the calculated slopes, $d\sigma^{13}$C-x/dR_{OH} for **1** compare quite well with the transmission coefficients estimated in ref 18.

Hydrogen-Bond Strength. A very important task is the development of parameters to gauge the strength of the hydrogen bond. As mentioned in the introduction, $^2\Delta$C(OD) and δO*H* have been used extensively.[10,13,16] The plot of $R_{O\cdots O}$ vs $^2\Delta$C(OD), the former based on calculations, shows a good correlation thereby confirming that $^2\Delta$C(OD) is a proper gauge for hydrogen bond strength. $\Delta R_{OH(D)}$ is the factor determining the magnitude of isotope effects in these intramolecularly hydrogen-bonded systems. This parameter is shown to be proportional to R_{OH}, which is again proportional to $R_{O\cdots O}$ so many parameters are actually good descriptors of hydrogen-bond strength.

The correlation between R_{OH} and $R_{O\cdots O}$ shows a good agreement with the data of Gilli et al.[3], but less so with those of Ichikawa.[57]

^{1}H Chemical Shifts. OH and NH chemical shifts of hydrogen-bonded systems have been used extensively as markers of hydrogen bonding.[4,11,12,14,25] The O*H* chemical shifts are calculated very well in the RAHB cases of this paper even using moderate basis sets (see the Experimental Section). This is not the case for e.g. NH protons of proteins[56] in which environmental factors other than the hydrogen-bond partner may contribute significantly and the geometrical uncertainties likewise.

^{13}C Chemical Shifts. Calculation of ^{13}C chemical shifts have been discussed with respect to different methods. No significant differences were found[60] between LORG[58] and the IGLO[59] method or between the LORG and the GIAO[32,33] methods.[56] Recently, ^{13}C chemical shifts have been calculated on the basis of MM3, MMX, or B3LYP optimized structures.[34] Calculations of ^{13}C chemical shifts have also been investigated in protein fragments (end-capped amino acids)[56] and in proteins in general.[35] In the present case a very good correlation is found (Figure 1b). ^{13}C chemical shifts can be predicted to an accuracy of 2 × 1.85 ppm (2 × RMSD), which is extraordinary. A slope different from −1 is obtained (see Figure 1b), as has also been found in other studies.[34] A key to the successful calculations is the blend of DFT theory in the BPW91 version with only the exchange terms in the calculation of chemical shifts,[46] the use of fully optimized DFT ab initio geometries,[34] and probably to a lesser extent use of polarization basis functions at the chelate proton in the geometry optimization.

Steric Factors. The effect of steric hindrance can be divided into two, in some instances possibly mutual interactions as demonstrated in Figure 5a. One is the steric effect on the OH group caused by the methyl group of an acetyl group leading to a decrease in the angle A (Figure 5a) and the other one is steric compression of a carbonyl group caused by an oxygen and the methyl group of the acetyl group leading to a decrease of angle B. This is also seen from the angles C-2,C-1,C=O and C-1,C-2,O (see previously). A support for a steric model is the finding that structure calculations of **7**−**13** clearly show how the acetyl group leads to a larger decrease of $R_{O\cdots O}$ compared to a formyl group. For a given steric motif the results are similar whether a formyl or acetyl group are in the noninteracting positions (compare e.g. **3** and **11**). This is interesting as the formyl and acetyl groups are electronically different.

Conclusions

Structures of intramolecularly hydrogen-bonded *o*-hydroxy acyl aromatics are calculated to a good accuracy using DFT methods.

O*H* chemical shifts of these systems can be calculated to a very good accuracy using ab initio methods in moderate basis sets. In addition ^{13}C chemical shifts can be calculated well. A prerequisite is the use of fully optimized DFT geometries.[42,43]

It is demonstrated that $^2\Delta$C(OD) isotope effects and δO*H* reflect the strength of the hydrogen bond well. The dominant factor of the $^n\Delta$C(OD) isotope effects is the variation of the vibrational average of the O−H(D) bond length upon deuteriation rather than the derivative of the nuclear shielding with respect to OH bond shortening, $d\sigma/dR_{OH}$.

For the benzene derivatives having multiple OH and acyl groups, $^n\Delta$C(OD) and the hydrogen bond strength are seen to increase due to an inductive effect (small) combined with a stronger steric compression effects.

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Supporting Information Available: Two figures showing plots of experimentally determined $^n\Delta$C(OD) isotope effects vs d^{13}C/dR, $^n\Delta$C(OD) and plots of $A_{C-C(=O)CH_3}$ vs $R_{O\cdots O}$ and $A_{C1,C2-O(H)}$ vs $R_{O\cdots O}$ and a table giving calculated distances for **7**−**13** (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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