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A DFT Study on Intramolecular Hydrogen Bonding in 2-Substituted Phenols: Conformations, Enthalpies, and Correlation with Solute Parameters

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For a series of 61 2-substituted phenols, 2-X−PhOH, forming a total of 73 intramolecular hydrogen bonds, the intramolecular hydrogen bond enthalpy, $\Delta H_{\mathrm{intra-HB}}$, has been determined by density functional theory (DFT) calculations on the B3LYP/6-31G(d,p)//B3LYP/6-31G(d,p) level. The $\Delta H_{\mathrm{intra-HB}}$ was defined as the enthalpy difference between the hydrogen-bonded (HB) form and the lowest-energy conformer in which the OH is rotated into the "away" position. The correlation of $\Delta H_{\mathrm{intra-HB}}$ with geometrical factors such as r(O−H), or r(OH···A), with A as the hydrogen bond accepting atom, was generally very poor, showing that none of these parameters can be used as an universal descriptor for the hydrogen bond strength. The relation between $\Delta H_{\mathrm{intra-HB}}$ and $\nu(\mathrm{O-H})_{\mathrm{intra-HB}}$ is also insignificant, in contrast with previous estimates. The data clearly demonstrate that the genuine $\Delta H_{\mathrm{intra-HB}}$ of a phenolic compound cannot be unequivocally derived by simple rotation of the OH group into the "away" orientation, because additional steric and/or electronic 1,2 interactions may take place which are difficult or even impossible to be separated from the sole H-donor/acceptor interaction. Nevertheless, a good correlation has been found between computed and experimental liquid phase ν(O−H)s obeying $\nu(\mathrm{O-H})_{\mathrm{DFT}} = 1.0097\nu(\mathrm{O-H})_{\mathrm{exp}} + 159.5$. It could be established with the use of solute acidity, α_2^{H}, and solvent basicity, β_2^{H}, parameters, that the strength of an intramolecular hydrogen bond is noticeably fortified for electron withdrawing groups. Furthermore, it was found that with the proper non-HB geometries the bond dissociation enthalpy, BDE(O−H), in the series of 25 2-X-PhOHs correlates quite well with σ^+, in the same way as has been found for 4-X-substituted phenols.

Introduction

The phenomenon of intra- and intermolecular hydrogen bonding plays a pivotal role in quite a number of (bio)chemical transformations. Next to the actual chemical change, cleavage and formation of hydrogen bonds can be regarded as the major driving force.[1] Phenolic compounds are as antioxidants essential for the conservation of foodstuff or more in general for sustaining life, because they are capable of suppressing radical-mediated oxidative damage by curtailing reactive species. The most crucial reaction is the abstraction of the hydroxylic hydrogen by radical species. Formation of an intermolecular hydrogen bond between the phenolic compound as a hydrogen donor and a hydrogen bond accepting (HBA) solvent reduces the chain breaking potency, because of a lower apparent concentration of the antioxidant. In general, this decrease can be quite well quantified for any hydrogen donating compound using the acidity parameter, α_2^{H}, of the solute and the basicity parameter, β_2^{H}, of the solvent.[2]

Combination of a donor and an acceptor moiety in one molecule, such as in 2-X-substituted phenol, leads to the formation of an intramolecular hydrogen bond. Recently, we have shown by means of thermodynamic and kinetic methods that in a non-HBA solvent 2-methoxyphenol exists almost entirely in the HB form, whereas in a HBA solvent, the acceptor interacts with the intra-HB hydrogen to create a bifurcated complex.[3] Moreover, in contrast with an inter-HB hydrogen, the intra-HB hydrogen is still available for reaction, although its reactivity is substantially diminished.[3b]

Despite the general importance of phenols, only a limited number of experimental studies are available dealing with the determination of their intramolecular hydrogen bond dissociation enthalpy, $\Delta H_{\mathrm{intra-HB}}$. In our thermodynamic examination of polymethoxy phenols, we were able to show that the agreement for $\Delta H_{\mathrm{intra-HB}}$ obtained by experiment and by density functional theory (DFT) calculations at the B3LYP/6-31G(d,p) level was quite satisfactory.[3a] At the same time, DFT predicted almost no change in entropy, $\Delta S_{\mathrm{intra-HB}}$, between the intra-HB and non-HB conformers for a five-membered HB, in agreement with an earlier prediction.[3a] By way of contrast, for *inter*molecular hydrogen bonds, the applied DFT method grossly overestimates the entropy change most likely resulting in an overestimation of $\Delta H_{\mathrm{inter-HB}}$ at this level of theory.[4] The more reliable performance of DFT for the computation of $\Delta H_{\mathrm{intra-HB}}$ may be associated with a cancellation of errors because the number of moles does not change in the course of the hydrogen bond formation.

Therefore, the B3LYP/6-31G(d,p) DFT procedure may be the instrument of choice in computing accurately the thermodynamic parameters for intramolecular hydrogen bonds. This fact allows the determination of $\Delta H_{\mathrm{intra-HB}}$ for compounds which are synthetically not easily accessible and/or which are difficult to investigate with current experimental methods. Some detailed computational reports are available in the recent literature dealing with the geometrical aspects and energetics of the

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intramolecular phenolic hydrogen bond for one particular substituent or for a family of closely related compounds.[5] We have adopted a different strategy. The thermodynamic features for intramolecular hydrogen bonds of an extensive set of 2-substituted phenols, 2-X−PhOH, have been computed with the aim to search for correlations between the DFT energies and computed structural features or experimentally accessible parameters. As 2-X substituents, only uncharged groups are considered. The rationale for selecting the substituents is that they represent a wide spectrum of prototypal HB interactions, which may be found in biological structures or in artificial supramolecular entities.

Computational Methods

The calculations were performed with the Gaussian 98, revision A.7, program package,[6a] using the B3LYP[6b,c] method with the 6-31G(d,p) basis set for the geometry optimization and frequency calculation, in combination with the unrestricted formalism for the radicals. Zero-point vibrational energies were scaled by a factor of 0.9805.[6d] The starting geometries of the phenols and related radicals were always slightly distorted from planarity in order to avoid optimization to saddle points (transition structures). The default values of Gaussian 98 were used for the geometry optimization criteria. In cases where more than one conformer was possible, care was taken to obtain the genuine global lowest-energy conformer. In toto, 267 structures were calculated. The intramolecular hydrogen bond enthalpy, $\Delta H_{\text{intra-HB}}$, was computed by comparing the DFT enthalpies at 298 K for the intra-HB conformer and the lowest-energy (fully optimized) conformer, in which the hydroxyl group is pointing away from the substituent. The bond dissociation enthalpy for the phenolic hydrogen, BDE(O−H), has been computed as the difference between the lowest-energy conformer of the closed-shell molecule in the away conformation and the lowest-energy conformation for the corresponding phenoxyl radical.

Results

Intramolecular Hydrogen Bonds: Structures and Enthalpies. Selected structural parameters for the intramolecular hydrogen-bonded conformers of the investigated 2-X-phenols are presented in Table 1, showing the variations in the distance between phenolic hydrogen and the acceptor atom, r(OH···A), the O−H bond length, r(O−H), the bond angles related to the hydroxyl group, ∠(C−O−H) and ∠(O−H···A), and the O−H stretching frequencies, ν(O−H). For comparison, liquid phase (CCl_4) experimental ν(O−H)s from the literature are included as well. Table 1 also contains the computed values for r(O−H) and ν(O−H) for the lowest-energy non-hydrogen-bonded species in which the hydroxyl group is pointing away. The hydrogen bond accepting atom of the substituent is given in italics. Several substituents studied hold two acceptor atoms; in these cases, the data for both hydrogen bonds are presented. A complete graphical representation of all calculated structures, showing the (idealized) conformational arrangements and their relative energies (ΔH_{rel} and ΔG_{rel}), is given as Supporting Information. From Table 1, it can be seen that for non-hydrogen-bonded phenols, the r(O−H) is almost invariant with the nature of the substituent at the 2-position with an average of 0.9663 ± 0.0004 Å, identical to the r(O−H) for phenol of 0.9663 Å. A similar tendency holds for the ν(O−H) of the non-hydrogen-bonded phenols ranging from 3836 to 3801 cm^{-1}, close to that for phenol at 3820 cm^{-1}. Despite the electronic variations in the closed-shell molecules, the change in the O−H stretching frequency is quite modest (35 cm^{-1}). Nevertheless, it has been proposed that a linear relationship exists between $\nu(\text{O-H})_{\text{non-HB}}$ and pK_a.[16a] With the 2-XPhOH studied here, such a correlation could not be detected.[16b,c]

In contrast, for the intramolecularly hydrogen-bonded phenols, a considerable variation in r(O−H) from 1.0000 to 0.9663 Å and ν(O−H) from 3836 to 3136 cm^{-1} is found. A relationship can be retrieved between r(O−H) and ν(O−H), obeying a linear regression line of $\nu(\text{O-H}) = -20859.9r(\text{O-H}) + 23991.3$ with $n = 74$, $r^2 = 0.992$ (Figure 1).

This correlation demonstrates the consistency of the computational method and may be used to predict the ν(O−H) by employing the less computational time-consuming geometry optimization protocol.

When a hydrogen bond is formed, the C−O−H bond angles vary from 111° to 103°, close to the one for unsubstituted phenol (108.9°). The O−H···A hydrogen bond angles, however, depend considerably on the size of the HB ring, ranging from 107.2° (2-*N*H−NH_2) for five-membered to 162.9° (2-NHCH*O*) for seven-membered rings.

In Table 2, the thermodynamic data, i.e., $\Delta H_{\text{intra-HB}}$ and $\Delta S_{\text{intra-HB}}$, are collected. The change in $\Delta S_{\text{intra-HB}}$ is quite modest, and for five-membered rings, it approaches zero. In a hydrogen-bonded ensemble, the OH stretching vibrational frequency is reduced, whereas at the same time, the O−H bending is hampered (increased frequency). Provided that no major structural change takes place, the shift in the frequency distribution occurs in such a way that the $\Delta S_{\text{intra-HB}}$ remains close to zero.

A frequently used definition for $\Delta H_{\text{intra-HB}}$ is the enthalpy difference between two conformers with the hydroxyl group pointed either away or toward the hydrogen bond accepting substituent. However, this approach may lead to an overestimation of the $\Delta H_{\text{intra-HB}}$ as the lowest-energy conformational arrangement of the 2-substituent in the non-hydrogen-bonded form may not be the same as in the HB form. The tabulated enthalpic values in Table 2 refer to the *lowest-energy* conformer (global minimum) of the non-HB species. For comparison, we have computed, where appropriate, other non-HB structures (local minima) for which the orientation of the acceptor group is retained. The corresponding results are given in parentheses in Table 2. Only six out of our 61 substituents, namely F, Cl, Br, CN, NC, and C≡CH, are per se conformational invariant toward rotation of the OH group into the away position. For all other phenols, more than one conformation is possible for the non-hydrogen-bonded form. We have divided the computed structures into four categories (A−D) according to their structural relationships. Group A encompasses the phenols for which the conformation of the 2-substituent in the HB form is largely retained in the lowest-energy non-HB form when rotating the phenolic OH group into the away position. With the exception of the above monatomic or linear substituents, small conformational changes did occur. For practical reasons, we have included in group A all structures for which a possible variation of the dihedral (twist) angle of the 2-substituent with respect to the phenyl plane remains below 30°. This holds for 28 of the 74 computed HB structures. In group B, 30 structures are collected for which the conformation of the lowest-energy non-HB form is distinctively different from the HB form. The energetics of the hydrogen bond compared to the retained conformation, a non-HB species of higher energy, are presented in parentheses in Table 2. A third category, group C, comprises those structures (12 in total) where an intramolecular hydrogen bond between a hydrogen atom of the substituent to the phenolic oxygen, named “reverse” hydrogen bonding, is present in the

TABLE 1: Selected DFT Calculated Structural Data and O−H Stretching Frequencies for Intramolecular Hydrogen-Bonded and Non-Hydrogen-Bonded 2-Substituted Phenols

		intra-HB						non-HB	
		bond lengths (Å)		bond angles (°)		ν(O−H) (cm^{-1})			
no.	2-X-phenol[a]	OH- -A[b]	O−H	C−O−H	O-H-A	calc	exp[c]	*r*(O−H) (Å)	ν(O−H) (cm^{-1})
				Five-Membered Rings[d]					
1	H	2.2927	0.9663	108.9	103.5	3819.7	3610[e]	0.9663	3819.7
2	F	2.1769	0.9686	107.6	113.3	3794.3	3592[f]	0.9660	3827.5
3	Cl	2.4169	0.9695	108.8	119.7	3763.6	3548[g]	0.9661	3826.3
4	Br	2.4681	0.9715	108.6	123.2	3724.9	3528[h]	0.9663	3823.1
5	CH_3	2.3834	0.9653	109.4	113.5	3835.6	3615[i]	0.9660	3823.3
6	C≡CH[j]	2.2718	0.9716	108.2	113.7	3726.8	3535[k]	0.9663	3820.8
7	CN[j]	2.3180	0.9704	110.0	111.0	3755.5	3558[l]	0.9664	3823.9
8	*N*H$_2$[m]	2.0412	0.9801	103.9	121.3	3586.2		0.9653	3836.1
9	*N*═CH$_2$	2.0243	0.9792	104.7	119.3	3603.9		0.9664	3820.0
10	*N*≡C	2.2826	0.9697	109.3	111.0	3769.3		0.9661	3828.4
11	*N*Me$_2$	2.0382	0.9819	103.4	122.0	3549.9		0.9661	3821.1
12	*N*HCHO[m]	2.2294	0.9716	107.1	115.0	3733.3		0.9659	3829.3
13	*N*MeCHO	2.2501	0.9708	107.3	114.1	3747.6		0.9662	3822.6
14	*N*H−NH$_2$[m]	2.2599	0.9712	106.6	107.2	3733.2		0.9663	3833.6
15	*N*Me-NH$_2$	2.1294	0.9755	104.9	116.4	3662.1		0.9660	3822.6
16	*N*═NMe	2.0720	0.9768	105.6	117.7	3641.1		0.9666	3815.3
17	*N*$_3$	2.1409	0.9705	107.9	114.7	3754.5		0.9658	3831.0
18	*N*O	2.1006	0.9774	106.5	116.3	3635.5		0.9669	3813.0
19	*O*H	2.1239	0.9690	107.4	114.6	3784.8	3569[n]	0.9661	3825.3
20	*O*Me	2.0766	0.9697	106.9	115.5	3769.8	3558[o]	0.9661	3820.9
21	*O*Ph	2.1394	0.9706	106.9	115.2	3758.2		0.9662	3825.1
22	*O*COMe	2.1258	0.9689	107.3	114.8	3784.9	3585[p]	0.9659	3829.4
23	*O*NO	2.1746	0.9699	107.5	114.1	3769.4		0.9663	3823.1
24	*P*H$_2$	2.4425	0.9720	109.0	121.2	3704.3		0.9660	3826.7
25	*P*Me$_2$	2.3924	0.9757	108.8	123.2	3632.7		0.9663	3818.8
26	*S*H[f]	2.4074	0.9745	107.4	122.4	3665.0		0.9658	3829.8
27	*S*Me	2.3797	0.9764	106.8	123.0	3629.6	3415[q]	0.9663	3821.0
28	*S*CN	2.4780	0.9712	109.2	119.5	3731.7		0.9665	3823.3
29	*S*(O)Me	2.5722	0.9692	109.5	113.3	3763.2		0.9663	3823.6
	average	2.2486	0.9722	107.4	116.2	3718.3		0.9962	3824.3
	± sd	0.1510	0.0041	1.7	4.8	73.1		0.0003	5.1
				Six-Membered Rings					
30	C*F*$_3$	1.9471	0.9677	110.0	137.7	3801.9	3622[r]	0.9662	3823.9
31	CH$_2$*F*	1.8827	0.9708	108.2	142.6	3743.6		0.9660	3825.8
32	CH$_2$*Cl*	2.4380	0.9701	109.7	142.9	3743.9		0.9660	3826.4
33	CH$_2$*Br*	2.4695	0.9728	109.5	146.1	3685.6		0.9660	3826.8
34	CH$_2$CN[j]	2.2424	0.9689	110.9	158.3	3767.8		0.9661	3826.3
35	CH$_2$CH═CH$_2$[j]	2.2763	0.9703	109.5	138.5	3728.1	3549[s]	0.9660	3824.9
36	CH$_2$*O*H	1.8693	0.9776	107.6	145.5	3601.2	3438[t]	0.9660	3825.8
37	2-tetrahydrofuryl	1.7338	0.9788	107.3	148.7	3558.8		0.9662	3820.2
38	CH$_2$*N*Me$_2$	1.8259	0.9908	106.4	149.1	3320.7	2970[u]	0.9660	3823.1
39	CH$_2$*S*Me	2.3821	0.9755	108.8	143.7	3623.5		0.9659	3827.7
40	CH═*N*H	1.6700	1.0000	107.3	147.7	3136.4		0.9672	3802.9
41	CH═*N*Me	1.7137	0.9994	107.0	148.4	3143.1	2900[v]	0.9672	3801.5
42	CH═*N*OH	1.7966	0.9841	108.6	144.8	3440.4	3220[w]	0.9670	3806.6
43	2-pyridyl	1.6607	0.9963	106.4	149.1	3125.8		0.9662	3818.7
44	2-imidazyl[m,x]	1.7222	0.9950	108.2	148.1	3229.0		0.9664	3816.3
45	2-imidazyl[y]	2.4651	0.9686	108.1	100.8	3777.3		0.9664	3816.3
46	4-imidazyl[x]	1.7477	0.9880	108.2	148.0	3363.1		0.9660	3822.7
47	CH*O*	1.7305	0.9897	107.0	147.6	3359.7	3171[z]	0.9662	3823.4
48	C*O*Me	1.6541	0.9943	106.2	148.7	3265.5	3060[aa]	0.9665	3815.2
49	C*O*NH$_2$[m]	1.6436	0.9960	106.0	149.4	3241.2	3098[bb]	0.9664	3817.5
50	CO*N*H$_2$[m]	1.9836	0.9751	108.9	133.8	3635.9		0.9664	3817.5
51	C*O*NMe$_2$	1.6871	0.9910	105.8	147.8	3341.1	3200[cc]	0.9662	3821.2
52	CO*N*Me$_2$	2.0058	0.9768	108.0	139.4	3601.2		0.9662	3821.2
53	C*O*OH[m]	1.7269	0.9870	107.1	147.0	3417.3	3210[dd]	0.9668	3810.9
54	CO*O*H[m]	1.7900	0.9728	109.1	142.1	3688.6		0.9668	3810.9
55	C*O*OMe	1.7203	0.9873	107.0	147.3	3409.3	3203[ee]	0.9671	3803.9
56	CH*S*	2.0767	0.9937	109.4	152.1	3235.0		0.9678	3815.6
57	C*S*Me	1.9936	0.9980	109.1	152.2	3138.4		0.9670	3806.6
58	NH-*N*H$_2$[m]	1.8326	0.9838	106.2	145.8	3466.3		0.9663	3817.6
59	N═*N*Me	1.6967	0.9977	106.0	144.9	3168.1		0.9666	3815.3
60	N*O*	1.6502	0.9971	105.4	146.5	3202.2		0.9669	3813.0
61	N*O*$_2$	1.6886	0.9878	106.3	145.0	3404.4	3240[ff]	0.9676	3801.5
62	O*N*O	1.8914	0.9705	109.5	140.8	3708.1		0.9661	3827.4
63	PH$_2$*O*	1.7562	0.9891	109.6	155.5	3374.8		0.9662	3835.7

TABLE 1: Continued

		intra-HB						non-HB	
		bond lengths (Å)		bond angles (°)		ν(O−H) (cm^{-1})			
no.	2-X-phenol[a]	OH- -A[b]	O−H	C−O−H	O−H-A	calc	exp[c]	r(O−H) (Å)	ν(O−H) (cm^{-1})
		Six-Membered Rings[d]							
64	P(*O*)(OH)$_2$[m]	1.7435	0.9877	109.2	154.7	3399.8		0.9659	3825.6
65	P(*O*)(OMe)$_2$	1.7405	0.9887	109.1	155.0	3380.2		0.9660	3825.6
66	S(*O*)Me	1.6926	0.9966	108.1	154.4	3219.2		0.9663	3823.6
67	S(*O*)$_2$Me	1.7878	0.9830	108.6	150.5	3498.0	3330[gg]	0.9663	3823.6
68	S(*O*)OMe	1.7147	0.9889	108.5	152.5	3366.5		0.9664	3820.0
69	S(*O*)$_2$OMe	1.8298	0.9800	109.5	148.5	3561.3		0.9664	3821.3
	average	1.8720	0.9847	108.0	146.0	3446.8		0.9664	3818.8
	± sd	0.2424	0.0010	1.4	8.9	210.5		0.0005	8.1
		Seven-Membered Rings							
70	CH$_2$CH═*N*Me	1.8250	0.9875	110.7	160.0	3369.2		0.9661	3823.6
71	CH$_2$CH*O*	1.8508	0.9780	110.4	158.1	3576.8		0.9661	3825.2
72	NHCH*O*[f]	1.6537	0.9902	109.5	162.9	3320.4		0.9659	3829.3
73	NMeCH*O*	1.6764	0.9873	107.4	156.3	3388.8		0.9662	3824.1
74	OC*O*Me	1.7366	0.9805	107.5	154.6	3531.3	3410[hh]	0.9659	3829.4
	average	1.7485	0.9847	109.1	158.3	3437.3		0.9660	3826.3
	± sd	0.0088	0.0052	1.6	3.2	110.6		0.0001	2.8

[a] Hydrogen bond accepting atom in italics. [b] Hydrogen bond length. [c] Average value of available solution phase IR data from literature. [d] Number of atoms in the ring formed by the intramolecular hydrogen bond. [e] Reference 7a−o. [f] References 5f, 7g, 7i, 8a−c. [g] References 5f, 7g, 7i, 8b−c, 9. [h] References 7g−i, 8b−c, 9. [i] References 7b, 7h, 9. [j] Hydrogen bonded to π-electrons, hydrogen bond distance r(OH-A) to the carbon atom of the double bond closest to the phenyl ring. [k] Reference 7k. [l] References 5f, 7i, 9. [m] In the lowest-energy away conformer a hydrogen bond is formed between a hydrogen of the substituent and the phenolic oxygen. [n] References 7a, 7d, 7f, 7i, 9, 10. [o] References 7e−g, 8a, 9, 11a, 11b. [p] Reference 11a. [q] Reference 7g. [r] Reference 12. [s] Reference 13. [t] References 7c, 7f, 14. [u] Reference 15a. [v] Reference 5f. [w] Reference 5f. [x] Hydrogen bonded to sp^2 nitrogen. [y] Hydrogen bonded to sp^3 nitrogen. [z] References 5f, 7c, 7g, 7i, 11b. [aa] References 5f, 7 g, 11b, 15b. [bb] Reference 5f, 7j. [cc] Reference 5f. [dd] Reference 5f. [ee] References 5f, 7c, 7g, 11b, 15b. [ff] References 5f, 7c, 7e, 7g, 7i. [gg] Reference 7g. [hh] Reference 11a.

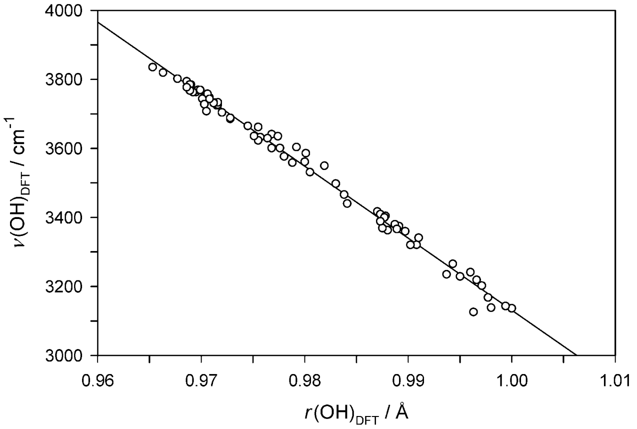

Figure 1. Correlation of B3LYP/6-31G(d,p)-computed OH vibrational frequencies and O−H bond lengths in intramolecularly hydrogen-bonded 2-substituted phenols. The regression line (r^2 = 0.992, n = 74) corresponds to a frequency change of 208.6 cm^{-1} per 0.01 Å change in OH bond length.

lowest-energy away entity. The corresponding energetics for these species are given between brackets in Table 2. To obtain a realistic $\Delta H_{\text{intra-HB}}$, the lowest-energy conformers with the substituent's hydrogen pointed away have been used. However, for 2-NH$_2$, the non-HB entity exists only as a rotational transition state according to DFT, and therefore, a $\Delta H_{\text{intra-HB}}$ could not be derived. For 2-S(O)Me (to sulfur), 2-Me, and 2-CH$_2$CN (denoted as group D), the non-HB form is lower in energy than the HB form, resulting in a positive $\Delta H_{\text{intra-HB}}$. Pertinent examples are displayed in Figures 2 (group A, X = NO$_2$), 3 (group B, X = CHO), and 4 (Group C, X = COOH).

In the non-hydrogen bonded 2-CHO-PhOH, Figure 3, with the hydroxyl group in the away position, the carbonyl can be oriented either away or toward (as in the hydrogen bonded form) with respect to the phenolic hydroxyl. With the latter unfavorable conformer, the $\Delta H_{\text{intra-HB}}$ changes from −9.2 to −11.9 kcal mol^{-1} because of repulsion between the lone pairs of the oxygen atoms and now includes an additional enthalpic contribution not associated with the donor−acceptor interaction.

The energetics as given in Table 2 in brackets for group C do not refer to the properties of a single hydrogen bond but merely reflect the difference between two HB entities as illustrated in Figure 4 for 2-COOH-PhOH. Relative to the fully non-HB form, the $\Delta H_{\text{intra-HB}}$ becomes −11.4 kcal mol^{-1} for the HB to the oxygen of the carbonyl and −7.3 kcal mol^{-1} for the HB to the oxygen of the hydroxyl group.

Bond Dissociation Enthalpies for 2-X−PhOH. The oxygen−hydrogen bond dissociation enthalpies, BDE(O−H), for the non-hydrogen-bonded away conformers of the 2-X-phenols have been computed as well and the data are summarized in Table 3 as relative BDEs, ΔBDE(O−H)s, to PhOH. Similar to the $\Delta H_{\text{intra-HB}}$, the BDE(O−H) is calculated using the lowest-energy conformer for the radical (see Figures 3 and 4 and the Supporting Information), and hence, conformational changes are incorporated. When the conformation in the radical is retained, the values are given in bold. The BDE(O−H) obtained by DFT for phenol of 82.8 kcal mol^{-1} clearly deviates from the average experimental value of 87 kcal mol^{-1} implying that at this level of theory the underestimation by our computational method is about 4 kcal mol^{-1}.[17a] Computations employing other methodologies and/or more extended basis sets are required to reproduce the genuine BDE(O−H) in phenol.[17b] Nevertheless, it has been demonstrated that for 4-substituted phenols reliable ΔBDE(O−H)s can be obtained at this level of theory.[17c] For quite a number of substituents, viz. 2-CONH$_2$, 2-COOH, 2-imidazyl, 2-NH$_2$, 2-NHCHO, 2-NH−NH$_2$, 2-OH, 2-PO(OH)$_2$, and 2-SH, the lowest-energy conformer of the radical contains an intramolecular hydrogen bond between a hydrogen of the substituent and the phenolic oxygen, and their ΔBDE(O−H)s are presented in brackets. To determine only the effect of substitution on the BDE(O−H), this additional enthalpic contribution needs to be separated. For 2-COOH, 2-NHCHO, 2-OH, and 2-SH a lowest-energy non-HB radical could be computed, for the remaining

TABLE 2: B3LYP/6-31G(d,p)-Calculated Intramolecular Hydrogen Bond Enthalpies and Entropies for 2-Substituted Phenols at 298 K[a]

no.	2-X-phenol[b]		$\Delta H_{\mathrm{intra-HB}}$	$\Delta S_{\mathrm{intra-HB}}$	no.	2-X-phenol[b]		$\Delta H_{\mathrm{intra-HB}}$	$\Delta S_{\mathrm{intra-HB}}$
Five-Membered Rings[c]									
1	H	A	0.0	0.0	16	$\mathit{N}{=}\mathrm{NMe}$	A	−7.3	−3.0
2	F	A	−3.0	−0.3	17	N_3	B	−3.4 (−4.1)	−2.0 (−1.0)
3	Cl	A	−3.0	−0.0	18	$\mathit{N}\mathrm{O}$	A	−7.1	−1.7
4	Br	A	−3.9	−0.7	19	$\mathit{O}\mathrm{H}$	A	−4.1	0.3
5	$\mathrm{CH_3}$	D	0.5	−0.3	20	$\mathit{O}\mathrm{Me}$	A	−4.4	0.3
6	$\mathrm{C{\equiv}CH}$[e]	A	−3.8	−0.7	21	$\mathit{O}\mathrm{Ph}$	A	−3.8	−0.3
7	CN[e]	A	−2.6	−0.3	22	$\mathit{O}\mathrm{COMe}$	B	−2.0	0.3
8	$\mathit{N}\mathrm{H_2}$	C	[−0.4][g]	[1.7]	23	$\mathit{O}\mathrm{NO}$	B	−3.3	−0.3
9	$\mathit{N}{=}\mathrm{CH_2}$	B	−7.0	1.0	24	$\mathit{P}\mathrm{H_2}$	B	−0.8	−0.3
10	$\mathit{N}{\equiv}\mathrm{C}$	A	−2.8	−0.3	25	$\mathit{P}\mathrm{Me_2}$	B	−3.0	0.3
11	$\mathit{N}\mathrm{Me_2}$	B	−4.8	1.3	26	$\mathit{S}\mathrm{H}$	C	−3.3 [−2.3]	1.0 [−4.0]
12	$\mathit{N}\mathrm{HCHO}$	C	−3.9 [2.3]	0.3 [1.8]	27	$\mathit{S}\mathrm{Me}$	B	−4.2	0.7
13	$\mathit{N}\mathrm{MeCHO}$	A	−1.7	0.0	28	$\mathit{S}\mathrm{CN}$	A	−2.2	0.7
14	$\mathit{N}\mathrm{H{-}NH_2}$	C	−4.7 [1.2]	0.0 [2.0]	29	$\mathit{S}\mathrm{(O)Me}$	D	1.3	−1.3
15	$\mathit{N}\mathrm{Me\text{-}NH_2}$	A	−3.0	0.0					
Six-Membered Rings									
30	$\mathrm{C}\mathit{F}_3$	A	−2.4	−0.7	50	$\mathrm{CO}\mathit{N}\mathrm{H_2}$	C	−5.8 [0.4]	−3.0 [2.7]
31	$\mathrm{CH_2}\mathit{F}$	B	−2.1	−2.3	51	$\mathrm{C}\mathit{O}\mathrm{NMe_2}$	B	−8.0	−2.7
32	$\mathrm{CH_2}\mathit{Cl}$	A	−1.0	−1.3	52	$\mathrm{CO}\mathit{N}\mathrm{Me_2}$	A	−2.9	−3.0
33	$\mathrm{CH_2}\mathit{Br}$	A	−2.5	−2.0	53	$\mathrm{C}\mathit{O}\mathrm{OH}$	C	−11.4 [−10.5]	−3.0 [−2.7]
34	$\mathrm{CH_2CN}$[e]	D	1.2 (0.4)	1.0 (2.4)	54	$\mathrm{CO}\mathit{O}\mathrm{H}$	C	−7.3 [−6.4]	−1.7 [−2.0]
35	$\mathrm{CH_2CH{=}CH_2}$[e]	B	−1.6 (−1.6)	−2.0 (−1.7)	55	$\mathrm{C}\mathit{O}\mathrm{OMe}$	A	−12.2	−1.0
36	$\mathrm{CH_2}\mathit{O}\mathrm{H}$	B	−5.6 (−7.1)	−4.0 (−4.0)	56	$\mathrm{CH}\mathit{S}$	B	−7.8 (−11.8)	−2.7 (−2.7)
37	2-tetrahydrofuryl	B	−4.7	+2.0	57	$\mathrm{C}\mathit{S}\mathrm{Me}$	B	−9.4 (−13.0)	−2.3 (−3.3)
38	$\mathrm{CH_2}\mathit{N}\mathrm{Me_2}$	A	−8.3	−3.0	58	$\mathrm{NH\text{-}}\mathit{N}\mathrm{H_2}$	C	−9.2 [−3.3]	−2.7 [−2.3]
39	$\mathrm{CH_2}\mathit{S}\mathrm{Me}$	A	−2.4	−2.3	59	$\mathrm{N{=}}\mathit{N}\mathrm{Me}$	B	−11.2 (−13.3)	−4.4 (−4.7)
40	$\mathrm{CH{=}}\mathit{N}\mathrm{H}$	B	−10.7 (−14.7)	−3.0 (−2.6)	60	$\mathrm{N}\mathit{O}$	B	−10.9 (−12.5)	−2.7 (−3.0)
41	$\mathrm{CH{=}}\mathit{N}\mathrm{Me}$	B	−10.5 (−14.2)	−3.0 (−2.7)	61	$\mathrm{N}\mathit{O}_2$	A	−11.9	−3.4
42	$\mathrm{CH{=}}\mathit{N}\mathrm{OH}$	B	−7.2 (−10.0)	−2.7 (−2.0)	62	$\mathrm{O}\mathit{N}\mathrm{O}$	A	−0.7	0.7
43	2-pyridyl	B	−9.4 (−12.7)	−1.0 (−1.3)	63	$\mathrm{PH_2}\mathit{O}$	B	−5.5	−0.7
44	2-imidazyl[d]	C	−13.8 [−6.1]	−2.0 [−1.0]	64	$\mathrm{P(}\mathit{O}\mathrm{)(OH)_2}$	C	[−7.0][h]	[0.3]
45	2-imidazyl[f]	C	−4.2 [3.5]	−0.3 [0.3]	65	$\mathrm{P(}\mathit{O}\mathrm{)(OMe)_2}$	B	−9.6	−0.7
46	4-imidazyl[d]	B	−6.5 (−12.0)	−1.0 (−2.0)	66	$\mathrm{S(}\mathit{O}\mathrm{)Me}$	B	−7.1 (−11.4)	−1.7 (−2.4)
47	$\mathrm{CH}\mathit{O}$	B	−9.2 (−11.9)	−2.7 (−2.7)	67	$\mathrm{S(}\mathit{O}\mathrm{)_2Me}$	A	−6.9	−0.7
48	$\mathrm{C}\mathit{O}\mathrm{Me}$	B	−10.2 (−14.1)	−2.7 (−3.7)	68	$\mathrm{S(}\mathit{O}\mathrm{)OMe}$	A	−10.7	−2.7
49	$\mathrm{C}\mathit{O}\mathrm{NH_2}$	C	−13.3 [−7.1]	−2.7 [−2.3]	69	$\mathrm{S(}\mathit{O}\mathrm{)_2OMe}$	A	−7.5	−2.0
Seven-Membered Rings									
70	$\mathrm{CH_2CH{=}}\mathit{N}\mathrm{Me}$	B	−5.2 (−6.1)	−3.7 (−4.3)	73	$\mathrm{NMeCH}\mathit{O}$	B	−3.6	−4.0
71	$\mathrm{CH_2CH}\mathit{O}$	B	−2.9	−4.0	74	$\mathrm{OC}\mathit{O}\mathrm{Me}$	A	−4.2	−2.0
72	$\mathrm{NHCH}\mathit{O}$	C	−8.9 [−2.7]	−3.3 [−2.0]					

[a] $\Delta H_{\mathrm{intra-HB}}$ in kcal mol^{-1}, $\Delta S_{\mathrm{intra-HB}}$ in cal mol^{-1} K^{-1} identified as the difference between the hydrogen-bonded structure and the lowest-energy non-hydrogen-bonded (away) conformer. Capital letters denote the grouping according to the conformational relationship of the hydrogen bonded and the non-hydrogen bonded form (see text). For cases where the orientation of the 2-substituent in the hydrogen bonded form is not (approximately) retained in the lowest-energy away form but a “retained” form is found, the HB enthalpy and entropy of the latter are given in parentheses. For cases where in the lowest-energy away conformer a hydrogen atom of the 2-substituent forms a hydrogen bond to the phenolic oxygen, the values given in square brackets represent the energy difference of the two hydrogen-bonded forms. The leading number hence is the energy difference to the lowest-energy “true” non-HB form, that is, the one in which no “reverse” HB is present. [b] Hydrogen bond accepting atom in italics. [c] Number of atoms in the ring formed by the intramolecular hydrogen bond. [d] Intra-HB to sp^2 nitrogen. The bracketed number refers to the lowest-energy away orientation, with a hydrogen bond from the sp^3 nitrogen to the phenolic oxygen. [e] Hydrogen bond to π-system. [f] HB to sp^3 nitrogen. [g] The retained non-HB form is a rotational transition structure of 7.6 kcal mol^{-1} barrier height. [h] No other conformer calculated.

substituents the DFT geometry optimization always rendered a HB conformation. Comparing the non-HB form of e.g. 2-OH−PhOH, in which the two hydroxyl groups are pointed away from each other, with the radical in the same conformation yields a ΔBDE(O−H) of −4.5 kcal mol^{-1} demonstrating the substituent effect of the 2-OH group (which is almost identical to that for 2-MeO). However, when comparing the HB entities for the closed-shell molecule and the radical, the ΔBDE(O−H) decreases to −14.1 kcal mol^{-1}. The $\Delta H_{\mathrm{intra-HB}}$ in the molecule is −4.1 kcal mol^{-1} (see Table 2) implying that the $\Delta H_{\mathrm{intra-HB}}$ *increases* upon formation of the radical by −14.1−(−4.5) − (−4.1) = −5.5 kcal mol^{-1}, which increment has been confirmed experimentally.[18]

Discussion

Correlation of $\Delta H_{\mathrm{intra-HB}}$ with Structural Parameters. The definition used in this study for the $\Delta H_{\mathrm{intra-HB}}$ refers to the enthalpy difference at 298 K between the hydrogen-bonded and the lowest-energy non-hydrogen bonded structure. Only in this way a direct comparison with experimentally determined values may be possible (see below), because, upon cleavage of the hydrogen bond, the molecule will always relax to the lowest-energy conformation. In contrast with $\Delta H_{\mathrm{inter-HB}}$, defined as the enthalpy difference between the infinitely separated donor and acceptor and the hydrogen-bonded species, $\Delta H_{\mathrm{intra-HB}}$ relates to a conformational change within a single entity. Another clear distinction between an inter- and intra-HB bond in solution is that the former adopts an almost linear arrangement, whereas the latter consists of a cyclic ensemble in which the angle between the acceptor atom and the hydrogen is in most cases less than 150°.

Some general intuitive trends can be noticed between the geometrical and enthalpic data provided in Tables 1 and 2. The (O−H) distance, r(O−H), in the HB conformer increases while

TABLE 3: B3LYP/6-31G(d,p)-Calculated Changes in O−H Bond Dissociation Enthalpies for Non-Hydrogen-Bonded 2-Substituted Phenols, ΔBDE(O−H), in kcal mol^{-1} at 298 K

no.	2-X-phenol	ΔBDE[a]	σ_p^{+} [b]
1	H	0.0	0.00
2	F	−1.9	−0.07
3	Cl	−1.2	0.11
4	Br	−1.2	0.15
5	CH_3	−2.0	−0.31
6	CF_3	1.3	0.61
7	CH_2F	−1.9	
8	CH_2Cl	−0.7	−0.01
9	CH_2Br	−0.9	0.02
10	CH_2CN	−1.5	0.16
11	$CH_2CH{=}CH_2$	−2.4	−0.22
12	$CH_2CH{=}NMe$	−2.2	
13	CH_2CHO	−2.0	
14	CH_2NMe_2	−1.1	
15	CH_2OH	−3.0	−0.04
16	CH_2SMe	−2.2	
17	CCH	−1.6	0.18
18	CH═NH	−1.7	
19	CH═NMe	−2.3	
20	CH═NOH	−3.2	
21	CN	1.4	0.66
22	CHO	0.6	0.47
23	COMe	−0.4	0.50
24	2-tetrahydrofuryl	−2.2	
25	$CONH_2$	[−3.1][c]	0.36
26	$CONMe_2$	−1.1	
27	COOH	1.7 [−4.7]	0.42
28	COOMe	1.9	0.49
29	CHS	−4.4 (−1.0)	
30	CSMe	−8.1 (−1.9)	
31	2-pyridyl	−3.7	
32	2-imidazyl	[−8.4][c]	
33	4-imidazyl	−6.0	
34	NH_2	[−11.4][c]	−1.30
35	NMe_2	−10.4	−1.70
36	NHCHO	[−8.1][c]	
37	NMeCHO	−3.4	
38	$N{=}CH_2$	−2.8	
39	NC	−0.3	
40	$NH{-}NH_2$	[−12.5][c]	
41	$NMe\text{-}NH_2$	−11.0	
42	N═NMe	−1.5 (−0.4)	
43	N_3	−7.2	
44	NO	−12.5 (−7.9)	
45	NO_2	2.7	0.79
46	OH	−4.5 [−14.1]	−0.78
47	OMe	−5.0	−0.78
48	OCOMe	−2.3	−0.19
49	OPh	−3.2	−0.50
50	ONO	−6.8	
51	PH_2	−2.0	0.06
52	PH_2O	0.0	
53	PMe_2	−3.0 (−1.4)	
54	$P(O)(OH)_2$	[−2.2][c]	
55	$P(O)(OMe)_2$	−0.8	
56	SH	−4.3 [−6.8]	−0.03
57	SMe	−4.5	−0.60
58	SCN	0.8	
59	S(O)Me	−1.7	
60	$S(O)_2Me$	0.4	
61	S(O)OMe	1.8	
62	$S(O)_2OMe$	2.4	

[a] Difference in reaction enthalpy of the reaction 2-X-PhOH → 2-X-PhO$^{\bullet}$ + H$^{\bullet}$ relative to the bond dissociation enthalpy of 82.8 kcal mol^{-1} for phenol (X = H), using the lowest-energy non-hydrogen-bonded conformer for the molecule and the lowest-energy conformer of the phenoxyl radical for which no "reverse" hydrogen bond exists in the non-HB (away) form nor in the radical. Bold face numbers denote those cases where the conformation of the 2-substituent in the HB form is retained in the non-HB form as well as in the phenoxyl radical. For cases where the 2-substituent in the lowest-energy phenoxyl radical has a different orientation than in the parent lowest-energy non-hydrogen bonded form, the BDE to the "retained" form of the radical is given in parentheses, provided such a conformation is found. For cases where the 2-substituent forms an intramolecular hydrogen bond to the phenolic oxygen in the away conformer and/or the phenoxyl radical the values are given in square brackets. [b] All values for σ_p^{+} from ref 19, with σ_p^{+} (COMe) = σ_p(COMe) = 0.50; σ_p^{+} (CHO) = 0.47 (Selassie, C. D.; Shuterman, A. J.; Kapur, S.; Verma, R. P.; Zhang, L.; Hansch, C. *J. Chem. Soc. Perkin Trans. 2* **1999**, 2729−2733). [c] No non-HB radical possible or found.

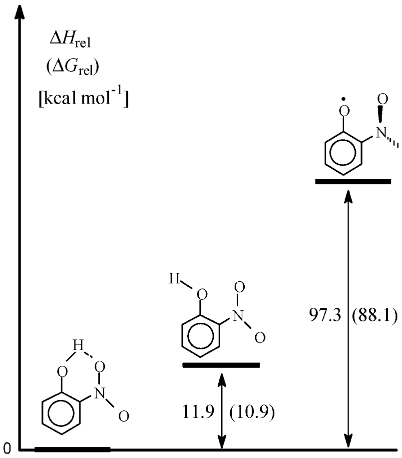

Figure 2. B3LYP/6-31G(d,p) energy scheme for 2-nitro-phenol as prototype for group A (see text) 2-substituted phenols.

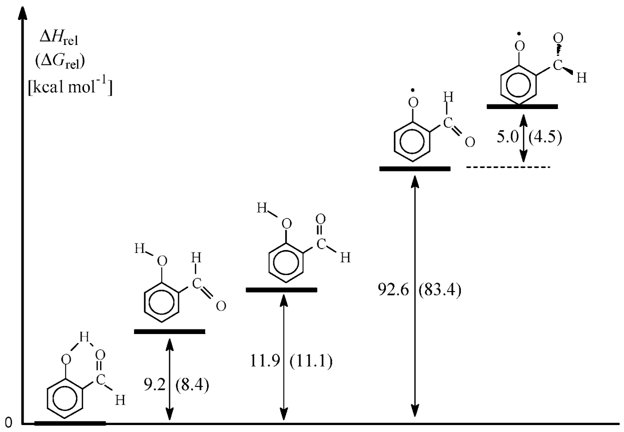

Figure 3. B3LYP/6-31G(d,p) energy scheme for 2-hydroxybenzaldehyde as prototype for group B (see text) 2-substituted phenols.

at the same time the length of the hydrogen bond, r(OH⋯A), decreases with $\Delta H_{intra-HB}$. Although this may be right in a qualitative fashion, no straightforward correlation appears to exist. This is illustrated in Figures 5 and 6, in which $\Delta H_{intra-HB}$ is plotted against r(O−H) or r(OH⋯A) for all of the data. A further refinement, i.e., distinguishing between the nature of the hydrogen bond accepting atom (O, N, and S), the subcategories A−D, or the size the HB ring does not lead to any significant improvement.[20]

For intermolecular hydrogen bonds, the change in the O−H stretching frequency has been frequently correlated with $\Delta H_{inter-HB}$ in a linear fashion.[21] To validate our computed ν(O−H) for the intra-HB conformer, a comparison has been made with experimentally determined OH frequencies in solution (CCl_4) as presented in Table 1. A quite satisfying linear least-squares fit

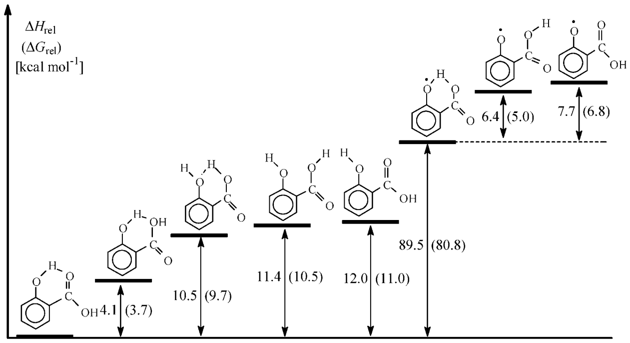

Figure 4. B3LYP/6-31G(d,p) energy scheme for 2-hydroxybenzoic acid as prototype for group C (see text) 2-substituted phenols.

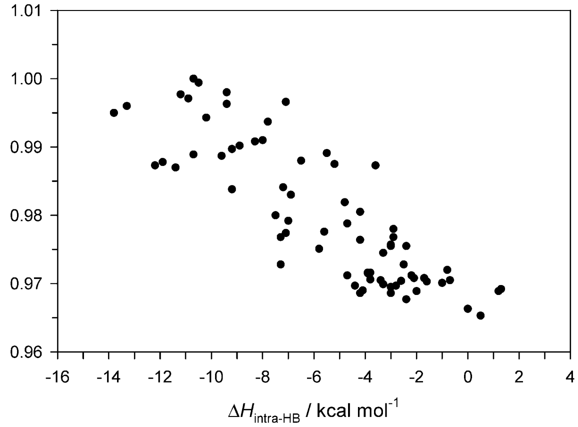

Figure 5. Plot of B3LYP/6-31G(d,p)-computed O−H bond lengths versus hydrogen bond enthalpies of intramolecularly hydrogen-bonded 2-substituted phenols.

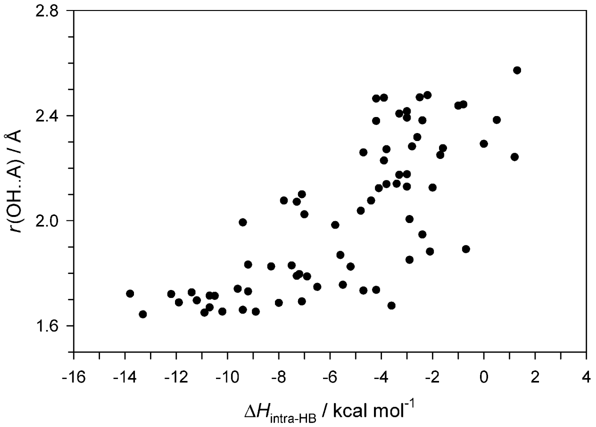

Figure 6. Plot of B3LYP/6-31G(d,p)-computed hydrogen bond lengths versus hydrogen bond enthalpies of intramolecularly hydrogen-bonded 2-substituted phenols.

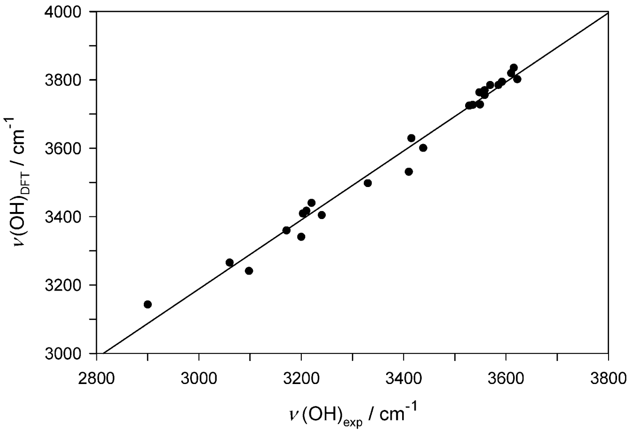

Figure 7. Correlation of B3LYP/6-31G(d,p)-computed and experimental OH vibrational frequencies in intramolecularly hydrogen-bonded 2-substituted phenols. Regression line: $\nu(\mathrm{O{-}H})_{\mathrm{DFT}} = 1.0097\nu(\mathrm{O{-}H})_{\mathrm{exp}} + 159.5$ ($r^2 = 0.982$, $n = 25$).

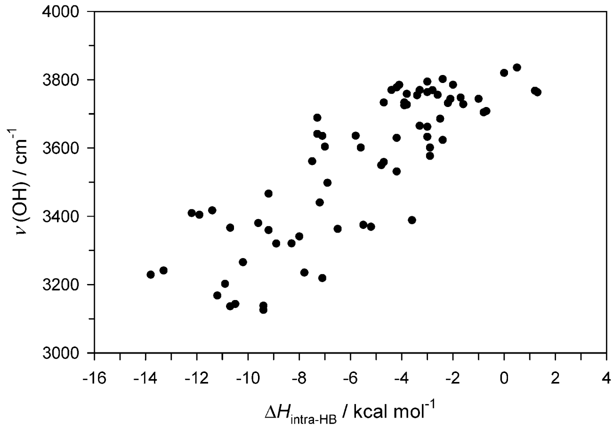

Figure 8. Plot of B3LYP/6-31G(d,p)-computed OH vibrational frequencies versus hydrogen bond enthalpies of intramolecularly hydrogen-bonded 2-substituted phenols.

is obtained obeying $\nu(\mathrm{O{-}H})_{\mathrm{DFT}} = 1.0097\nu(\mathrm{O{-}H})_{\mathrm{exp}} + 159.5$ with $n = 25$ and $r^2 = 0.982$ (Figure 7). Hence, the well-known overestimation by DFT of the $\nu(\mathrm{O{-}H})_{\mathrm{exp}}$ in CCl_4 amounts at this level of theory to a constant value of about 160 cm^{-1}.[22]

However, a plot of ν(O−H) versus $\Delta H_{\mathrm{intra-HB}}$ for all compounds, see Figure 8, reveals at best a crude relationship.

It is tempting to correlate $\Delta H_{\mathrm{intra-HB}}$ with a single parameter. However, the hydrogen bond energy is the result of interactions such a dipole−dipole interaction, electron-pair repulsion, dispersion, or steric hindrance. This study, enclosing a broad range of HB acceptors, demonstrates that without a comprehensive understanding of the basic features determining $\Delta H_{\mathrm{intra-HB}}$ such an effort is destined to fail.[23] Therefore, each individual intra-HB (model) interaction needs to be computed separately, which is a straightforward "experiment" with the currently available computational methodology.

An alternative method to furnish $\Delta H_{\mathrm{intra-HB}}$ has been suggested by using isodesmic reactions such as eq 1, where the reaction enthalpy is taken to be directly proportional to the strength of the hydrogen bond:[5k]

$$\text{2-X−PhOH} + \text{PhH} \rightarrow \text{PhOH} + \text{PhX} \qquad (1)$$

A DFT computation employing a 6-31+G(d,p) basis set reveals an energy difference for X = OH between the intra-HB and the non-HB conformer of −4.2 kcal mol^{-1}, in full agreement with our result with the 6-31G(d,p) basis set. In marked contrast, when the enthalpy change for eq 1 is taken as its measure, the $\Delta H_{\mathrm{intra-HB}}$ reduces to −0.5 kcal mol^{-1}.[5k] The reason is that the introduction of a second electron-donating group in an electron donor-substituted benzene leads to a relative destabilization of the 2-X-substituted phenol, an effect which is not related to the phenomenon of HB formation.[23b] Conversely, with X as a strong electron acceptor group, e.g., CHO, and using eq 1 and our DFT method, a similar hydrogen bond strength (−8.7 kcal mol^{-1}) is found compared with the direct approach (−9.2 kcal mol^{-1}). When the ground-state effects are not properly taken into account, an assessment of $\Delta H_{\mathrm{intra-HB}}$ on the basis of eq 1 inevitably leads to erroneous results.

Experimental and DFT Intramolecular Hydrogen Bond Enthalpies. Table 4 provides an extensive literature survey of

TABLE 4: Experimental Intramolecular Hydrogen Bond Enthalpies Determined by Various Methods, Given as $-\Delta H_{\mathrm{intra-HB}}$ in kcal mol^{-1}

2-X-phenol	cal[a]	cal[b]	GLC[c]	NMR[d]	far-IR[e]	IR[f]	IR[g]	IR[h]	IR[i]	DFT[j]
F			2.3		1.44	0.9		1.19		3.0
Cl	1.4		3.3	2.36	1.62		3.41	1.44		3.0
Br	1.1		3.9	2.14	1.57		3.13	1.21		3.9
I			3.4	1.65	1.45		2.75	1.08		
OMe	2.2		3.8		2.00	4.1				4.4
CHO	5.2		8.2			8.1				9.2
NO_2		4.8	8.3			6.2				11.9
COOH		4.3								11.4
COOMe			7.5							12.2
OEt					2.31					
CN					1.73					2.6
Ph					2.73					
$CH{=}CH_2$									0.46	
CH_2Ph									0.33	
$C(CH_3){=}CH_2$									0.76	

[a] Calorimetric method based on solvation enthalpies, ref 24. [b] Calorimetric method based on sublimation enthalpies, ref 25. [c] Gas−liquid chromatography, ref 26. [d] Reference 27. [e] Reference 28. [f] Reference 29. [g] Reference 30. [h] Reference 31. [i] Reference 32. [j] This study (see Table 2).

experimentally determined $\Delta H_{\mathrm{intra-HB}}$s, supplemented by our DFT data. The most direct way to obtain the $\Delta H_{\mathrm{intra-HB}}$ is by tracing the equilibrium ratio between the intra-HB and non-HB entities as a function of temperature in a non-HBA solvent, using an analytical tool such as IR or NMR. Imposed by detection limits, however, only hydrogen bonds with a $\Delta H_{\mathrm{intra-HB}}$ up to -4 kcal mol^{-1} can be characterized in this way. For a $\Delta H_{\mathrm{intra-HB}}$ of about -4 kcal mol^{-1}, like in 2-MeO-PhOH, the ratio between the two conformers is already 10^3, whereas for 2-NO_2-PhOH with an $\Delta H_{\mathrm{intra-HB}}$ of -11.9 kcal mol^{-1} the ratio in the gas phase or in a non-hydrogen-bonding solvent reaches 10^8 at 298 K, preventing any experimental determination.

Employing the direct IR or NMR detection method, several $\Delta H_{\mathrm{intra-HB}}$ values for (weak) hydrogen bonds have been reported.[30−32] Without studying the temperature dependence, the $\Delta H_{\mathrm{intra-HB}}$s can also be retrieved from rotational barriers computed from the phenolic OH torsion frequency as detected by far-IR.[28] Alternatively, for the OH- -$\pi_{\mathrm{C=C}}$ interaction in 2-allylphenol, a 2:1 equilibrium ratio at 298 K has been determined in the gas phase by means of photoelectron spectroscopy, corresponding to $\Delta G_{\mathrm{intra-HB}} = -0.4$ kcal mol^{-1}, in good agreement with the -1.0 kcal mol^{-1} from our DFT procedure.[33]

Experimental enthalpic data for stronger hydrogen bonds have been obtained by studying the competition between intra- versus inter-hydrogen-bond formation for 2-X−PhOH using an absorption/desorption (GLC), calorimetric, or IR detection method.[24,26,29] In these studies, it is always assumed that the acceptor moiety (i.e., stationary phase, solute, or solvent) solely interacts with the non-HB conformer and that for the purpose of calibration the $\Delta H_{\mathrm{inter-HB}}$ is equal for 2- and 4-substituted phenols. By way of contrast, it has been demonstrated that for, for example, 2-MeO-PhOH, the inter-HB formation occurs primarily with the intra-HB conformer, because that is energetically the most favorable route.[3] More importantly, the $\Delta H_{\mathrm{inter-HB}}$ of an additional inter-HB with the intra-HB form, forming a bifurcated complex, is less than the (hypothetical) $\Delta H_{\mathrm{inter-HB}}$ with the non-HB species. For weaker intra-HBs, the concentration of the entity with only an inter-HB increases, and a complex (equilibrated) mixture of up to four different species arises (A−D, see Figure 9).

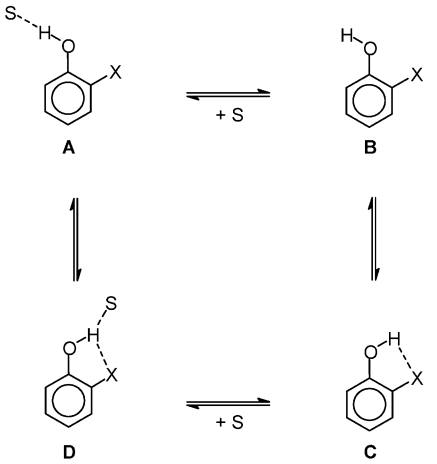

Figure 9. Four possible entities for a 2-X-phenol in the presence of a hydrogen bonding acceptor (S).

Consequently, the direct extraction of a single enthalpic value appears to be an impossible task.[34] Similar problems are encountered with the calorimetric determination based on sublimation enthalpies, where $\Delta H_{\mathrm{intra-HB}}$ is calculated from the decrease in $\Delta H_{\mathrm{inter-HB}}$ on going from a 4-X−PhOH to an 2-X−PhOH, thereby ignoring the presence of intra−inter (bifurcated) species.[25] In conclusion, it is most likely that the experimental $\Delta H_{\mathrm{intra-HB}}$s presented in columns 2, 3, 4, and 7 of Table 4 are underestimates. Besides, the available experimental data obtained by different methods, as given in Table 4, show a substantial scatter. For example, the $\Delta H_{\mathrm{intra-HB}}$ ranges from -4.8 to -8.3 kcal mol^{-1} for 2-NO_2-PhOH and deviates significantly from the -11.9 kcal mol^{-1} as found in this study. Thus, in view of the experimental uncertainties, it appears to be virtually impossible to verify our DFT-computed $\Delta H_{\mathrm{intra-HB}}$s. As outlined before, for 2-MeO, a good agreement between DFT and experiment has been found.[3a] In general, energetic data obtained by DFT are certainly reliable in a relative fashion (most likely as a result of cancellations of errors) as has been demonstrated for computations of the ΔBDE(C−H)s in hydroaromatics[35] or ΔBDE(O−H)s in phenols[17c] at this level of theory.[36] It is therefore reasonable to assume that the (relative) enthalpies provided in Table 2 are sufficiently accurate and can be used for further physical-organic interpretations.

Correlation with Solute and Solvent Parameters. An empirical way to quantify the energetics of an intermolecular hydrogen bond is using the Abraham's parameters for the hydrogen bond acidity, α_2^{H}, for the solute[37a] and the hydrogen bond basicity, β_2^{H}, for the solvent.[37b] A well-established correlation exists between log $K_{\mathrm{inter-HB}}$ or, equivalently, $\Delta G_{\mathrm{inter-HB}}$ for a 1:1 hydrogen-bonded complex in CCl_4, in which log $K_{\mathrm{inter-HB}}$ equals $7.354\alpha_2^{\mathrm{H}}\beta_2^{\mathrm{H}} - 1.094$.[38] A vast number of these parameters are available or can be obtained easily by experiment, and therefore, the $\Delta G_{\mathrm{inter-HB}}$ for virtually any intermolecular hydrogen bond can be established in this way. To investigate if such a relationship also exists for the DFT-derived $\Delta G_{\mathrm{intra-HB}}$, we have used the β_2^{H} for the substituted benzene, PhX, together with α_2^{H} values for the corresponding 4-X-PhOH compiling a data set for 25 2-X−PhOHs.[39] In contrast with the inter-HBs, no relationship could be found between $\Delta G_{\mathrm{intra-HB}}$ or $\Delta H_{\mathrm{intra-HB}}$ and $\alpha_2^{\mathrm{H}}\beta_2^{\mathrm{H}}$. For comparison, a $\Delta H_{\mathrm{intra-HB}}$ of -11.9 kcal mol^{-1} is computed for 2-NO_2-PhOH, whereas according to Abraham's equation, and accepting $\Delta S_{\mathrm{inter-HB}}$ of -11 cal mol^{-1}K^{-1},[17a] the $\Delta H_{\mathrm{inter-HB}}$ between 4-NO_2-PhOH and $PhNO_2$ amounts to -3.7 kcal mol^{-1}. Thus, with the same structural elements, the inter-HB is substantially weaker, by more than 8 kcal mol^{-1}, than the intra-HB. According to the same procedure the difference between $\Delta H_{\mathrm{intra-HB}}$ and $\Delta H_{\mathrm{inter-HB}}$ for 2-MeO-PhOH is quite

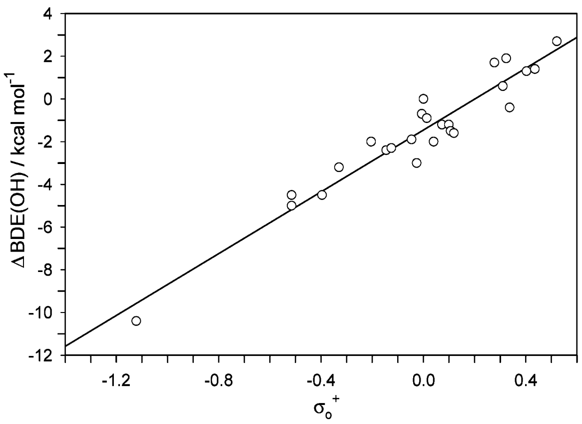

Figure 10. Correlation of B3LYP/6-31G(d,p)-computed differences in OH bond dissociation enthalpies of non-hydrogen-bonded 2-substituted phenols and σ_o^+ parameters (from $\sigma_o^+ = 0.66\sigma_p^+$). Regression line: ΔBDE(O−H) = $7.24\sigma_o^+ - 1.45$ ($r^2 = 0.92$, $n = 25$).

modest (−4.4 vs −3.3 kcal mol^{-1}). The hydrogen bond donating ability, α_2^H, of 4-NO_2-PhOH is superior when compared with phenol. In 2-NO_2-PhOH, the combination of a donor and a strongly electron withdrawing group as the acceptor leads to an amplification of the internal acidity of OH (and the basicity of the acceptor) by means of a push−pull mechanism, and consequently, the intra-HB strength is fortified (this phenomenon is also referred to as resonance-assisted hydrogen bonding). On the other hand, for an electron-donating group, such as MeO, the influence on the acidity of 4-MeO-PhOH is already marginal, and therefore, the relative strengthening of the intra-HB in the 2-MeO-PhOH is not expected to be significant. This analysis shows that in order to establish a general equation predicting $\Delta G_{\text{intra}-\text{HB}}$ (or $\Delta H_{\text{intra}-\text{HB}}$) similar to the one for intermolecular hydrogen bonds, a different set of α_2^H and β_2^H values needs to be developed to accommodate the intramolecular electronic interactions.

Correlation of BDE(O−H) with Substituent Constant σ^+. The effect of substituents on the BDE(O−H) for phenolic compounds has been investigated extensively. Experimentally, by means of photoacoustic studies on the BDE(O−H)s for a number of (poly)substituted phenols (including electron withdrawing and donating groups), an excellent linear Hammett type relation, eq 2, has been found between the ΔBDE(O−H) and the Brown substituent constant σ^+, with a range for σ_p^+ of −1.4 to +0.6 and a regression coefficient, r^2, of 0.98:[40]

$$\Delta\text{BDE(X-PhO−H)} = 6.89\sigma_p^+ + 0.23 \qquad (2)$$

To derive a similar relationship for non-HB 2-X−PhOH, an additional equation of $\sigma_o^+ = 0.66\sigma_p^+$ is required, which has been originally proposed for only three 2-X substituents: Cl, MeO, and Me.[41] From the present study, computed ΔBDE(O−H)s are now available for a broad range of 2-X−PhOH compounds (Table 3), and a similar plot (see Figure 10) has been constructed yielding eq 3 with $r^2 = 0.920$ and $n = 25$:[42]

$$\Delta\text{BDE(2-X−PhO−H)} = 7.24\sigma_o^+ - 1.45 \qquad (3)$$

The slope is quite similar to the one determined experimentally for other phenols (eq 2), underscoring the general validity of $\sigma_o^+ = 0.66\sigma_p^+$ in conjunction with DFT computations.[43] It should be noted, however, that the listing of σ_p^+ might not be perfect, which substantially influences the quality of such a correlation.[44]

Conclusion

The computation of a broad range of intramolecular hydrogen bond enthalpies in 2-X-phenols has revealed little correlation with selected geometrical parameters. Possible single descriptors such as the length of the phenolic O−H bond, *r*(O−H), the distance between the phenolic hydrogen and the acceptor atom, *r*(OH···A), or the shift in O−H stretching frequencies, Δ*ν*(O−H), do not correlate reasonably with $\Delta H_{\text{intra}-\text{HB}}$ even when using the lowest-energy non-HB conformer, i.e., the one with an optimal conformational arrangement of X as the reference. The main reason is that the $\Delta H_{\text{intra}-\text{HB}}$ contains enthalpic contributions not associated with the donor−acceptor interaction. The accuracy of the experimental $\Delta H_{\text{intra}-\text{HB}}$s for medium and strong hydrogen bonds can be questioned. In the absence of an adequate experimental method, DFT computations as presented in this work can be used advantageously to obtain $\Delta H_{\text{intra}-\text{HB}}$ values for a wide range of hydrogen bond accepting substituents. It has been shown that the well-established Hammett correlation for 4-X-phenols can also be applied to obtain relative BDE(O−H)s for non-HB 2-X-phenols.

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Supporting Information Available: Graphical representations (13 pages) displaying all DFT calculated structures including Δ*G* and Δ*H*, arranged in the order of Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) We have computed the O−H frequencies, ν(O−H), for inter-HB formation with species B and C (see Figure 9) of 2-MeOPhOH with three (model) hydrogen bond acceptors. The following ν(O−H) were obtained for the inter-HB (A) and inter-intra-HB (D) entities; with CH_2═NH: 3475.1 and 3479.2 cm^{-1}; with CH_2═O: 3643.9 and 3643.2 cm^{-1}; with Me_2O 3580.9 and 3539.1 cm^{-1}, respectively. In all cases, species D is the lowest-energy conformer but no or rather a small shift occurs in the ν(O−H) relative to that for A. With an IR detection method, it will therefore be difficult or even impossible to distinguish between these two species.

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(36) To explore a possible influence of the basis set employed, we have recalculated the structural and thermodynamic parameters for 2-X-PhOH (X = CF_3, MeO, CHO, and NO_2) with 6-31+G(d,p) instead of 6-31G-(d,p).[4] The results (see below) indicate only marginal changes in the structural parameters. The variations in $\Delta H_{\text{intra−HB}}$, $\Delta S_{\text{intra−HB}}$, and ΔBDE-(O−H) are quite modest as well and reinforces our conclusion that the computed data given in Table 2 are sufficiently accurate. Computational results for 2-X-PhOH with X = CF_3, MeO, CHO, NO_2: $r(\text{OH- -A}) = 2.0319$ (1.9471), 2.1085 (2.0766), 1.7531 (1.7305), 1.7076 (1.6886) Å; r(O−H) in phenol 0.9661 (0.9663) Å, $r(\text{O−H})_{\text{intra−HB}} = 0.9673$ (0.9677), 0.9697 (0.9697), 0.9886 (0.9897), 0.9863 (0.9878) Å; ν(O−H) for phenol 3828.7 (3819.7) cm^{-1}, $\nu(\text{O−H})_{\text{intra−HB}} = 3813.9$ (3801.9), 3777.9 (3769.8), 3386.3 (3359.7), 3435.2 (3404.4) cm^{-1}, with values in parentheses from Table 1. $\Delta H_{\text{intra−HB}} = −1.7$ (−2.4), −4.5 (−4.4), −8.4 (−9.2), −11.0 (−11.9) kcal mol^{-1}; $\Delta S_{\text{intra−HB}} = −0.3$ (−0.7), 0.0 (0.3), −2.7 (−2.7), −3.0 (−3.4) cal $mol^{-1}K^{-1}$ with values in parentheses from Table 2. BDE(O−H) in phenol 83.4 (82.8) kcal mol^{-1}; ΔBDE(O−H) = 1.9 (1.3), −5.9 (−5.0), 0.9 (0.6), 2.6 (2.7) with values in parentheses from Table 3.

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(39) This exercise includes the following 2-X−PhOH compounds: H, F, Cl, Br, CN, OH, OMe, OPh, SH, SMe, SCN, CH_2Cl, CH_2Br, CH_2CN, CH_2OH, CH_2NMe_2, 2-pyridyl, CHO, COMe, $CONH_2$, COOH, COOMe, NO_2, SOMe, and OCOMe. Because α_2^H values for 4-substituted phenols are only available for 10 of the substituents studied, others were derived from the correlation with substituent constant σ: A plot of α_2^H for para-

and meta-substituted phenols (including poly-substituted compounds) versus σ values yields a straight line following $\alpha_2^{H} = 0.26\ \sigma + 0.60$ with $r^2 = 0.96$.[19,37a]

(40) (a) Dorrestijn, E.; Laarhoven, L. J. J.; Arends, I. W. C. E.; Mulder, P. *J. Anal. Appl. Pyrolysis* **2000**, *54*, 153−192. (b) Mulder, P.; Saastad, O. W.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 4090−4092.

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(42) For the linear regression analysis, we have omitted ΔBDE(O−H) for $CONH_2$ and NH_2, because the non-HB radical does not exist. Also the value for 2-X = SH has not been incorporated; it seems highly unlikely that for a second row element the σ_p^+ for SH (−0.03) is so far apart from the σ_p^+ for SMe (−0.60). In Table 3, we have used an alternative value for σ_p^+ (OH) = −0.78 instead of −0.92, as outlined before.[17c]

(43) The equation for ΔBDE(O−H) derived by DFT needs to be treated with some caution. At the same level of theory for DFT, the linear regression for 4-substituted phenols yields $\Delta\text{BDE(4-X-PhO−H)} = 6.28\sigma_p^+ - 0.73$, with X = NH_2, OH, OMe, H, CF_3, NO_2, ($r^2 = 0.994$).[17c] This relationship deviates somewhat from eq 3 implying that some scatter between the computed BDE(O−H)s for polysubstituted phenol and $\sum\sigma_p^+$, i.e., deviation from linearity, can be expected.

(44) Not all σ_p^+ values have been determined by one single method, i.e., from the solvolysis of the corresponding *tert*-cumyl chlorides.[17c,19]