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Water Effect on the O−H Dissociation Enthalpy of Para-Substituted Phenols: a DFT Study

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The effect of water on the O−H bond dissociation enthalpy (BDE) of para-substituted phenols has been investigated by means of DFT calculations. It is shown that the experimental BDE values are fairly well-reproduced by simple B3LYP/6-31G* calculations carried out on the phenol/phenoxyl−water complexes taking into account only hydrogen-bonding (HB) interactions of water molecules with molecular sites (HB model). On the contrary, the BDE values computed with the polarizable continuum model (PCM/B3LYP/6-31G*) are overestimated by about 3−4 kcal/mol. Discrepancy between theory and experiment increases using the PCM method in addition to the HB model. Calculations show that, in general, the HB interaction with water molecules decreases the BDE of phenols bearing electron-releasing groups while increasing the BDE of phenols bearing electron-withdrawing substituents. This opposite effect is explained by considering the resonance structures with charge separation both in phenols and in phenoxyl radicals. With electron donors, the phenoxyl radical is preferentially stabilized by the HB acceptor interaction with two water molecules, while with electron acceptors the phenol is preferentially stabilized by the HB donor interaction with one water molecule.

Introduction

Knowledge of the O−H bond dissociation enthalpy (BDE) of phenols is of essential interest for understanding a wide range of redox processes in which molecules containing the phenolic moiety are involved, such as the activity[1] and the regeneration[2] of antioxidants, the redox cycle of enzyme cofactors,[3] and green plant photosynthesis.[4] The O−H BDE of phenols has been demonstrated to depend not only on the electronic effect of the ring substituents[1] but, to a considerable extent, also on the hydrogen-bonding (HB) interactions of the reactive center with nearby functional groups as in the case of *o*-methoxy[5] and *o*-hydroxy[6] phenols and bisphenols.[7] In all these cases, the overall effect on the BDE has been nicely explained in terms of differential stabilization of the couple phenol/phenoxyl radical. The thermochemical properties of the phenolic OH group were influenced also by the interaction with suitable solvents. In particular, solvents capable of accepting hydrogen bonds have been reported to enhance the BDE by stabilizing phenol with respect to the phenoxyl radical.[8] The increase in the BDE value has been demonstrated to be directly related to the strength of the hydrogen bond that can be estimated by evaluating the free energy of interaction between phenol, a hydrogen-bond donor (HBD) molecule, and the hydrogen-bond acceptor (HBA) solvent by means of the α^{H}_{2} and β^{H}_{2} Abraham scale.[9] The equilibrium constant relative to the interaction between a donor AH (α^{H}_{2}) and an acceptor B (β^{H}_{2}) is given by

$$\mathrm{AH} + \mathrm{B} \overset{K_1}{\rightleftharpoons} \mathrm{AH}\cdots\mathrm{B} \qquad (1)$$

$$\log K_1 = 7.354\alpha^{H}_{2}\beta^{H}_{2} - 1.094 \qquad (2)$$

The HBA and HBD properties of phenol and some relevant solvents are reported in Table 1.

Such observations led to the assumption that the apparent O−H bond strength for phenol and structurally related compounds should be considerably larger in

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TABLE 1. Selection of Some Relevant α^{H}_{2} and β^{H}_{2} Values[a]

compound	α^{H}_{2}	β^{H}_{2}
water	0.35	0.38
methanol	0.41	0.37
t-butanol	0.32	0.49
acetone	0.04	0.50
acetonitrile		0.44
benzene		0.14
HFP	0.77	0.03
phenol	0.60	0.22

[a] From ref 9.

TABLE 2. Comparison between the O−H BDE Values (kcal/mol) of Para-Substituted Phenols, *p*-X-PhOH, Determined Experimentally in Benzene and in Water

X	benzene[a]	water[b]
H	88.3	88.2
CH_3	86.2	86.1
OCH_3	82.8	82.6
OH	83.1[c]	80.2
NH_2	79.5[d]	75.5
$N(CH_3)_2$		74.1
Cl	87.9[e]	87.6
$COCH_3$		90.3
CHO	89.7[e]	
CN	89.7[e]	92.9
NO_2	90.4[e]	94.2

[a] Measured by the EPR equilibration technique (ref 1a). [b] Determined by the EC cycle.[13,14] [c] Estimated by adding to the BDE of the *p*-methoxyphenol the difference in the BDE between *p*-methoxy-2,6-di-*t*-butylphenol[1a] and 2,6-di-*t*-butylhydroquinone.[11] [d] From ref 11. [e] Estimated by subtracting the contribution of the ortho *t*-butyl groups (ref 1a) from the O−H BDE value measured for the para substituted 2,6-di-*t*-butylphenols (ref 1b).

solvents of high polarity than in apolar solvents.[8] Results obtained with the EPR equilibration technique[10] have recently shown that this statement needs to be revised because in using a strong HBD solvent (i.e., 1,1,1,3,3,3-hexafluoropropan-2-ol (HFP)), a preferential interaction with the phenoxyl radical leads to a significant decrease in the BDE[11], while *t*-butyl alcohol slightly increases the phenolic BDE by about 1−2 kcal/mol depending on the steric crowding around the oxidrilic group.[12] These findings opened the possibility that solvents capable of both accepting and donating hydrogen bonds, such as alcohols and water, could either enhance or decrease the phenolic BDE, the overall effect depending upon the difference between the interactions with phenol and the phenoxyl radical. It can be inferred from the α^{H}_{2} and β^{H}_{2} values reported in Table 1 that water is a better donor but a poorer acceptor of hydrogen bonds than alcohols and should be capable of better solvating the phenoxyl radical and solvating the parent phenol less. As a consequence, the effect of water should be either to enhance the O−H BDE, although less than *t*-butyl alcohol, or to decrease the BDE value with respect to apolar solvents, as found for HFP.

These expectations are supported by the results reported in Table 2, where the O−H BDE values estimated in water are compared to those obtained by EPR equilibration in benzene, a very weak HBA solvent (see Table 1) that is believed to not significantly enhance the BDE with respect to the gas phase. From Table 2, it appears that water has little effect on the BDE of phenol, whereas its influence is much greater with para-substituted phenols. According to the previous considerations, the effect can be of opposite sign depending on the electronic nature of the substituent.

By contrast, the O−H BDE of phenol was recently computed[15] to greatly increase (of ca. 7 kcal/mol) on going from benzene to water using DFT calculations with the polarizable continuum model (PCM). In particular, apolar solvents such as *n*-heptane and benzene had negligible effects on the BDE of phenols as expected. On the other hand, strongly HBA solvents (i.e., with an high β^{H}_{2} value) such as acetone and acetonitrile increased only slightly the BDE value by 1−2 kcal/mol, whereas H-bonding solvents capable of interacting both as acceptors and as donors of hydrogen bonding, such as methanol, ethanol, and water, largely increased the BDE value by 6−7 kcal/mol owing to their higher polarity. This trend is in clear contrast with what is expected from the α^{H}_{2} and β^{H}_{2} values. Thus, we decided to study in detail the effect of water on the O−H BDE of some para-substituted phenols by means of DFT calculations that have proven to give satisfactory results when used for predicting the thermochemical behavior of phenols.[11,16]

Computational Methods

DFT calculations with the B3LYP functional[17,18] were carried out on para-substituted phenols, *p*-X-PhOH (X = H, CH_3, CN, $COCH_3$, NH_2, $N(CH_3)_2$, NO_2, OH, OCH_3, Cl), and on their parent phenoxyl radicals using the GAUSSIAN98 system of programs[19] to estimate the O−H BDE values. Unrestricted wave function was used for radical species. A valence double-ζ basis set supplemented with polarization *d*-functions on heavy atoms (6-31G*)[20] was employed.

The effect of water on the O−H BDE values was investigated by means of the microsolvation approach that explicitly considers the interaction of a finite number of H_2O molecules with phenols and phenoxyl radicals (hydrogen-bonding model).

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(13) The O−H BDE values tabulated in ref 14 were determined by EC cycle using the measured one-electron reduction potential of the phenoxy radicals in water. They have been viewed as upper limits to the gas-phase values since they were obtained by setting to zero the difference between the free energy of solvation of phenols and phenoxyl radicals. On the other hand, these values can be considered as the O−H BDE of phenols in water solution. Indeed, the correct BDE values in water can be obtained by substituting in the EC cycle the small contribution due to the difference in entropy between phenol and phenoxyl radical calculated in the gas phase (−0.43 kcal/mol for phenol) with the corresponding value in water. The effect of solvation on this small contribution due to the entropy difference is expected to be very small.

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The O−H BDE values were computed using the isodesmic reaction

$$p\text{-X-PhOH-}n\text{H}_2\text{O} + \text{PhO}^\bullet \rightleftharpoons p\text{-X-PhO}\bullet\text{-}n\text{H}_2\text{O} + \text{PhOH} \quad (3)$$

in conjunction with the experimental O−H BDE value for phenol in benzene (88.3 kcal/mol)[1a] as

$$\text{BDE}_{\text{calc}}(p\text{-X-PhOH-}n\text{H}_2\text{O}) = \text{BDE}_{\text{exp}}(\text{PhOH}) + \Delta\text{BDE}_{\text{calc}}(p\text{-X-PhOH-}n\text{H}_2\text{O}) \quad (4)$$

where

$$\Delta\text{BDE}_{\text{calc}}(p\text{-X-PhOH-}n\text{H}_2\text{O}) = [E_{\text{calc}}(p\text{-X-PhO}^\bullet\text{-}n\text{H}_2\text{O}) - E_{\text{calc}}(p\text{-X-PhOH-}n\text{H}_2\text{O})] - [E_{\text{calc}}(\text{PhO}^\bullet) - E_{\text{calc}}(\text{PhOH})] \quad (5)$$

is the variation of the BDE with respect to that computed for the unsubstituted phenol in the absence of water. Analogous calculations were carried out also on the PhOH/PhO$^\bullet$-2-isooctane complexes. The nature of the located stationary points was ascertained by computation of harmonic vibrational frequencies (zero imaginary frequency). BDE values in water were also estimated with the PCM method carrying out calculations at the optimum geometries (PCM(solvent = water)/B3LYP/6-31G*//B3LYP/6-31G*).

Results and Discussion

Solvation Model of the Couple Phenol/Phenoxyl Radical. Water molecules can create clusters so the number and the position of the solvent molecules surrounding the phenolic OH group as well as the para substituents could influence the computed BDE values. Costa Cabral and co-workers[21] found that interaction of one to two molecules of water with the OH/O$^\bullet$ groups has little effect on the O−H BDE of phenol, while interaction with three to four molecules of water largely increases the BDE by about 6−8 kcal/mol at the B3LYP/D95V(d,p) level. They concluded that inclusion of a few water molecules (n = 3, 4) in the first coordination shell can provide a reliable estimation of the BDE of phenol in solution since the computed O−H BDE values are in accord with the experimental data in benzene and isooctane. This conclusion is questionable since isooctane is expected to have little effect on the BDE of phenol. Indeed, preliminary calculations performed at the B3LYP/6-31G* level placing two molecules of isooctane near the OH/O$^\bullet$ groups showed that the O−H BDE of phenol decreases by 0.4 kcal/mol. It is likely that the enhancement of the BDE value of phenol due to the presence of three to four molecules of water counterbalance the underestimation of the absolute BDE value computed with the B3LYP method in the gas phase.

TABLE 3. Effect of the Number (*n*) and Organization of Water Molecules on the O−H BDE (kcal/mol) of Phenol Calculated at the B3LYP/6-31G* Level

n	arrangement	BDE	ΔBDE
0		88.3	0.0
2	no mutual interactions	87.5	−0.8
2	ring cluster	95.3	7.0
3	ring cluster	97.6	9.3
4	ring cluster	97.9	9.5
5	ring cluster	98.2	9.9
5	cage cluster	90.1	1.8

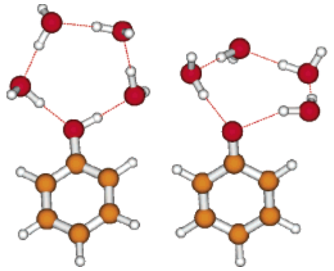

FIGURE 1. Structure of the phenol−4H$_2$O and phenoxyl−4H$_2$O complexes at theB3LYP/6-31G* level.

Thus, we have computed the O−H BDE of phenol interacting with n molecules of water (n = 2−5) using the isodesmic approach at the B3LYP/6-31G* level. We have recently shown[11] that this simple approach provides BDE values for para-substituted phenols in excellent agreement with those measured in benzene with the ESR equilibration technique. Interestingly, the estimate of zero-point vibrational energy (ZPVE), thermal correction to the enthalpy, and enlargement of the basis set (6-311++G**) were found to have negligible effect. Furthermore, the effect of HBD, HBA, and apolar solvents on the BDE was well-reproduced by placing two molecules of solvent near both the OH/O$^\bullet$ group and the para-substituent groups.

The results reported in Table 3 show that the O−H BDE of phenol increases by 7−9 kcal/mol when the molecules of water form a cycle around the OH/O$^\bullet$ groups (ring cluster) and are in line with the ones reported by Costa Cabral and co-workers. Figure 1 shows that in the phenol−4H$_2$O complex the H-bonds are oriented in the same direction (homodromic structure).[22]

This regular distribution has been reported to exist in particular environments (i.e., crystallized cyclodextrines[23]) and to considerably strengthen the overall interaction. Such a solvent organization is not possible in the phenoxyl radical, where one water molecule is forced to form a bifurcated H-bond (antidromic structure) to close the ring cluster. This different organization of the water molecules around the OH and O$^\bullet$ groups is responsible of the large difference between the BDE values computed in the presence and in the absence of water.

There is, however, evidence that this effect is reduced when one takes into account interaction with a large

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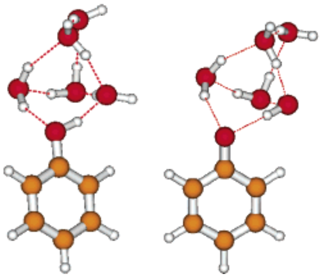

FIGURE 2. Cage structure of the phenol−$5H_2O$ and phenoxyl−$5H_2O$ complexes at the B3LYP/6-31G* level.

number of water molecules. It was previously shown that the clusters of n water molecules form a cyclic structure for $n \leq 5$.[24] However, the water molecules tend to form a cage cluster for $n = 6$. This structure should be more stable than the ring cluster also in the phenol−$5H_2O$ complex. Indeed, the cage cluster is computed to be significantly more stable than the ring cluster by 2.7 kcal/mol. Interestingly, Table 3 shows that the interaction with water in the cage structure increases the O−H BDE of phenol by only 1.8 kcal/mol with respect to the gas phase.

This is because in the cage cluster, antidromic structures are present not only in the phenoxyl−water complex but also in the phenol−water complex (Figure 2) since some water molecules have three HB interactions. It is therefore evident that the large increase in BDE of phenol previously reported is mainly an artifact due to the limited number of H_2O molecules used in the calculations that amplify the energy difference between the homodromic and antidromic distributions around the phenol/phenoxyl functional groups.

In the bulky system, all water molecules around the OH/O$^\bullet$ group should tend to more than two HB interactions so this effect should be further reduced. In fact, Table 2 shows that the BDE of phenol measured experimentally in water and in benzene are comparable. Interestingly, the effect on the BDE computed in the presence of two separated water molecules (−0.8 kcal/mol), as shown in Figure 3, is similar to the experimental result (−0.1 kcal/mol).

Hence, simulation of the effect of water by using a limited number of noninteracting solvent molecules gives reasonable results without time-consuming calculations. This is in line with what has been found by Chipman[25] who described in this way the structure, vibrational frequency, and hyperfine splitting constants of the phenoxyl radical.

Water Effect on the O−H BDE of Para-Substituted Phenols. Calculations were performed on para-substituted phenols by solvating the phenolic/phenoxyl group with two water molecules that did not interact with each other and the para substituents with the number of H_2O molecules necessary to saturate the HBA and HBD sites. To better understand the origins of the overall effect on the BDE, calculations were carried out also by solvating only the phenolic and phenoxyl groups. The effect of water on the O−H BDE of para-substituted phenols was investigated first on phenols bearing electron-releasing groups and then on phenols bearing electron-withdrawing groups.

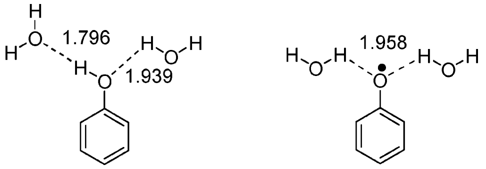

FIGURE 3. HB distances (Å) for the interaction of two separated water molecules with phenol and phenoxyl radical computed at the B3LYP/6-31G* level.

(a) Electron-Releasing Substituents. Phenols bearing OH or OR groups in the para position are very common in nature (Vitamine E, Co. Q) and are usually characterized by marked antioxidant effects due to the electron-releasing properties of these substituents that considerably reduce the O−H BDE value. Table 2 shows that the experimental BDE values of p-methoxyphenol and hydroquinone in benzene are almost identical. That is, in an apolar solvent, methyl substitution does not influence the electron-releasing property of the para oxygen atom. Interestingly, Table 4 shows that the experimental BDE values in benzene are well-reproduced by simple DFT calculations carried out in the gas phase ($n = 0$).

In water, the situation is dramatically different. The experimental BDE of hydroquinone in water is significantly smaller (by 2.8 kcal/mol) than that measured in benzene, whereas the influence of the solvent is negligible for p-methoxyphenol. This odd behavior can be understood by estimating the BDE of hydroquinone and p-methoxyphenol in the presence of a different number of H_2O molecules as shown in Table 4. Solvation of the phenolic/phenoxyl sites ($n = 2$) significantly decreases the BDE of hydroquinone and p-methoxyphenol by about the same amount with respect to the gas-phase value due to the preferential stabilization of the phenoxyl radical.

Actually, the phenoxyl oxygen acts as electron attractor so electron-donating para substituents such as OH and OCH_3 give rise to an enhanced charge separation, as shown in Scheme 1, which results in a better interaction with the water molecules in the phenoxyl radicals than in the parent phenols. By contrast, the oxygen atom of the para substituents in both phenoxyl radicals behaves as a worse HBA center than in their parent phenols since oxygen brings a partial positive charge in the radical as shown in Scheme 1. Thus, the HB interaction with water is weaker than in the parent phenols as evidenced from the lengthening of the HB distances reported in Figure 4. This leads to an increase in the BDE value that compensates the lowering due to the different solvation of the phenolic and phenoxyl groups. Indeed, Table 4 shows that for p-methoxyphenol, where only this interaction between para substituent and water is operative, the computed O−H BDE values in the gas phase ($n = 0$) and in water ($n = 3$) are similar as found experimentally. On the other hand, in the case of hydroquinone, there is also the HBA interaction of one water molecule with the hydrogen atom of the para OH group that is a better HBD site in the phenoxyl radical than in the parent phenol as evidenced by the shortening of the HB distance for this interaction reported in Figure 4. In fact, the resonance structure with charge separation shown in Scheme 1

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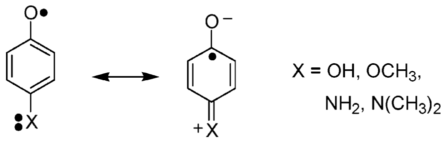
TABLE 4. O-H BDE (kcal/mol) for Para-Substituted Phenols *p*-X-PhOH Bearing Electron-Releasing Groups Interacting with *n* Molecules of Water Computed at the B3LYP/6-31G* Level[a]

	gas phase		water			
X	$n = 0$	exp in benzene	$n = 2$[b]	$n = 3$	$n = 4$	exp
H	88.3	88.3	87.5 (−0.8)			88.2 (−0.1)
OH	82.9 (−5.4)	83.1 (−5.2)	81.0 (−7.3)		79.6 (−8.7)	80.3 (−8.0)
OCH_3	82.9 (−5.4)	82.8 (−5.5)	80.7 (−7.6)	82.6 (−5.7)		82.7 (−5.6)
NH_2	79.8 (−8.5)	79.5 (−8.8)	76.4 (−11.9)		70.7 (−17.6)	75.6 (−12.7)
$N(CH_3)_2$	78.9 (−9.4)		74.8 (−13.5)			74.1 (−14.2)
CH_3	86.5 (−1.8)	86.2 (−2.1)	85.2 (−3.1)			86.1 (−2.2)
Cl	87.7 (−0.6)	87.9 (−0.4)	87.3 (−1.0)			87.6 (−0.7)

[a] ΔBDE values are reported in parentheses. [b] Near the phenolic/phenoxyl group.

SCHEME 1



suggests that the hydrogen atom of the para OH group should be more electron-deficient in the phenoxyl radical than in the parent phenol. Thus, this HB interaction stabilizes the radical species reducing significantly the BDE value with respect to the gas phase in accord with the experimental trend. Interestingly, Table 4 shows that the experimental results are well-reproduced by the DFT calculations in which the water molecules interact with all the HBA and HBD sites (i.e., $n = 3$ for X = p-OCH_3 and $n = 4$ for X = p-OH).[26]

Table 4 shows that the BDE value of *p*-aminophenol in benzene is well-reproduced by DFT calculations in the gas phase. The large decrease of the OH BDE observed experimentally on going from benzene to water is easily explained considering the interaction of water molecules with the phenolic/phenoxyl sites and with the hydrogens of the para NH_2 group. Both interactions stabilize the phenoxyl radical as discussed previously for X = OH. However, the BDE value computed solvating every HBA and HBD site (i.e., using four water molecules) was found to be much lower (by 4.9 kcal/mol) than the experimental one. This discrepancy is difficult to explain. Indeed, the stabilization of the phenoxyl radical due to the electron-releasing power of the para NH_2 group ($n = 2$) is computed to be slightly larger than that produced by the OH group as expected because of the greater electron-releasing capability of the nitrogen atom. Thus, the dimethylated derivative (*p*-dimethylamino phenol) in water was studied since there is no HB interaction between water and para substituent.

Table 4 shows that agreement between theory and experiment is excellent for *p*-dimethylamino phenol. The electron-releasing capability of the para nitrogen atom in water is well-described by the HB model. In particular, the decrease of the BDE value of *p*-dimethylamino phenol is larger than that computed for *p*-amino phenol solvating only the phenolic/phenoxylic sites ($n = 2$) as expected since the two methyl groups should enhance the electron-releasing capability of the nitrogen atom. Hence, the present hydrogen-bonding model is not able to describe the interaction of the amino group with water molecules probably owing to a particular organization of the water molecules around the para substituent. For example, complexation of the NH_2 group could involve directly more than two water molecules. It is noteworthy that the one-electron reduction potential of aminophenol radicals in water, used in the EC cycle to determine the BDE values, displays an anomalous trend with methyl substitution.[27] Thus, further theoretical studies on *p*-aminophenol are necessary to elucidate this point.

As expected, phenols substituted with weak electron-releasing groups such as CH_3 and Cl are computed to have about the same BDE both in gas phase and in water, in agreement with the experimental data measured in benzene and water.

(b) Electron-Withdrawing Substituents. Table 5 shows that water enhances the computed O−H BDE of para-substituted phenols bearing electron-withdrawing groups such as $COCH_3$, CN, and NO_2 in agreement with experimental data. This trend is opposite to that observed in the presence of electron-releasing groups.

Comparison of the HB distances in the unsubstituted phenol (Figure 3) and in the para-substituted phenols (Figure 5) shows that, in general, the interaction of water molecules with the phenolic/phenoxyl groups in the para-substituted phenols bearing electron-withdrawing groups is always stronger than in the unsubstituted phenol when water acts as a HBA solvent, whereas it is weaker when water works as an HBD solvent.

This common feature can be easily explained by considering the resonance structure shown in Scheme 2 for X = $COCH_3$.

In the phenol, a partial positive charge resides on the oxygen of the phenolic group reducing its HBA capability, while the polarization of the O−H bond increases its HBD property. The overall effect is a better solvation of the para-substituted phenol since the HBD interaction with water is more relevant than the HBA interaction, as can be quantitatively derived from eqs 1 and 2 and Table 1. On the other hand, the HBA interaction of the phenoxyl

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[26] A theoretical study on the effect of water on the BDE of para-substituted phenols was published when this paper was under examination by the referee (Fu, Y.; Liu, R.; Liu, L.; Guo, Q.-X. *J. Phys. Org. Chem*. **2004**, *17*, 282−288). The effect of water was simulated by placing one water molecule near the phenolic/phenoxyl group. Thus, this model cannot take into account the effect of water on the electronic properties of the para substituents that largely influence the BDE values of phenols. Indeed, this model does not reproduce the large decrease (2.8 kcal/mol) of the O−H BDE observed experimentally in water on going from hydroquinone to *p*-methoxyphenol. On the contrary, the BDE of hydroquinone has been computed to be 1.3 kcal/mol higher than that of *p*-methoxyphenol.

[27] The one-electron reduction potential of the dimethylaminophenoxyl radical decreases by 28 mV on substituting a methyl group with a hydrogen atom, but against any expectation, it increases by 43 mV on substituting both methyl groups with hydrogens. This apparent discrepancy was judged unclear by the authors.[28]

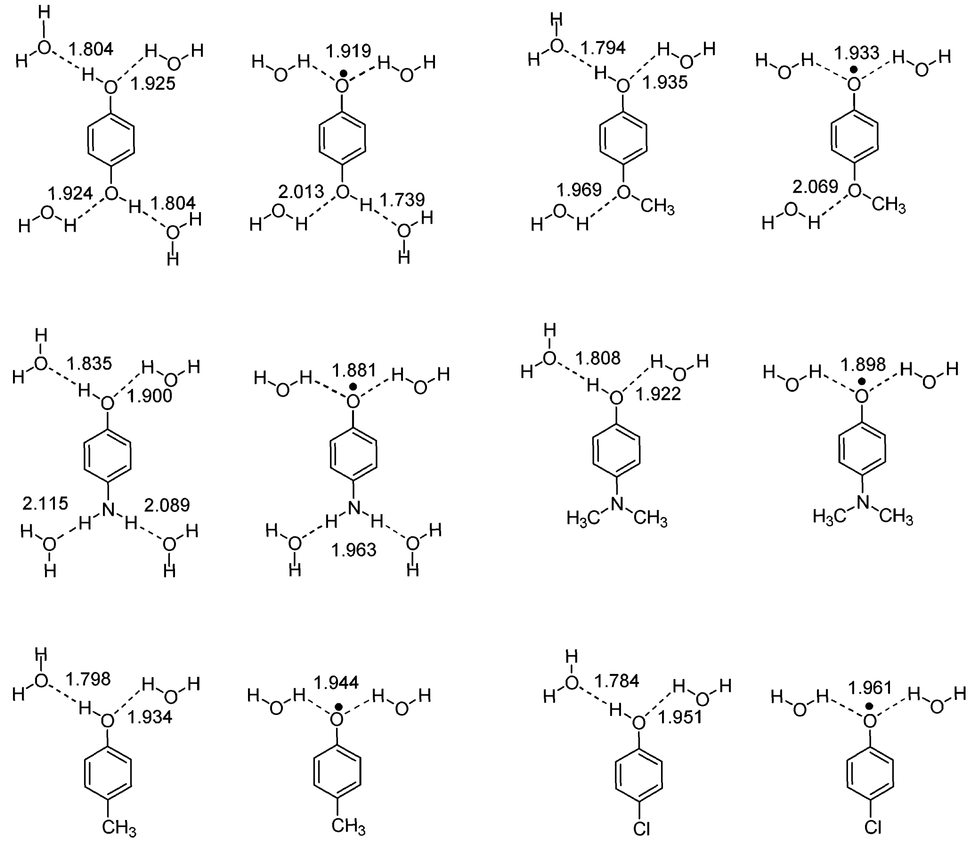

FIGURE 4. HB distances (Å) for the interaction of phenols and phenoxyl radicals bearing electron-releasing para substituents with water molecules computed at the B3LYP/6-31G* level.

TABLE 5. O−H BDE (kcal/mol) for Para-Substituted Phenols *p*-X-PhOH Bearing Electron-Withdrawing Groups Interacting with *n* Molecules of Water Computed at the B3LYP/6-31G* Level[a]

	gas phase		water			
X	$n = 0$	exp in benzene	$n = 2^b$	$n = 3$	$n = 4$	exp
H	88.3	88.3	87.5 (−0.8)			88.2 (−0.1)
$COCH_3$	90.4 (2.1)	89.7[c] (1.4)	90.4 (2.1)	91.6 (3.3)		90.3 (2.0)
CN	90.7 (2.4)	89.7 (1.4)	91.7 (3.4)	93.5 (5.2)		92.9 (4.6)
NO_2	92.8 (4.5)	90.4 (2.1)	94.5 (6.2)		96.0 (7.7)	94.2 (5.9)

[a] Δ*B*DE values are reported in parentheses. [b] Near the phenolic/phenoxyl group. [c] Value for X = CHO.

oxygen with water is always weaker in para-substituted phenols bearing electron-withdrawing groups than in the unsubstituted phenol since the O-atom is more electron-deficient. These two effects lead to an increase in the BDE on going from benzene to water that can be then modulated by the HB interactions of water with the para groups.

It is evident from Table 5 that DFT calculations slightly overestimate the O−H BDE of para-substituted phenol bearing electron-withdrawing substituents obtained in benzene solution. The reason may be ascribed to an excessive stabilization of π-delocalized structures that leads to the preferential stabilization of the parent phenol.[29] Indeed, this discrepancy increases with the capability of the X group to delocalize the π-electrons (*p*-NO_2 > *p*-CN, *p*-$COCH_3$). However, Table 5 shows that the variations of BDE on going from an apolar solvent to water are well-reproduced.

The approach of fully solvating the HB sites of *p*-$COCH_3$ phenol affords a satisfactory result. Unfortunately, the experimental value of the BDE in benzene is not available, but in such an apolar solvent, it should be reasonably similar to that of *p*-CHO phenol. Thus, the increase of BDE on going from an apolar solvent to water (0.6 kcal/mol) is fairly well-reproduced by calculations (1.2 kcal/mol). In particular, the HBD interaction of water with oxygen of the *p*-$COCH_3$ group increases slightly (1.2 kcal/mol) the computed O−H BDE value. This interaction stabilizes the resonance structure, present only in the phenol, which brings some negative charge to the oxygen of the keto group. For *p*-cyanophenol, the increase in the BDE value due to the HBD interaction of water with the cyano group is computed to be larger (1.8 kcal/mol), probably because the cyano group is more polarizable than the keto group. This increases significantly the BDE of *p*-cyanophenol as experimentally found. For what concerns *p*-nitrophenol, the calculations in the presence of four water molecules afforded an increase in the BDE

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(28) Steenken, S.; Neta, P. *J. Phys. Chem.* **1982**, *86*, 3661−3667.
(29) Guerra, M. *Theor. Chem. Acc.* **2000**, *104*, 455−460.

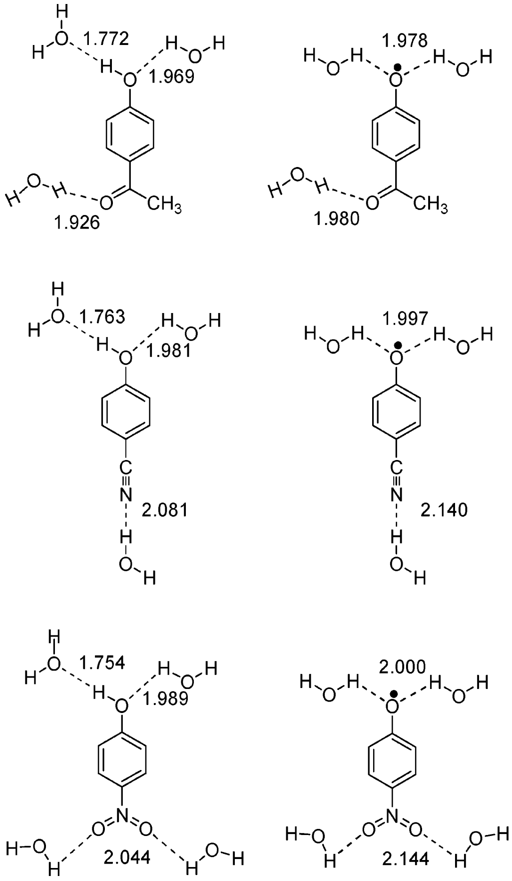
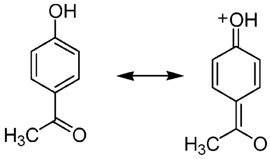


FIGURE 5. HB distances (Å) for the interaction of phenols and phenoxyl radicals bearing electron-withdrawing para substituents with water molecules.

SCHEME 2



of 3.2 kcal/mol, a value in fairly good agreement with the experimental one (3.8 kcal/mol). In this case, the HBD interaction of two water molecules with the oxygen atoms of the para nitro group produces an increase in the BDE value of 0.8 kcal/mol for each interaction that is slightly lower than that computed for the keto group.

(c) Comparison between Hydrogen-Bonding and Polarizable Continuum Models. It is interesting to see how the BDE values in water computed with the hydrogen-bonding model compare with those computed using the continuum solvation theory at the same level of theory. Table 6 shows that agreement between theory and experiment is fairly good for the HB model, while agreement is poor using the PCM approach (PCM/B3LYP/6-31G*), the BDEs being overestimated by about 3−4 kcal/mol. Importantly, the OH BDE values of para-substituted phenols bearing electron-releasing groups are computed with the PCM method to be much higher than those computed in the gas phase in evident contrast with the decrease of the experimental O−H BDE values on going from benzene to water (see Table 4) that is well-reproduced using the HB model. In particular, the PCM method underestimates significantly the large decrease of the O−H BDE measured experimentally in water on going from *p*-methoxyphenol to hydroquinone that is, instead, well-reproduced by the HB model. This is due to the fact that the PCM approach takes into account solvation effects only through long-range dipole−solvent interactions, whereas the HB model considers that in hydroquinone there is a HB interaction between the hydrogen atom of the hydroxy group and the oxygen atom of water that is absent in *p*-methoxyphenol. However, the overall trend of the relative BDE values in water is fairly good when reproduced by the PCM approach. We have then used the continuum solvation theory in addition to our HB model. Inspection of Table 6 shows that discrepancy between theory and experiment increases. In particular, the BDE values of para-substituted phenols bearing electron-withdrawing groups are largely overestimated by about 7 kcal/mol in evident contrast with experiment.

TABLE 6. O−H BDEs (kcal/mol) of Para-Substituted Phenols *p*-X-PhOH in Water Computed at the B3LYP/6-31G* Level with Different Models[a]

X	PCM	HB model	HB model plus PCM	exp[b]
H	90.6 (2.4)	87.5 (−0.7)	92.0 (3.8)	88.2
OH	83.7 (3.4)	79.5 (−0.8)	84.8 (4.5)	80.3
OCH_3	84.8 (2.1)	82.6 (−0.1)	86.4 (3.7)	82.7
$N(CH_3)_2$	78.1 (4.0)	74.5 (0.4)	76.9 (2.8)	74.1
CH_3	88.6 (2.5)	85.2 (−0.9)	89.6 (3.5)	86.1
Cl	91.1 (3.5)	87.3 (−0.3)	92.9 (5.3)	87.6
$COCH_3$	94.4 (4.1)	91.6 (1.3)	97.7 (7.4)	90.3
CN	95.6 (2.7)	93.5 (0.6)	99.2 (6.3)	92.9
NO_2	97.9 (3.7)	96.0 (1.8)	101.8 (7.6)	94.2
MAD[c]	3.2	0.8	5.0	

[a] Deviations from the experimental values are reported in parentheses. [b] From ref 14. [c] Mean absolute deviation.

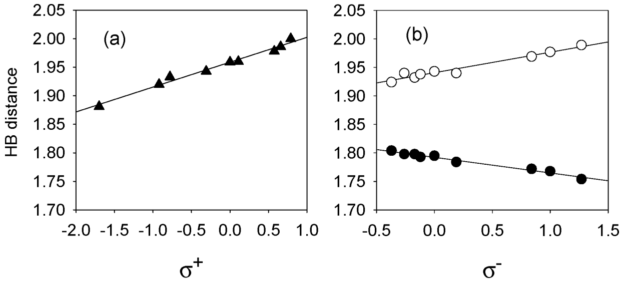


FIGURE 6. (a) Relation between the HB distance (Å) in the phenoxyl radical ($O^{\bullet}$−HOH) and the σ^+ value of para substituents. (b) Relation between the HB distances in the phenol and σ^- value of para substituents: (●) $OH-OH_2$ and (○) HO−HOH.

(d) Hammett Correlation of the Computed HB Distances with σ^+ and σ^- Constants of the Para Substituents. The effect of para substituents in determining the strength of the interaction of water molecules with the phenolic OH group and the phenoxyl radical $O^{\bullet}$ can be summarized by plotting the calculated distances of the hydrogen bonds ($d(OH-OH_2)$ and d(HO−HOH) in the phenol, $d(O^{\bullet}-HOH)$ in the phenoxyl radical) as a function of the σ^- and σ^+ constants of the para groups, respectively, as shown in Figure 6.[30] It is evident from eqs 6 and 7 that there is a good linear relation between

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[30] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

the two relevant distances in the parent phenol and the σ^- parameter, indicating that the extent of the considered interactions are dependent upon the resonance structures of Scheme 2. On the other hand, it has been found that the length of the hydrogen bonds between water and oxygen of the phenoxyl radical is in relation with the σ^+ parameter, as it can be expected considering the resonance structure of Scheme 1.

$$d(\mathrm{OH{-}OH_2}) = -0.027\sigma^- + 1.79;\ r^2 = 0.97 \quad (6)$$

$$d(\mathrm{HO{-}HOH}) = 0.036\sigma^- + 1.94;\ r^2 = 0.96 \quad (7)$$

$$d(\mathrm{O^{\bullet}{-}HOH}) = 0.044\sigma^+ + 1.96;\ r^2 = 0.98 \quad (8)$$

Conclusion

This work has demonstrated that it is possible to obtain realistic BDE values for para-substituted phenols in water by including few water molecules in relatively cheap DFT calculations using the isodesmic approach. Although some reservation could be maintained about the absolute BDE value for the usubstituted phenol, due to the lack of experimental values obtained with the same technique, there is no doubt that the relative values of BDE for each substituent are properly reproduced. It has also been shown that the widely accepted statement that water always enhances the O−H dissociation enthalpy of phenols is incorrect since either an increase or a reduction of the BDE can be expected, depending on which of the redox couple phenol/phenoxyl radical is better stabilized by the solvent. The overall effect was found to be greatly dependent upon the nature of the para substituents. Actually, electron-releasing groups lead to a better stabilization in water of the phenoxyl radical, whereas electron-withdrawing groups stabilize preferentially the parent phenol. All these observations were straightforwardly explained by means of the resonance structures that give rise to charge separation and therefore to a better solvation of the molecules.

Although BDE values represent fundamental data for the comprehension of the chemical behavior of phenolic molecules, it should be emphasized that they do not have a direct relation with the reactivity. Indeed, the kinetic rate constants for the reactions of phenols with radicals of various kinds are much slower in water than that in apolar solvents, as can be easily derived by means of the Kinetic Solvent Effect treatment developed by Ingold and co-workers that only considers the interaction of the parent phenol with the solvent.[31] The reason is that solvents capable of significantly solvating the phenoxyl radical such as HFP and water are not so good at stabilizing the transition state complex as demonstrated by studying the hydrogen abstraction from phenol by a methyl radical in the presence of two molecules of HFP with DFT calculations.[11] However, the BDE values in water are very useful in investigating processes where phenol/phenoxyl equilibria are involved, such as the cooperative effect of phenolic antioxidants in physiological conditions.

The study of the behavior of realistic molecules such as flavonoids and phenolic acids, characterized by more than one reactive phenolic OH and by a complex network of hydrogen bonds, will be a matter of further work.

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Supporting Information Available: Optimized geometries and total energies for the investigated species. This material is available free of charge via the Internet at http://pubs.acs.org.

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[31] Valgimigli, L.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1996**, *118*, 3545−3549.