Theoretical Calculation of Accurate Absolute and Relative Gas- and Liquid-Phase O–H Bond Dissociation Enthalpies of 2-Mono- and 2,6-Disubstituted Phenols, Using DFT/B3LYP

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DFT/B3LYP is used to calculate the gas-phase absolute and relative phenolic O–H bond dissociation enthalpies (BDEs) in hydroxy/methoxy ortho substituted phenols. The PCM and SCIPCM continuum models are applied to calculate the liquid-phase BDEs. This is the first theoretical determination of liquid-phase BDEs of phenols, the corresponding experimental data of which is rare. The solvated-phase optimized structures of both the parent phenols and their respective radicals are also presented for the first time. A systematic study on a series of 17 different basis sets on phenol, 2-hydroxyphenol (catechol), and 2-methoxyphenol (guaiacol) leads to the optimum 6-31+G(,3pd) basis set. Derived BDEs are among the most accurate of any gas-phase ones (deviations of the absolute gas-phase BDEs do not exceed 0.20 kcal/mol, relative to experiment, and those of the relative ones do not exceed 0.24 kcal/mol). Use of the optimum basis set to obtain the absolute gas-phase BDEs of 2,6-dimethoxyphenol (syringol) and 2,6-dihydroxyphenol (pyrogallol), the liquid-phase BDEs, the solvent, and substituent effects of phenols shows the usefulness of this approach. Seven solvents, differing in their H-bonding ability and polarity, *n*-heptane, benzene, acetone, acetonitrile, ethanol, methanol, and water, are used to model different environmental situations. Only the PCM model describes well the "bulk" solvent effects, which, depending on the E_N^T and/or α polarity parameter values of the solvent, modify the structure of the solute. Calculated liquid-phase BDEs are in close agreement with the experimental ones, where available, exceeding those in the gas-phase by as much as ca. 8 kcal/mol in some media. Solvent effects are common for catechol and phenol and different for guaiacol. Close agreement is derived between the theoretical and the experimental solvent effects for known phenolic antioxidants, namely, ubiquinols and flavonoids. The different ortho groups in catechol and guaiacol lead to different substituent effects in accordance with experimental findings.

Introduction

Solute–solvent interactions have a significant effect on the behavior of molecular systems; hence, understanding the influence of the solvent is required to make the connection to the solution environment, which is of principal experimental interest. Interestingly, although the vast majority of the bond dissociation enthalpy (BDE) determination in the literature refers to gas-phase reactions, most of the chemistry to which they are applied occurs in solution. As a consequence, the range of the solution values for the phenolic BDE(O–H) (hereafter denoted as BDE$_{solv}$ for the liquid-phase and BDE for the gas-phase) is well outside the claimed experimental errors of ca. ±2 kcal/mol. Following such evidence, a theoretical study will be presented in this paper on the "bulk" solvent effects on the BDE$_{solv}$ determination of some phenols. To the best of our knowledge, this is the first theoretical determination (using continuum models) of the liquid-phase BDEs of phenols, their experimental data being rare.[1–4] Thermochemistry in which this bond is broken is relevant to understanding both the antioxidant properties of phenolic antioxidants and the free radical reactions, in general. Moreover, knowledge of the BDE values is crucial in deciding whether a certain reaction is enthalpically favorable.

Phenolic compounds are useful antioxidants in both living organisms and life-supporting substances. For example, substituted phenols, such as α-tocopherol and ubiquinol-10, are natural antioxidants, important in the protection of human low-density lipoproteins (LDL); flavonoids are useful drugs in the treatment of several diseases. In addition, a variety of these compounds are widely used as additives in food technology.[5,6] Prediction of antioxidant activity is of vital importance nowadays, because it will improve the selection of new, more effective compounds with low toxicity and save experimental work. As a consequence, the interest in the relative evaluation of antioxidants, through the theoretical calculation of relevant molecular descriptors, increases.

The main mechanism of action of phenolic antioxidants (ArOH) is considered to be the scavenging of free radicals by donating their phenolic hydrogen atom,[7] namely

$$ROO^\bullet + ArOH \rightarrow ROOH + ArO^\bullet \qquad (1)$$

where ROO$^\bullet$ (formed as R$^\bullet$ + O$_2$ → ROO$^\bullet$), ArOH, ROOH, and ArO$^\bullet$ are a lipid peroxide radical, the parent phenolic antioxidant, the lipid hydroperoxide, and the respective antioxidant aroxyl radical, respectively. Their antioxidant character could be related to the readily abstractable phenolic H atom

$$ArOH \rightarrow ArO^\bullet + H^\bullet \qquad (2)$$

as a consequence of the rather weak phenolic O–H bond dissociation enthalpy, BDE, defined by eq 3

$$BDE(ArO–H) = H_f^0(ArO^\bullet) + H_f^0(H^\bullet) - H_f^0(ArOH) \quad (3)$$

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where, H_f^0's are the theoretically calculated gas-phase heats of formation (in kcal/mol at 298 K) of the aroxyl radical ArO•, the hydrogen atom H•, and the parent phenol ArOH. BDEs in solution are derived by an analogous equation, in which all of the H_f^0's have been replaced by their corresponding ones, H_f^S's, i.e., the enthalpies of solvation.

The formation and breaking of the O−H bonds can be calculated theoretically, with an accuracy of 1 kcal/mol in the gas phase. The G2 method of Curtiss et al.[8−10] gives heat of formation to within 2 kcal/mol for most systems. Nevertheless, this method is much more computationally demanding than even large-basis DFT calculations, because of the high-order dependence of the QCISD component of the calculation on the number of basis functions. On the contrary, DFT methods scale much more favorably with the size of basis set.[10,11] Because of the large size of the antioxidant molecules, semiempirical AM1 quantum-chemical methods have been employed for the structural optimization and the frequency calculations[12] and/or AM1 ones for the geometry optimization and frequency calculation, followed by a DFT single-point calculation with a large basis set.[13−16] Interestingly, this data is in better agreement than data[17] computed at a higher level of theory, namely, MP2 and MP4. Furthermore, Wu and Lai, found[18] that the JMW/DN level of theory afforded better BDE values than the nonlocal BLYP one, both with 6-31G(d) basis set.

Despite the rather extensive literature data, concerning the determination of the BDE of various antioxidants in the gas phase, there is a deficiency in regard to those in solution. EPR spectroscopy, electrochemical cycles (EC), photoacoustic calorimetry (PAC), and kinetic methodologies have been reported in the literature for the determination of BDE in the liquid phase. These latter methods, however, are mainly used for the determination of equilibrium and rate constants, pK_a's, etc., constituting the so-called kinetic solvent effect (KSE).[19−21] This is directly related to the hydrogen-bonding interactions between ArO−H and the solvent. It was shown that the experimental phenolic BDEs$_{solv}$ depend mainly on the experimental technique used. Hence, the agreement between the values measured with the various techniques is poor. Derived values are well outside the claimed experimental errors. Therefore, there is a great divergence between them and the selected value given in a recent review.[22]

Modeling of the solution environment is a growing area of interest within the computational chemistry. Reliable solvation models help this link to be accomplished in a quantitative fashion. Monte Carlo,[23] molecular dynamics techniques,[24] and continuum reaction field models[25,26] represent simple and popular approaches to describe the solution environment and have been explored extensively. The main advantage of the latter models is substantial savings of computational time; still they have been proved quite successful in a variety of applications.[27]

As part of a continuing investigation of the structure−activity relationships on phenolic antioxidants,[28−30] we have embarked on a project to investigate their energetics in both the gas- and the liquid-phase. Our aim is to establish a simple theoretical methodology, suitable for general application and capable to accurately calculate absolute and relative gas- and liquid-phase phenolic BDEs. The agreement with the experimental data should be within 1 kcal/mol or better. To accomplish this goal, the widely used DFT level of theory with the B3LYP function was employed, because it provides both a reliable and economical approach for prediction of phenol BDE,[17] as well as accurate geometries, vibrational frequencies, and spin densities for the phenoxyl radical.[31] A series of 17 different basis sets were tested

with DFT on phenol (its BDE provides a reference value for all phenolic antioxidants), catechol (2-hydroxyphenol, as model for flavonoids), and guaiacol, (2-methoxyphenol, as model for ubiquinol-0) and led to an optimum compromise between computational speed and accuracy. An application of our methodology, using the derived optimized basis set, has been the calculation of the gas-phase BDEs of syringol (2,6-dimethoxyphenol) and pyrogallol (2,6-dihydroxyphenol). The determination of the gas-phase BDE of pyrogallol had a predictive character, due to the absence of corresponding experimental data. It was decided that the continuum models PCM and SCIPCM, at the same level of theory, were to be used for the treatment of the solvent effects. These methods are most proper for the medium-sized molecules under study because[25,26,32] (i) they are much less time-consuming than comparative quantum-chemical calculations using explicit solvent molecules and (ii) have already been applied successfully for the calculation of many solvation processes. To model different environmental situations, seven dielectric media, ranging from strong polarity (water, ethanol, and methanol), via dipolar aprotic, acetonitrile, and acetone to the nonpolar, *n*-heptane and benzene, were selected. Hence, the absolute and relative solution-phase BDEs, the "bulk" solvent effects, and the substituent effects of the ortho substituents of some simple phenolic molecules have also been studied theoretically. In a recent paper, Wright et al.[16] identified the need of introducing a solvent model into the calculations, in an attempt to verify whether the solution-phase BDEs follow the same trends which are apparent in the gas-phase. This constitutes one of the main targets of the present study.

Method of Calculation

Gas Phase. All calculations reported in the present study were carried out using the density functional theory,[33] as implemented in the Gaussian 98 program suite.[34] Becke's 3-parameter hybrid functional combined with the Lee−Yang−Parr correlation functional, abbreviated as B3LYP level of density functional theory,[35−37] was used. Five-component Cartesian d polarization functions were used for the seventeen different basis sets. Full geometry optimization was performed, with tight convergence criteria, on each species and each particular basis. In all computations, no constrains were imposed on the geometry. All structures were true minima on the calculated potential surface, verified by final frequency calculations that provide energy minima with certainty. UB3LYP and ROB3LYP[14] were used for the geometry and vibrational frequency calculations of the respective radicals and the hydrogen atom. The latter method is the high-level model (HLM) described previously,[14] chosen because it is computationally feasible for our case (molecules with less than 15 heavy atoms); the former is a variation of the HLM introduced by us. Either method constitutes fully consistent calculation, because both the phenol and its respective radical are calculated at the same level of theory.

BDEs can be calculated by using eq 3. Theoretical values given in the present study are BDEs at 298 K, also known as heats of formation, ΔH_{298}^0. BDEs are the sum of the H_{298}^0 of the products (radicals) minus those of the reactants (parent molecules). In particular, the pure electronic energy of a molecule should be corrected thermochemically, to be parallel with the experimental one, by adding zero-point energy (ZPE), translational (3/2RT), rotational (3/2RT), and vibrational contribution, H_{vib}. Finally, RT (PV-work term) is added to convert the energy to enthalpy. The total enthalpy at 298 K for the parent molecules is the sum of the thermal correction to the enthalpy and the

B3LYP energy;[16] that for the radicals involves the thermal correction to the enthalpy and the UB3LYP or the ROB3LYP energies.[16]

Due to the fact that the theoretical harmonic vibrational frequencies are larger than the fundamentals observed experimentally,[38] generic frequency scaling factors are often applied. Because the thermal contribution to enthalpy is particularly sensitive to low-frequency vibrations, two different scale factors are used; one scale factor for the ZPE and another one for the thermal contribution to enthalpy. By following the comprehensive paper of Scott et al.,[39] a frequency scale factor of 0.9610 ($rms_{ov} = 26$ cm^{-1}) and scale factors of 0.9810 and 0.9985 for the DFT ZPEs and H_{vib}, respectively, were derived for our optimized basis set. However, the marginally close to one (0.9985) scale factor value results in an insignificant correction for the corresponding BDE. Actually, the BDE difference, derived between the BDE calculated by using two different scale factors (0.9810 for the ZPE and 0.9985 for the vibrational enthalpy) and that, in which the values of 0.9810 and 1.0000 was used, respectively, is only 0.0005 kcal/mol. Moreover, the corresponding increase of the BDE is only 0.15 kcal/mol, if only the scale factor for the DFT ZPEs is used. For this reason, one could work without resorting to ZPE and/or vibrational enthalpy scaling. In the BDE determination, the electronic energy values of the hydrogen atom for each particular basis set were used, instead of the exact electronic energy value (-0.50000 hartree).[14,40]

Solvation. Solvent effects were calculated using both the polarized continuum model (PCM)[41,42] and the self-consistent isodensity polarized continuum model (SCIPCM)[43] implemented in the Gaussian program.[34] The PCM analytical gradients, in its original dielectric formulation (D-PCM), available in the recent Gaussian 98 program, allows solution-phase geometry optimization within the PCM-UAHF[44] framework and also includes nonelectrostatic contributions to the solvation energy. This model was used for both the parent molecules and their respective radicals throughout, in the seven different media, specified only by their solvent dielectric constant value, ϵ. A wide spectrum of ϵ values was selected, ranging from 0 (*n*-heptane) to 78.39 (water). The cavity was described by a different number of tessarae, with average area of 0.4 Å^2, depending on each specific basis set, solute, and solvent. For the PCM calculation of the hydrogen radical, a van der Waals radius (Bondi's[45] or Pauling's[46] hydrogen radius) was assigned to the hydrogen, to built its cavity.

The cavity in the SCIPCM model is based upon an isosurface of the total electron density, and in our case, the value of 0.001 au isodensity contour was used for the isosurface level, ρ, as suggested by Zhan et al.[47] The most common convergence problems that appeared are mostly due to the multi-center integration procedure applied as default. Therefore, the single-center integration procedure, being a most accurate and stable method, was used with cavity surface points values of 770–974, for the special grids of the solutes studied. The SCIPCM calculation of the hydrogen radical itself did not show any difficulty, yielding to different energy value for each particular solvent.

For all molecules in solution, full geometry optimizations were carried out, with tight convergence criteria, at each corresponding B3LYP/basis level. For convergence reasons, the starting geometry was that optimized in solution, using a lower basis set. However, the very first starting geometry, for each particular solute, was that derived at the same lower level in the gas phase. Because of program limitations, the frequencies were calculated numerically, resulting in more time-consuming calculations. All of the final geometries and energies in both the gas- and the liquid-phase are available as Supporting Information (Tables S1 and S2).

Results and Discussion

Preliminary Calculations in the Gas Phase. In an attempt to approach the gas-phase absolute and relative BDEs of phenol, catechol, and guaiacol, the B3LYP functional along with a variety of basis sets were used. The BDE of phenol provides a reference value for all phenolic antioxidants. There are several reviews in the literature discussing the best experimental gas-phase value for phenol, the corresponding values being 87.0 ± 1,[1] 88.3 ± 0.8,[48] and/or 88.7 ± 0.5[22] kcal/mol. After the review of Dos Santos and Simoes,[22] the experimental BDE for phenol was taken to be 88.74 kcal/mol. The corresponding ones for catechol and guaiacol were taken to be[12] 81.64 and 84.54 kcal/mol, respectively.[12] It is worth mentioning here that the experimental value of the latter corresponds to the *away* conformer of guaiacol (being the one, in which the intramolecular H bond has been eliminated). In both experimental studies[4,12] for guaiacol, the Δ(BDE)s of the *away* conformer reported are ca. -4.2 kcal/mol. Moreover, it is clearly written[4] that the above Δ(BDE) corresponds to the pure O−H BDE, excluding all inter- and intramolecular hydrogen bond enthalpies, namely in the O−H BDE of the *away* conformer. Because, throughout preliminary calculations, our practice has been to simulate the available experimental O−H BDEs and Δ(BDE)s, the above Δ(BDE) for guaiacol has been used.

The variation in the phenolic BDE of phenol, catechol, and guaiacol (unscaled calculated BDEs for the DFT ZPE and enthalpy corrections are used in this section) as a function of seventeen different basis sets is shown in Figure 1a−c along with the corresponding experimental BDEs (dotted lines) for the same compounds. BDEs derived on the basis of 10 conventional basis sets (triangles) clearly show that, as expected,[13,49] all of the absolute BDEs lie well below the corresponding experimental values. The biggest conventional basis set of 6-311+G(2d,2p) gives a BDE which is still over 5.11, 7.20, and 5.97 kcal/mol too low for phenol, catechol, and guaiacol, respectively, (see also Table 1). A more careful inspection of Figure 1 also shows that (i) BDEs of the three phenols under study, increase by ca. 4.43 (phenol) to 4 (guaiacol) kcal/mol, going from the minimal to the largest basis set, (ii) if the basis set is reasonable [6-31+G(d,p) or larger] the resulting BDE is very close to the largest basis set one, (iii) the inclusion of diffuse functions on the heavy atoms basis sets results in an improvement of the absolute calculated BDEs, (iv) the opposite however, holds true for the concomitant inclusion of diffuse functions on the hydrogen atoms basis sets, (v) the inclusion of d polarized functions on the heavy atoms basis sets results in a decrease in the absolute calculated BDEs, and (vi) the inclusion of a second p polarization function on the hydrogen atoms basis sets approaches closer the corresponding experimental value than any other conventional basis set. Moreover, the accuracy achieved by the relative Δ(BDE)s is poor; they deviate [ΔΔ(BDE)% values] by as much as 36.6% (for catechol) and 28.6% (for guaiacol) from the experimental values (see also Table 1).

The above points (i−vi) could help to bring the absolute and relative BDEs into closer agreement with the experiment. It is evident that d functions should be avoided on the heavy atoms basis sets and diffuse functions on the hydrogen atoms ones, because they result to a decrease in the absolute calculated
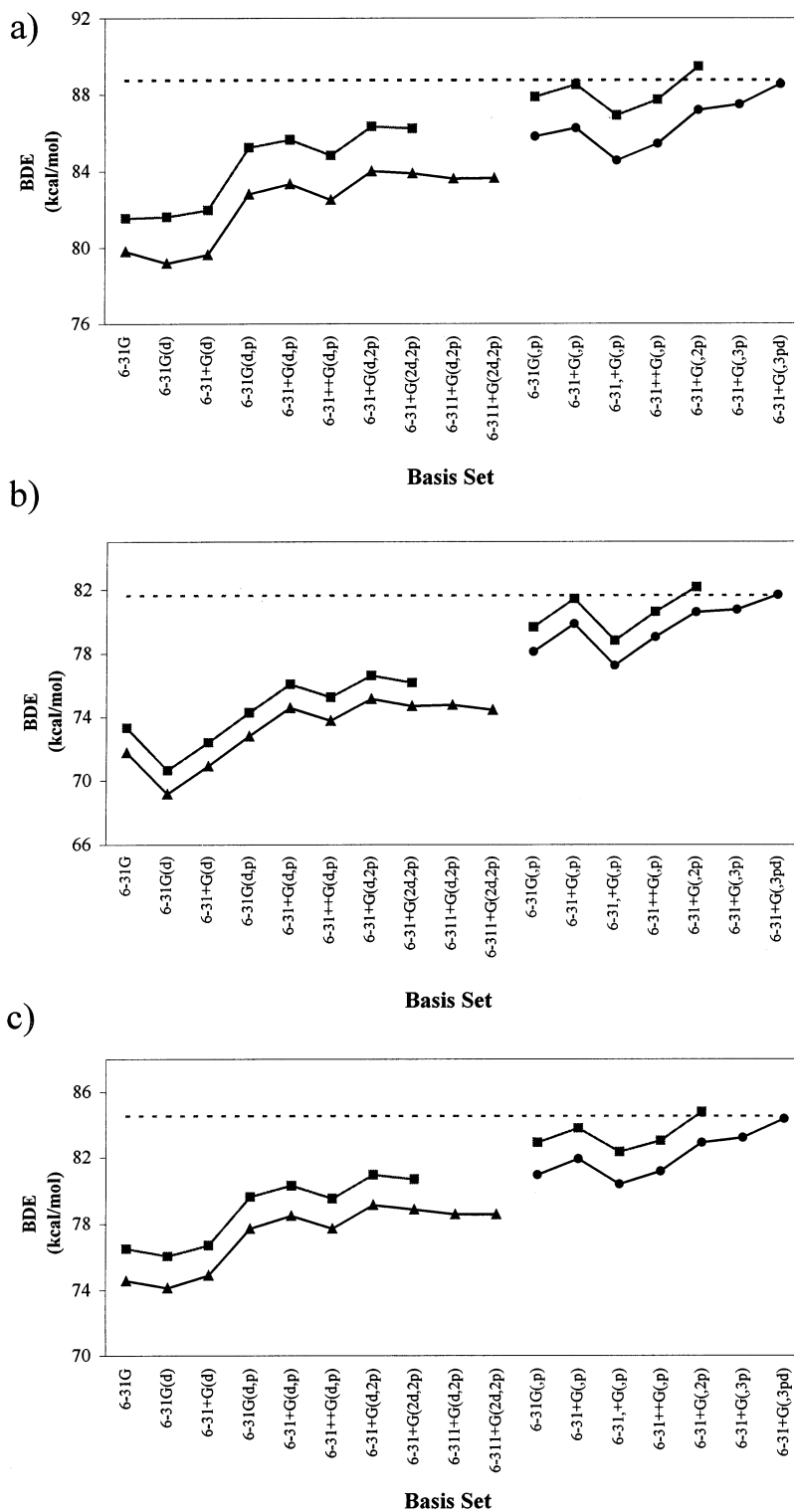
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Figure 1. Variation in the BDEs of the phenol (a), catechol (b), and guaiacol (c) as a function of the basis set.

BDEs. On the contrary, the inclusion of diffuse functions on the heavy atoms basis sets and a second p polarization function on the hydrogen atoms basis sets results in an improvement of the absolute calculated BDEs. Therefore, the use of unconventional basis sets results as a reasonable consequence of our detail study on the variation of BDEs on the basis set. Whether or not this is a reasonable choice must be verified a posteriori by the ability of this kind of basis sets to accurately reproduce the experimental BDEs.

Absolute BDEs, derived on the basis of this modification for seven unconventional basis sets (circles in Figure 1) show that (i) there is a significant improvement of the absolute BDEs, as compared to those of the conventional basis sets, (ii) there is a continuous approach of the experimental value from below, upon addition of a second p polarization function on the hydrogen atoms basis set [absolute BDEs, derived using the unconventional basis sets, 6-31+G(,p) and 6-31+G(,2p), lie within the experimental error of 1 kcal/mol], and (iii) the basis set 6-31+G-

TABLE 1: Calculated Gas-Phase BDEs (in kcal/mol) as a Function of Basis Sets

| phenols | basis set | sum of electronic and thermal enthalpies[a] | | BDEs[c] | ΔBDEs[d] | Δ(BDE)[e,f] | $\Delta\Delta$(BDE)%[g] |
		ArO[b]	ArOH				
phenol	6-311+G(2d,2p)[h]	−306.826675	−307.459739	83.63	−5.11		
catechol	6-311+G(2d,2p)[h]	−382.086208	−382.704628	74.44	−7.20	−9.2	29.6
guaiacol	6-311+G(2d,2p)[h]	−421.354724	−421.979733 (−421.986251)[j]	78.57 (82.66)	−5.97 (−7.42)	−5.1 (−1.0)	21.4
phenol	6-31+G(d,2p)[h]	−306.748047	−307.379817	84.00	−4.74		
catechol	6-31+G(d,2p)[h]	−381.982761	−382.600402	75.13	−6.51	−8.9	25.4
guaiacol	6-31+G(d,2p)[h]	−421.242822	−421.866852 (−421.873833)	79.14 (83.52)	−5.40 (−6.56)	−4.9 (−0.5)	16.7
phenol	6-31+G(d,2p)[i]	−306.744324	−307.379817	86.33	−2.41		
catechol	6-31+G(d,2p)[i]	−381.980410	−382.600402	76.61	−5.03	−9.7	36.6
guaiacol	6-31+G(d,2p)[i]	−421.239932	−421.866852 (−421.873833)	80.95 (85.33)	−3.59 (−4.75)	−5.4 (−1.0)	28.6
phenol	6-31+G(,p)[i]	−306.675142	−307.314110	88.51	−0.23		
catechol	6-31+G(,p)[i]	−381.886400	−382.514074	81.43	−0.21	−7.1	0
guaiacol	6-31+G(,p)[i]	−421.132517	−421.76394 (−421.773823)	83.78 (89.98)	−0.76 (−0.10)	−4.7 (+1.5)	11.9
phenol	6-31+G(,2p)[i]	−306.675949	−307.316425	89.46	0.72		
catechol	6-31+G(,2p)[i]	−381.888443	−382.517281	82.16	0.52	−7.3	2.82
guaiacol	6-31+G(,2p)[i]	−421.134115	−421.767144 (−421.776676)	84.79 (90.77)	0.25 (+0.69)	−4.7 (+1.3)	11.9
phenol	6-31+G(,3pd)[h]	−306.683824	−307.322822	88.53	−0.21		
catechol	6-31+G(,3pd)[h]	−381.896831	−382.524908	81.68	0.04	−6.9	2.82
guaiacol	6-31+G(,3pd)[h]	−421.143700	−421.776063 (−421.785284)	84.37 (90.16)	−0.17 (+0.08)	−4.2 (+1.6)	0

[a] All enthalpy values in hartrees. [b] The sum of electronic and thermal enthalpies for the hydrogen radical for all but the 6-311+G(2d,2p) basis set, being −0.499795 hartree, was calculated to be − 0.497912 hartree. [c] The experimental BDEs are 88.74, 81.64, 84.54, and 90.08 kcal/mol for phenol, catechol, guaiacol, and guaiacol-*toward*, respectively (for refs see text). [d] ΔBDE has been estimated as ΔBDE = BDE$_{calc}$ − BDE$_{exp}$. [e] Δ(BDE) has been estimated as Δ(BDE) = BDE$_{ArOH}$ − BDE$_{PhOH}$. [f] The experimental Δ(BDEs) are −7.1, −4.2, and +1.34 kcal/mol, for catechol, guaiacol, and guaiacol-*toward*, respectively (from ref 12). [g] $\Delta\Delta$(BDE)% has been estimated as $\Delta\Delta$(BDE)% = [Δ(BDE)$_{calc}$ − Δ(BDE)$_{exp}$] × 100/Δ(BDE)$_{exp}$. [h] The enthalpies of all radicals were derived at the UB3LYP level of theory. [i] The enthalpies of all radicals were derived at the ROHF level of theory. [j] Calculated values in parentheses correspond to the guaiacol-*toward* conformation.

(,3pd), derived upon addition of a third p and a fourth d polarization function on the hydrogen atoms basis set, leads to only 0.2, 0.04, and 0.17 kcal/mol deviations for the absolute BDEs from the experimental values of phenol, catechol, and guaiacol, respectively (see also Table 1). A considerable improvement was also derived for the Δ(BDE)s, by using the 6-31+G(,3pd) basis set; those of catechol and guaiacol deviate by only 2.82 and 0%, respectively, from the experimental values. This is the first well-documented and reasonable adoption of unconventional basis sets as a necessary tool in approaching the experimental BDEs and Δ(BDE)s of phenols, with our difference being in adopting this particular kind of basis set from the work of Wright et al.[13] Moreover, contrary to that work, which modified the normal *p*-exponent value on hydrogen from 0.75 to 1.00, this value was used unmodified in all of the unconventional basis sets tested in the present study.

Despite the accuracy achieved, the ROB3LYP formalism was our second modification to the usual DFT/B3LYP method, because it was shown that it plays a role[16] to obtaining a good absolute BDE accuracy. Absolute BDEs of this type (squares in Figure 1) also show that they vary with the corresponding basis set in the same way as the respective conventional and unconventional ones, derived at the UB3LYP level. In addition, there is an energy gain of 2.32, 1.52, and 1.87 kcal/mol (mean values) for the phenol, catechol, and guaiacol BDEs, respectively. All corresponding BDEs, derived using the conventional basis sets, lie well below the experimental values. The best conventional basis set of 6-31+G(d,2p) gives BDEs which are still 2.41, 5.03, and 3.59 kcal/mol low for phenol, catechol, and guaiacol, respectively. Nevertheless, BDEs calculated with the 6-31+G(,p) and 6-31+G(,2p) unconventional basis sets, lie within the experimental error of 1 kcal/mol. The improvement derived for the ΔBDEs of catechol is excellent, very good for guaiacol (see also Table 1). From this exercise, one could conclude that the standard DFT/B3LYP approach can achieve a 0.2 kcal/mol accuracy level for the absolute BDEs of the three phenols examined, along with a very good accuracy for the Δ(BDE)s, considering that unconventional basis sets in conjunc-

tion with UHF and/or ROHF level of theory are used. The only concern with the latter level is in regard to the determination of geometries and particularly vibrational frequencies for the molecules tested in the present study, which are very time-consuming. Therefore, the UB3LYP/6-31+G(,3pd) is adopted as our favorite level. It is worth noting here that the corresponding Figure 1 for the available theoretical value of the *toward* conformer of guaiacol (90.08)[13,22] is given as Supporting Information (Figure 1S). Figure 1S shows that the theoretical value of guaiacol is also well-calculated by our best basis set (vide infra also and Tables 1 and 4).

Preliminary Calculations in the Liquid Phase. Despite the optimum basis set derived in the previous section, attempts were also made to confirm its validity for the liquid-phase calculations. Figure 2 shows the variation in the BDE$_{solv}$ of phenol as a function of four unconventional basis sets for the three different solvents, (*n*-heptane (a), benzene (b), and acetonitrile (c)), for which experimental data is available. Results of one conventional basis set are also shown for comparison. The experimental BDEs$_{solv}$ for phenol in *n*-heptane, benzene, and acetonitrile are[22] 89.36, 90.51, and[3] 93.00 kcal/mol, respectively (dotted lines in the figure); calculated ones, corresponding to the five basis sets, are given as triangles. The experimental and the calculated gas-phase BDEs for phenol are also shown for comparison, as dashed lines and circles, respectively.

Inspection of the absolute BDEs$_{solv}$, presented in each individual drawing of Figure 2, clearly shows that (i) all calculated BDEs$_{solv}$ lie below the corresponding experimental values, however, (ii) all unconventional BDEs$_{solv}$ appear larger than the conventional one, (iii) the variation of the phenolic BDEs$_{solv}$ with the basis set is identical to that observed in the gas-phase calculations [for each particular basis set, the difference between the BDE and BDE$_{solv}$ values corresponds to the influence of the solvent and will be discussed in a following section], and (iv) on going from the conventional (6-31+G-(d,p)) to the largest unconventional one, 6-31+G(,3pd), the BDE$_{solv}$ of phenol increases by ca. 5 kcal/mol, for all three solvents. In particular, both 6-31+G(,2p) and 6-31+G(,3pd)

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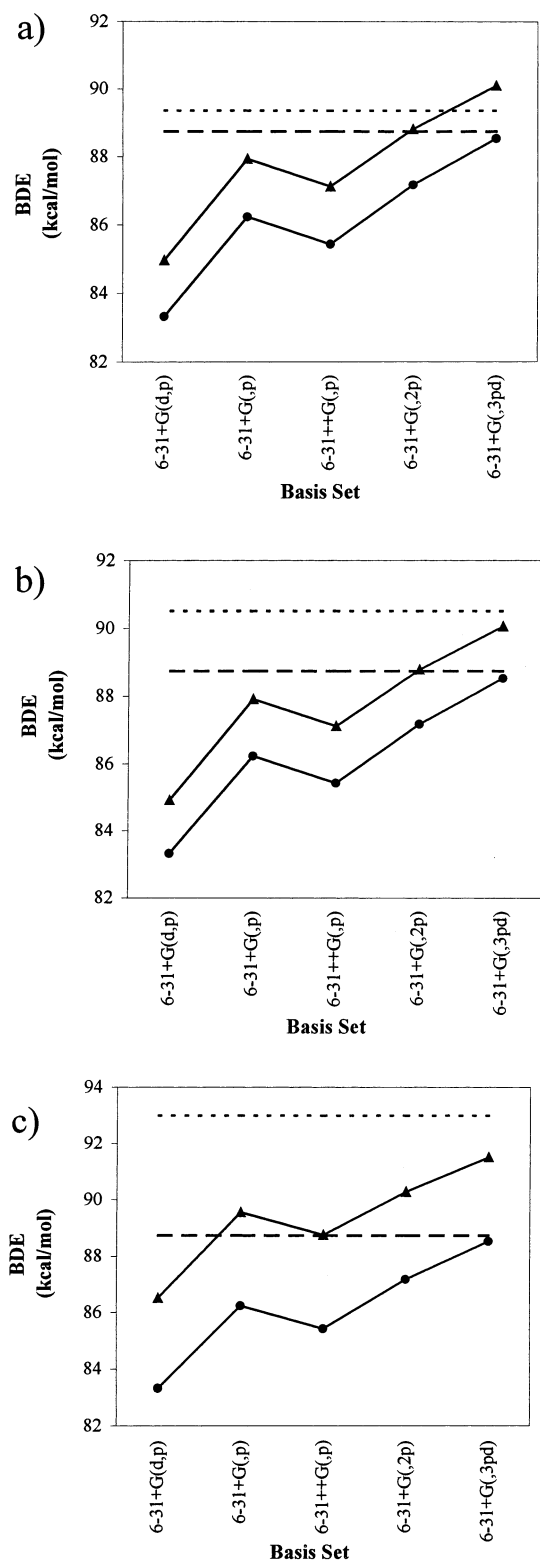*J. Phys. Chem. A, Vol. 107, No. 41, 2003* **8599**

Figure 2. Variation in the BDEs$_{solv}$ of phenol in the *n*-heptane (a), benzene (b), and acetonitrile (c) as a function of the basis set.

basis sets afford BDEs$_{solv}$, in *n*-heptane (Figure 2a), close to the experimental value. However, in benzene (Figure 2b), only the latter basis set affords BDEs$_{solv}$ in excellent agreement with the experimental value and to some extend in acetonitrile solution (Figure 2c). Based upon these results, we decided to use the 6-31+G(,3pd) basis set, because it afforded the least deviations from the experiment for the liquid-phase BDEs of phenol tested. The identical to the corresponding gas-phase

calculations basis set derived could both facilitate comparisons with them and account well for the accuracy of the BDEs$_{solv}$, which are to be calculated. It should be pointed out here that the 3pd polarization functions on the H atom basis set are quite common in the theoretical papers dealing with the study of inorganic,[50] organic[51] and/or simple H molecular systems.[52,53] In our case, use of extra functions on H could be considered as reasonable because, in the gas-phase, H atoms strongly participate in (a) the crucial phenolic O−H bond to be broken through an homolytic dissociation and (b) the formation of the also crucial intramolecular H-bonds, neighboring the phenolic O−H bond. In addition, in the liquid phase, both the above as well as the benzene-ring H atoms also participate in the solute−solvent "bulk" effects.

Equilibrium Geometries in the Gas and the Liquid Phase. As it was shown in the previous section, phenol and the phenoxyl radical were used as reference compounds in both the gas and liquid phase preliminary calculations. The gas-phase structure and properties of both molecules have been reported.[13,54] To compare with the previous results and to predict the influence of the solvents on their properties, these molecules are reinvestigated here with a series of different basis sets, as stated above. To our knowledge, experimental and/or theoretical liquid-phase geometrical data has not been published so far. The seven solvents tested throughout this study could be divided into three groups: (A) nonpolar, aprotic (*n*-heptane and benzene), (B) dipolar, aprotic (acetone and acetonitrile), and (C) polar, protic (methanol, ethanol, and water); this notation will be used hereafter. This classification scheme stems from their Dimroth and Reichardt's,[38] E_N^T and Kamlet−Taft,[55,56] α polarity parameters values. The E_N^T parameter shows[57] the ability of a protic solvent to donate a hydrogen bond to a solute in addition to its polarity per se; the α parameter is a measure of the hydrogen bonding ability of solvents that was designed to be devoit of contributions from the polarity and electron-pair donicity.

Despite the various geometrical parameters of phenol obtained in the present study, only those of the 6-31+G(,3pd) optimized basis set in the gas and the liquid phase, and those of the largest one in the gas-phase are compared with the experimental[54] values in Table 2. Our gas-phase optimized results from the 6-31+G(,3pd) basis set are in very good agreement with the experimental values, the corresponding average absolute deviation (error) being 0.006 Å. This error is of the same order of magnitude to that (0.007 Å) of ref 13, in which an unconventional 6-31(,p′) basis set was also used. Our largest basis set, however, gives the smallest error of 0.001 Å.

In an attempt to study the influence of the solvent on the structure of phenol in solution and because of the absence of experimental and/or theoretical structural data, its PCM liquid-phase data was compared to the corresponding gas-phase ones derived at the same level of theory. An inspection of these data, summarized in Table 2, clearly shows that the liquid-phase structural data, derived for the group A and group B solvents, does not deviate much from the gas-phase one. Moreover, the liquid-phase structural data, derived in the group C solvents, is identical to each other. However, there are some minor to moderate bond-length variations with respect to the gas-phase data, related to a minor lengthening of all C−C bonds, ranging from 0.001 (group A) to 0.004 Å (group C). Contrary to the absence of variations in the group A solvents, the C$_2$−H and C$_6$−H bonds, ortho- to the phenolic OH group (see Scheme 1), present a lengthening of 0.01 Å in the group C solvents; still the C$_3$−H, C$_4$−H, and C$_5$−H bonds become longer by ca. 0.005

TABLE 2: Comparison of Bond Lengths and Bond Angles at the Optimized Geometry for Phenol, in Both the Gas- and the Liquid-Phases (PCM model, B3LYP/6-31+G(,3pd))[a]

| | gas phase | | | solution | | | | | | |
struct. param.	6-31+G(,3pd)[b]	6-311+G(2d,2p)[c]	exp[d]	heptane	benzene	acetone	acetonitrile	ethanol	methanol	water
C_1C_2	1.400	1.393	1.391	1.400	1.400	1.400	1.400	1.401	1.401	1.401
C_2C_3	1.402	1.391	1.394	1.401	1.401	1.402	1.402	1.403	1.403	1.403
C_3C_4	1.401	1.390	1.395	1.401	1.401	1.402	1.402	1.404	1.404	1.404
C_4C_5	1.404	1.393	1.395	1.403	1.403	1.403	1.403	1.405	1.405	1.405
C_5C_6	1.399	1.389	1.392	1.399	1.399	1.400	1.400	1.403	1.404	1.403
C_6C_1	1.399	1.393	1.391	1.399	1.399	1.400	1.400	1.402	1.402	1.402
C_2H_8	1.083	1.084	1.086	1.081	1.081	1.082	1.083	1.092	1.092	1.092
C_3H_9	1.081	1.082	1.084	1.081	1.080	1.081	1.082	1.085	1.085	1.085
C_4H_{10}	1.081	1.081	1.080	1.080	1.079	1.081	1.081	1.085	1.085	1.084
C_5H_{11}	1.081	1.082	1.084	1.081	1.080	1.081	1.082	1.086	1.086	1.086
C_6H_{12}	1.080	1.081	1.081	1.079	1.078	1.081	1.081	1.090	1.090	1.090
C_1O_7	1.403	1.370	1.375	1.402	1.402	1.403	1.402	1.405	1.405	1.405
O_7H_{13}	0.966	0.962	0.957	0.967	0.966	0.970	0.970	0.981	0.981	0.981
$C_1C_2C_3$	119.5	119.7	119.4	119.4	119.4	119.3	119.3	119.2	119.2	119.2
$C_2C_3C_4$	120.4	120.5	120.5	120.4	120.4	120.5	120.5	120.5	120.5	120.5
$C_3C_4C_5$	119.5	119.3	119.2	119.5	119.5	119.5	119.5	119.6	119.6	119.6
$C_4C_5C_6$	120.6	120.7	120.8	120.6	120.6	120.5	120.5	120.6	120.6	120.6
$C_5C_6 C_1$	119.4	119.6	119.2	119.3	119.3	119.3	119.3	119	119	119
$C_6C_1C_2$	120.7	120.1	120.85	120.8	120.8	120.9	120.9	121.3	121.3	121.3
$C_1C_2H_8$	120.2	120.0	120.0	120.2	120.2	120.1	120.1	119.9	119.9	119.9
$C_5C_6H_{12}$	121.5	121.4	121.6	121.4	121.4	121.2	121.1	120.9	120.9	120.9
$C_1O_7H_{13}$	110.7	109.7	108.8	110.7	110.7	110.7	110.7	110.1	110.0	110.0

[a] All bond lengths are in Å, and bond angles are in degrees. [b] Average absolute deviation error 0.006 Å from experimental values. [c] Average absolute deviation error 0.001 Å from experimental values. [d] Experimental data from ref 54.

TABLE 3: Comparison of Bond Lengths and Bond Angles at the Optimized Geometry for Phenoxyl Radical, in Both the Gas- and the Liquid-Phases (PCM Model, B3LYP/6-31+G(,3pd))[a]

| | gas phase | | | solution | | | | | | |
R	6-31+G(,3pd)[b]	6-31G(p′)	6-311+G(2d,2p)	heptane	benzene	acetone	acetonitrile	ethanol	methanol	water
C_1C_2	1.443	1.443	1.449	1.443	1.443	1.444	1.444	1.445	1.445	1.444
C_2C_3	1.386	1.385	1.372	1.385	1.385	1.385	1.384	1.385	1.385	1.384
C_3C_4	1.413	1.412	1.406	1.413	1.413	1.414	1.414	1.416	1.416	1.416
C_2H_8	1.080	1.083	1.081	1.080	1.080	1.081	1.081	1.084	1.084	1.084
C_3H_9	1.081	1.084	1.082	1.081	1.081	1.081	1.081	1.082	1.082	1.082
C_4H_{10}	1.081	1.084	1.081	1.080	1.080	1.081	1.081	1.085	1.085	1.085
C_1O_7	1.298	1.296	1.253	1.298	1.298	1.299	1.299	1.300	1.300	1.300
$C_1C_2C_3$	120.5		120.8	120.5	120.4	120.4	120.4	120.2	120.2	120.2
$C_2C_3C_4$	120.1		120.3	120.2	120.2	120.2	120.2	120.3	120.3	120.3
$C_3C_4C_5$	120.6		120.7	120.6	120.6	120.6	120.6	120.5	120.5	120.5
$C_6C_1C_2$	118.1		117.2	118.2	118.2	118.3	118.3	118.5	118.5	118.5
$C_1C_2H_8$	117.5		117.1	117.6	117.7	117.8	117.8	118	118	118

[a] All bond lengths are in Å, and bond angles are in degrees. [b] Average absolute deviation of 0.008 Å from the results of the 6-311+G(2d,2p) calculation.

SCHEME 1
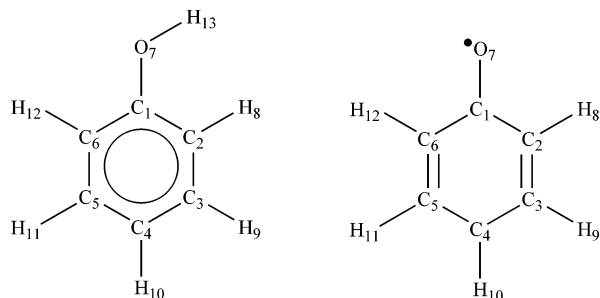
Å. A minor lengthening of ca. 0.002 Å is observed for the C—O bond. Variations, ranging to a lengthening of as much as 0.015 Å, are observed for the O—H bond. This bond remains unchanged in the group A solvents, whereas a minor lengthening of 0.004 Å is observed in the group B and a moderate one of 0.015 Å in the group C solvents. Only the group C solvents structural data presents bond-angle variations as compared to the gas-phase one. The C_6—C_1—C_2 bond angle increases by ca.

0.6°, whereas the C_1—C_2—C_3 and C_1—C_2—H_8 ones decrease by ca. 0.3°, C_1—C_6—C_5 by 0.4°, C_5—C_6—H_{12} by ca. 0.6°, and C_1—O_7—H_{13} by 0.7°. The moderate variations in bond lengths and angles in the protic solvents could be the result of a hydrogen bond formation between the phenolic OH group with the appropriate groups of the protic solvents. Moreover, the minor lengthening of all C—C and C—H bonds could be the result of an induced "bulk" solvent effect on the molecular geometry of the solute (phenol) in the group C solvents. It is noteworthy that the phenolic O—H bond in the four aprotic solvents remained unchanged, with respect to the gas-phase one, accounting for almost equal phenolic BDEs in both the liquid and the gas phase. On the contrary, the same O—H bond in the three protic solvents became longer. This could account for unequal phenolic BDEs between the liquid and the gas phase. All of these will be discussed in detail in the next section. It should be stressed at this point that all corresponding SCIPCM liquid-phase structural data is not shown in Table 2, because it is identical to each other and to that of the gas-phase one. This equality could account for its failure to describe well the "bulk"

BDEs of 2-Mono- and 2,6-Disubstituted Phenols

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TABLE 4: B3LYP/6-31+G(,3pd) BDEs for Phenol, Catechol, Guaiacol, Syringol, and Pyrogallol[a]

phenols	BDE[b]	BDE[g]	ΔBDE[h]	Δ(BDE)[b,i]	Δ(BDE)[j]
phenol	88.74[c]	88.53	−0.21	0.00	
		(88.69)	(−0.05)		
catechol	81.64[d]	81.68	0.03	−7.10[d]	−6.86
		(81.83)	(0.19)		
guaiacol	84.54[d]	84.37	−0.17	−4.20[d]	−4.16
		(84.52)	(−0.02)		
guaiacol	90.08[c]	90.16	+0.08	+1.34[c]	+1.63
		(90.32)	(+0.24)		
syringol	83.75[e]	84.31	−0.56	−4.99[e]	−4.22
		(84.47)	(−0.72)		
pyrogallol	n.a.[f]	77.26		n.a.[f]	−11.29
		(77.40)			

[a] All absolute and relative enthalpy values in kcal/mol. [b] Experimental values. [c] From ref 22. [d] From ref 12. [e] Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, *61*, 9259. [f] Non available. [g] Our unscaled and scaled (parentheses) calculated BDEs. [h] Calculated ΔBDE has been estimated as ΔBDE = BDE_{calc} − BDE_{exp}. [i] Δ(BDE) has been estimated as Δ(BDE) = BDE_{ArOH} − BDE_{PhOH}. [j] Our calculated Δ(BDE)s.

effects. The SCIPCM structural data is given as Supporting Information (Table S1).

For the phenoxyl radical, there are three theoretical studies in the gas-phase.[13,58,59] Two of them[58,59] used an identical CAS−SCF/6-311G(2d,p) level, which yielded relatively short C−O (1.229 Å) and C−H (ca. 1.073 Å) bonds. However, C−O bond would be expected to be intermediate between the benzoquinone value[60] (1.225 Å) and the single C−O bond distance in phenol[54] (1.375 Å); C−H bond would be of the order of ca. 1.084 Å. Therefore, we decided to use the B3LYP/6-311+G(2d,2p) calculation as a reference for the gas-phase structural studies. With that choice, our B3LYP/6-31+G(,3pd) structural data, shown in Table 3, gives a very good error at 0.008 Å and of the same order of magnitude to that of ref 13, derived at the B3LYP/6-31G(,p′) level. Certainly, both calculations yield C−O bond lengths that are too long (of the order of 1.296 Å). Moreover, contrary to the parent phenolic molecule, that of its radical indicates a quinoid structure, evidenced by the significant lengthening of both C_1−C_2 and C_1−C_6 bonds (1.443 Å) and C_4−C_3 and C_4−C_5 bonds (1.413 Å), followed by a concomitant shortening of both C_2−C_3 and C_5−C_6 bonds (1.386 Å).

No experimental and/or liquid-phase structural data exists for the phenoxyl radical. The influence of the solvent on the phenoxyl radical structural data was also studied, by comparing its PCM liquid-phase data to the gas-phase one, derived at the same level. Inspection of these data (see Table 3) clearly shows that (i) all liquid-phase phenoxyl radicals also present the quinoid structure, observed in the gas-phase study, (ii) data in all aprotic solvents is identical to the corresponding gas-phase, however, (iii) radical structural data in the three protic solvents presents only minor bond-length variations, with respect to gas-phase one. The C_2−H_8 and C_6−H_{12} bonds as well as the C_4−H_{10} one (see also Scheme 1) present a lengthening of ca. 0.004 Å, and this is also the case (lengthening of ca. 0.002 Å) with the C_1−C_2 and C_1−C_6 and C_3−C_4 and C_4−C_5 bonds. The minor lengthening of both C−C and C−H bonds could again be the result of an induced "bulk" solvent effect of the protic solvents only on the solute (phenoxyl radical) molecular geometry. A hydrogen-bonding effect is not obvious in the case of the phenoxyl radical structural data in protic solvents, in close agreement with the experimental findings.[21,22,61] SCIPCM liquid-phase structural data is not presented in Table 3, because it is identical to each other and to that of the gas-phase one. The SCIPCM structural data is given as Supporting Information.

SCHEME 2
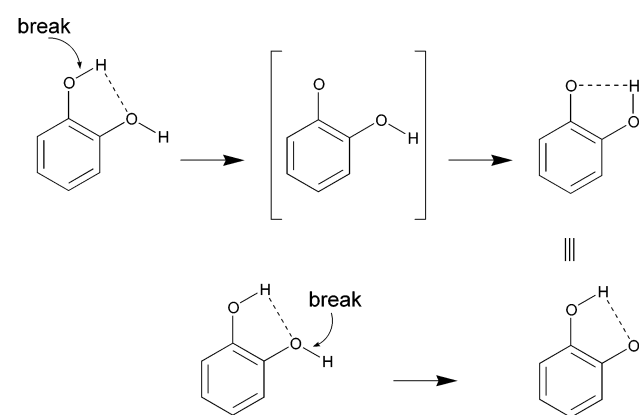
DFT-Computed BDEs and Conformers in the Gas Phase. It is well-known that[17,31] spin contamination significantly affects the calculated BDEs. The value of the spin operator $\langle S^2 \rangle$ computed through the Gaussian program, although not that of a real system, provides reasonable estimates of spin contamination.[17,31] Earlier studies have also shown that the spin contamination in DFT calculations generally is low even when the methods are applied to aromatic radicals. The values of the spin operator $\langle S^2 \rangle$ for the phenoxyl, catechoxyl, and guaiacoxyl radicals are 0.82, 0.80, and 0.78, respectively; that is, they were all found to be close to the expected value of a pure doublet wave function, 0.75. Therefore, the results of our DFT calculations are less affected by spin contamination in the gas-phase. All of these could be reflected to the computed energies. Hence, accurate computed absolute BDEs, as compared to the experimental ones, should be expected as well.

The fully consistent calculations of the present study, in which both the phenol and its respective radical are calculated at the same level of theory, are not expected to introduce any systematic error in the BDEs. The relative error over a family of phenols is also expected to largely cancel out, because in all cases we are looking at the conversion from a phenol (substituted or not) to the corresponding radical (substituted or not) plus the H radical.

The DFT-computed gas-phase absolute and relative BDEs at 298 K are summarized in Table 4. Values refer to the lowest energy conformers of the parent phenolic compound and the respective radical.

Calculations have shown that both unscaled and ZPE scaled BDEs of phenol are in excellent agreement with the experiment; they differ by only 0.21 and 0.05 kcal/mol, respectively.

For catechol, calculations have shown that the hydrogen-bonded *toward* parent−radical conformers pair, having both hydroxyl groups in the plane of the phenyl ring, affords an almost identical to the experiment BDE of 81.83 kcal/mol. We consider here that there is only one BDE value for catechol, regardless of which O−H bond is broken in the parent molecule. This is because the radical is allowed to rearrange, at room temperature, affording the most stable *toward* conformer[16] (Scheme 2). The calculated enthalpy difference between the *away* and the *toward* parent conformers is 5.07 kcal/mol. The calculated Δ(BDE) relative to phenol (−6.86 kcal/mol) is in very good agreement with the experiment[12] (−7.1 kcal/mol). Moreover, the calculated absolute hydrogen bond enthalpy (= BDE_{aw} − BDE_{tow}) of −5.07 kcal/mol lies between the two published corresponding values of[4] −4.4 and[16] −5.7 kcal/mol.

All possible conformers for the parent guaiacol and the respective radicals were investigated in our calculations. The

SCHEME 3
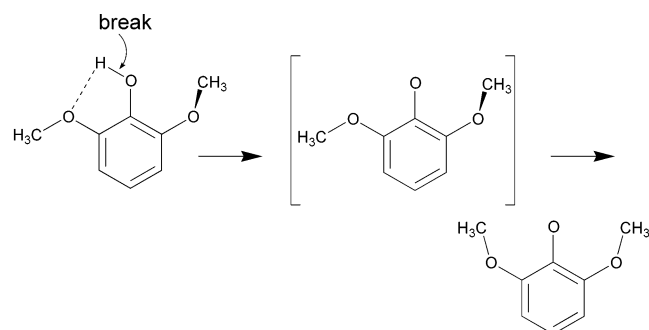
parent compound has three stable conformers, of which *toward* is the most stable one; *away* is energetically less stable by 5.80 kcal/mol, the third by 5.73 kcal/mol. In this latter conformer, the OMe group is tilted out of the phenyl plane by ca. 61° and is pointing toward the OH group, which is pointing away from the OMe group. For the respective radical, two planar conformers were identified. The lowest energy conformation has the OMe group pointing toward the radical O atom. The less stable one adopts the away conformation, its enthalpy difference from the former being 2.59 kcal/mol. The *away* parent conformer affords a scaled calculated BDE of 84.52 kcal/mol along with a Δ(BDE) (−4.16 kcal/mol), relative to phenol, and an absolute hydrogen bond enthalpy, (5.79 kcal/mol), in excellent agreement with the experimental values of[12,22] +84.54, −4.2, and[13] +5.70 kcal/mol, respectively. De Heer et al.[4] also found the same lowest energy *toward* parent−radical conformers pairs. However, the two parent conformers, chosen by Wright et al.,[13] have the OMe group pointing away and toward the OH group, respectively, affording BDEs, which deviate by 2.43 and 3.26 kcal/mol from the experiment, respectively. In this paper, information regarding the two radicals chosen for the BDE determination is not provided. The *toward* parent conformation with its respective radical yields a scaled BDE of 90.32 kcal/mol, deviating by only 0.24 kcal/mol from the existing theoretical value[13,22] and Δ(BDE) in close agreement with the corresponding theoretical value.

Gas-phase BDE study on phenol, catechol and guaiacol clearly shows that DFT calculations provide very accurate Δ(BDE) and absolute hydrogen bond enthalpies, once the absolute BDE has been approached. This is another evidence for the correctness of our method.

The successful implementation of our optimum basis set on the calculation of the gas-phase BDEs, Δ(BDE)s, and absolute hydrogen bond enthalpies of the above phenols, prompted us to apply it also on the calculation of those of 2,6-dimethoxyphenol (syringol) and 2,6-dihydroxyphenol (pyrogallol).

Calculations have shown that the most stable parent conformer of syringol has the hydrogen-bond accepting OMe group pointing away from the OH group, the other OMe group is tilted out of the phenyl plane, by 55°, pointing toward the hydroxyl group (Scheme 3). This conformer, however, presents a significant difference compared to the fully planar one of ref 13:one of its OMe groups is tilted out of the phenyl plane. Moreover, our conformer is more stable by 0.40 kcal/mol than the planar corresponding one of ref 4, which has the two OMe groups pointing away from the OH group. The most stable conformer of the aroxyl radical is the one, in which the two OMe groups lie in the phenyl plane and are pointing toward the radical O atom. This conformer is more stable by 0.88 kcal/mol than that coming from our most stable parent one. Moreover, it is more stable by 2.94 kcal/mol than the radical

conformer of ref 4, which has the one OMe group pointing toward and the other away from the radical O atom. Additional calculations, using multiple starting points, in which either both or only one of the OMe groups were tilted out of the phenyl ring, have been performed to ensure that optimized parent and radical structures were found. The calculated BDE of 84.47 kcal/mol, derived by assuming that the most stable conformers correspond to the experimental BDE value, is in very good agreement with the experiment. This is also the case with the calculated Δ(BDE) (−4.22 kcal/mol compared to −4.99 kcal/mol).

The most stable conformer of the parent compound of pyrogallol has one OH group pointing toward the central OH group and the second pointing away. Moreover, two radicals, possessing two intramolecular hydrogen bonds, are formed through an H radical elimination from the central OH group; the second radical is formed from either one of the two outer hydroxyl groups. The dissociation of these outer groups leads to the same radical conformer, by assuming that the OH group at the one end is rotated to the more stable radical conformer[16] (Scheme 4).

The calculated absolute BDE, corresponding to the dissociation from the central OH group, is 77.40 kcal/mol; its Δ(BDE) is −11.29 kcal/mol. Furthermore, the absolute BDE, corresponding to the dissociation from any one of the outer OH group, is 82.89 kcal/mol; its Δ(BDE) is −5.80 kcal/mol. The former Δ(BDE) deviates by ca. 2.9 kcal/mol, and the latter by ca. 1.8 kcal/mol from the two analogous theoretical values appeared recently.[16] Nevertheless, our calculated Δ(BDE) of the outer OH group is roughly half that of the central group, in close agreement with the difference calculated by the same authors. Unfortunately, neither BDE nor Δ(BDE) experimental values exist in the literature for comparisons to be made. Therefore, calculated pyrogallol values can only be used for predictive purposes.

DFT-Computed BDEs and Conformers in the Liquid Phase. Calculated $\langle S^2 \rangle$ values of the phenoxyl radical in the seven different solvents tested were all found to be below 0.80 (ranging from 0.78 to 0.79) in both PCM and SCIPCM models. Therefore, the results of our DFT calculations are less affected by spin contamination in the liquid-phase, too; hence, accurate absolute BDEs$_{solv}$ should be expected as well.

Table 5 summarizes the calculated absolute B3LYP/6-31+G-(,3pd) BDEs$_{solv}$ along with the Δ[BDE]s and Δ(BDE)s$_{solv}$ of the three phenols studied. The absolute SCIPCM BDEs$_{solv}$ for phenol only are also presented. All BDEs$_{solv}$ refer to the lowest energy conformers of the parent phenolic compound and the respective radical. Contrary to phenol, experimental liquid-phase BDEs are missing for catechol and are scarce for guaiacol.

The SCIPCM model fails to describe the solvent effect, as evidenced by its almost equal to the gas-phase BDEs$_{solv}$ for phenol (ca. 88 kcal/mol) in all media. This was also the case with the BDEs$_{solv}$ of catechol and guaiacol; therefore, these values are not shown in the table. This failure may arise from[44,61] the incorrect defined cavity size and shape, derived from the solute charge distribution isosurface. The inability of the SCIPCM model to provide nonelectrostatic contributions could be another reason for its failure. Moreover, because hydrogen-bonding is neglected in this model, both protic (water) and aprotic (acetonitrile) solvents would show the same solvation energy differences.[59] This is actually the case with the above results regarding the three phenols.

Contrary to the SCIPCM absolute BDEs$_{solv}$, PCM ones for all phenols considered appear different than their gas-phase

BDEs of 2-Mono- and 2,6-Disubstituted Phenols

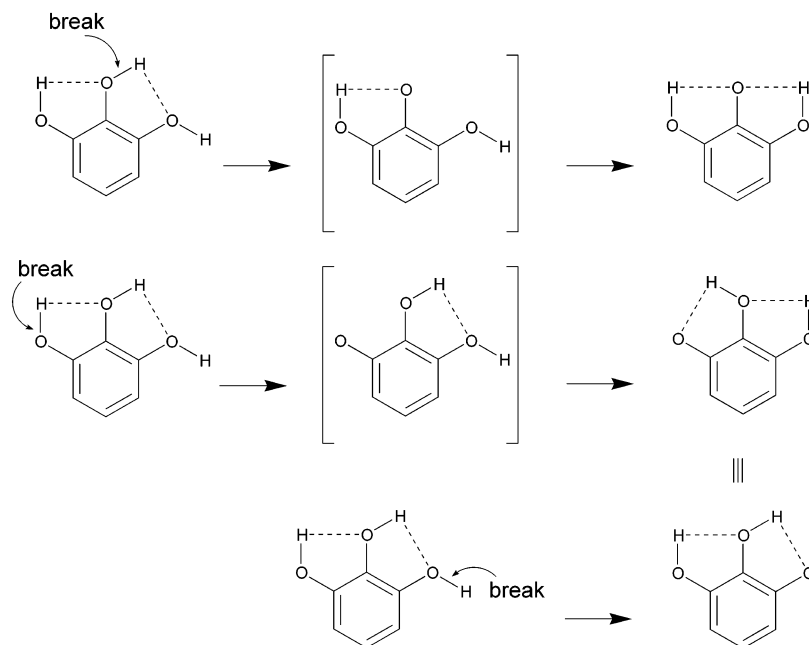*J. Phys. Chem. A, Vol. 107, No. 41, 2003* **8603**

SCHEME 4

TABLE 5: B3LYP/6-31+G(,3pd) BDEs_solv for Phenol, Catechol, and Guaiacol, Calculated in the Liquid Phase with the PCM Model, along with Those of Phenol with the SCIPCM One[a]

ArOH	solvent	$E_r{}^b$	$E_h{}^b$	$E_p{}^b$	BDE	BDE_exp^c	Δ[BDE]^d	Δ(BDE)_solv^e
				SCIPCM				
phenol	gas phase	−306.683824	−0.497912	−307.322822	88.53			
	n-heptane	−306.688160	−0.497958	−307.326524	88.11	89.36		
	benzene	−306.689041	−0.497965	−307.327314	88.04	90.51		
	acetone	−306.695145	−0.498003	−307.333317	87.96			
	acetonitrile	−306.695566	−0.498005	−307.333777	87.98	93 (95)		
	ethanol	−306.695295	−0.498004	−307.333480	87.96			
	methanol	−306.695498	−0.498005	−307.333702	87.98			
	water	−306.695865	−0.498006	−307.334108	88.00			
				PCM				
phenol	gas phase	−306.683824	−0.497912	−307.322822	88.53		0	
	n-heptane	−306.688875	−0.496407	−307.328869	90.10	89.36	1.57	
	benzene	−306.686017	−0.495751	−307.325290	90.06	90.51	1.53	
	acetone	−306.691173	−0.496193	−307.332227	90.90		2.37	
	acetonitrile	−306.686622	−0.495442	−307.327899	91.51	93 (95)	2.98	
	ethanol	−306.695518	−0.495970	−307.344330	95.91		7.38	
	methanol	−306.698643	−0.496325	−307.347766	95.88		7.35	
	water	−306.695652	−0.495546	−307.345316	96.71		8.18	
catechol	gas phase	−381.896831	−0.497912	−382.524908	81.68		0	
	n-heptane	−381.901885	−0.496407	−382.531517	83.60		1.92	−6.50
	benzene	−381.898991	−0.495751	−382.527895	83.55		1.87	−6.51
	acetone	−381.904306	−0.496193	−382.535679	84.83		3.15	−6.07
	acetonitrile	−381.899378	−0.495442	−382.530917	85.40		3.72	−6.11
	ethanol	−381.912183	−0.495970	−382.549950	88.98		7.30	−6.93
	methanol	−381.915676	−0.496325	−382.553795	88.98		7.30	−6.90
	water	−381.912646	−0.495546	−382.551285	89.79		8.11	−6.92
guaiacol	gas phase	−421.143700	−0.497912	−421.785284	90.16		0	
	n-heptane	−421.150672	−0.496407	−421.791092	90.37		0.21	0.27
	benzene	−421.147368	−0.495751	−421.787169	90.39	88.6 ± 1.5	0.23	0.33
	acetone	−421.155493	−0.496193	−421.792615	88.43		−1.73	−2.47
	acetonitrile	−421.150200	−0.495442	−421.786735	88.54		−1.62	−2.97
	ethanol	−421.164348	−0.495970	−421.803297	89.72		−0.44	−6.19
	methanol	−421.168447	−0.496325	−421.807403	89.50		−0.66	−6.38
	water	−421.165000	−0.495546	−421.803930	89.97		−0.19	−6.74

^{a} Gas-phase values are also presented for comparison (all values in kcal/mol). ^{b} Absolute enthalpy data for the parent, p, its respective radical, r, and the hydrogen radical, h, are in hartrees. ^{c} Values from refs 22, 3, (1), and 4. ^{d} Δ[BDE] has been estimated as Δ[BDE] = BDE_solv − BDE_gas. ^{e} Δ(BDE)_solv has been estimated as Δ(BDE)_solv = BDE_solv,ArOH − BDE_solv,PhOH.

BDEs. This difference, implying an inherent solvent effect, leads to larger BDEs_solv for phenol and catechol in all media and smaller for guaiacol. This is the result of a stronger stabilization of the parent molecules in the two former relative to that of

their radicals. Actually, in guaiacol, radicals are stabilized slightly stronger in solution, relative to the parent compounds, evidenced by the E_p and E_r value differences (Table 5). Moreover, the BDEs − BDEs_solv differences derived could

TABLE 6: PCM Calculated BDEs$_{solv}$[a] for Phenol, Catechol, and Guaiacol along with the ϵ, E_N^T, and α Parameters of the Seven Solvents Used

solvent	ϵ	E_N^T	α	BDE$_{solv}$ phenol	catechol	guaiacol
n-heptane	1.92	0.012	0	90.10	83.60	90.37
benzene	2.247	0.111	0	90.06	83.55	90.39
acetone	20.7	0.355	0.08	90.90	84.83	88.43
acetonitrile	36.64	0.460	0.19	91.51	85.40	88.54
ethanol	24.55	0.654	0.86	95.91	88.98	89.72
methanol	32.63	0.762	0.98	95.88	88.98	89.50
water	78.39	1.000	1.17	96.71	89.79	89.97

[a] All BDEs$_{solv}$ in kcal/mol.

suggest that the PCM model describes "bulk" solvent effect phenomena well. The solvent effect will be discussed in the next section. Table 5 also shows that the three phenols exhibit similar BDEs$_{solv}$, in pairs (*n*-heptane-benzene, acetone-acetonitrile), and/or in triads (methanol, ethanol and water) of the solvents tested. Based upon this particular solvent dependence of the absolute BDEs$_{solv}$, the seven solvents could be divided into three groups in excellent agreement with (i) the A, B, and C groups, derived previously and (ii) their E_N^T and α parameters scale values (see also Table 6). Both E_N^T and α parameters present similar parameter value-trends to each other, which are not in line with that of the dielectric constant values, ϵ of the same solvents.

Calculated BDEs$_{solv}$ for phenol in *n*-heptane (90.10 kcal/mol) and in benzene (90.06 kcal/mol) are in excellent agreement with the available experimental ones[22] of 89.36 kcal/mol (in isooctane) and 90.51 kcal/mol (in benzene). However, the calculated BDE$_{solv}$ for phenol in acetonitrile (91.51 kcal/mol) is not in good agreement with the experiment (95 kcal/mol).[1] As it was mentioned in the Introduction, the experimental BDEs$_{solv}$ depend on both the technique used and the solvation enthalpy value for the hydrogen atom used in their determination. Because solvation enthalpy for hydrogen cannot be measured experimentally, it is either used as a constant in all solvents or defined with the standard state of the H atom in the gas phase. This latter approach yielded an experimental BDE$_{solv}$ of[3] 93 kcal/mol for phenol in acetonitrile, deviating by only 1.5 kcal/mol from our calculated value.

PCM calculations for catechol have shown that the planar hydrogen-bonded *toward* parent−radical conformers pair is the most stable in all solvents tested. The *toward* conformer of catechol forms an intramolecular hydrogen bond, which does not constrain its ability to form intermolecular hydrogen bonds with some solvents. To the best of our knowledge, all calculated absolute BDEs$_{solv}$ for catechol in the different media of Table 5 are the first ever predicted.

Experimental studies[4,62] have shown that guaiacol may be present, in solution, in four different forms, of which the *toward* and the *away* conformers are the most important. Moreover, even in strong hydrogen bond accepting (HBA) solvents, guaiacol was found entirely in the *toward* conformation, in excellent agreement with the results of our calculations. Calculated BDEs$_{solv}$ for guaiacol in heptane and benzene are almost identical to each other (ca. 90.4 kcal/mol) and to the gas-phase *toward* conformer value. Our calculated BDE$_{solv}$ for guaiacol in benzene is in very good agreement with the only existed experimental one[4] (88.6 ± 1.5 kcal/mol).

As it can be easily calculated, on the basis of the E_h values given in Table 5, the variation between the DFT enthalpies for hydrogen atom in various solvents ranges between 1 and 1.55
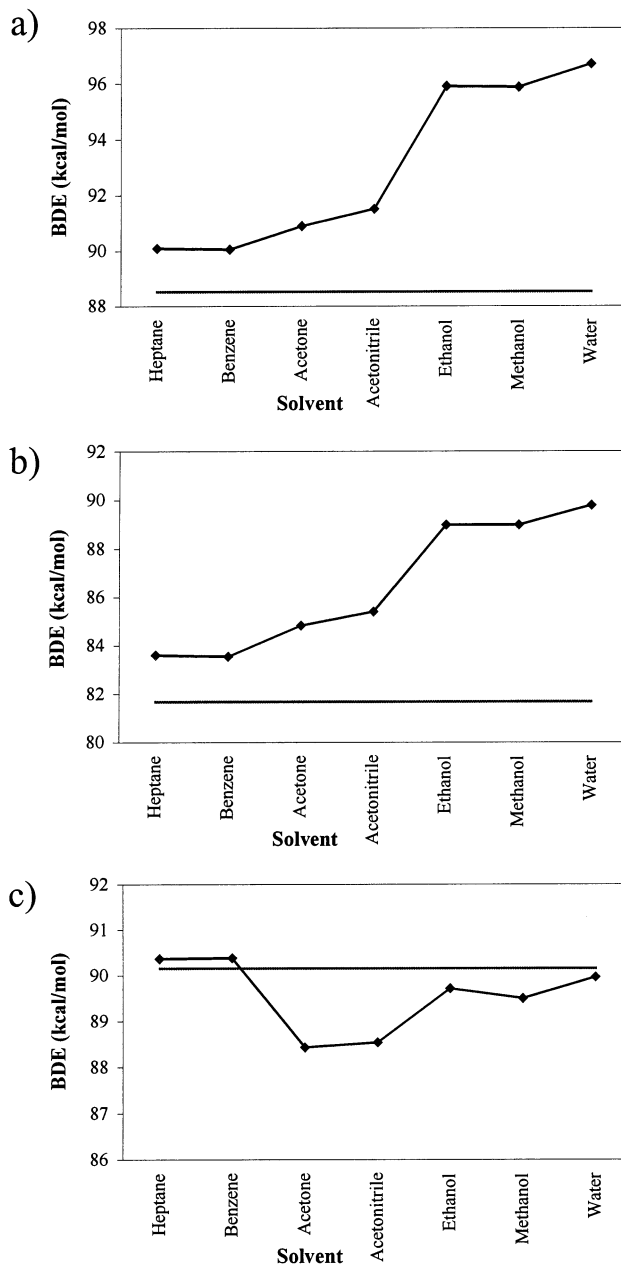

Figure 3. Solvent effect on the phenol (a), catechol (b), and guaiacol (c). Gas-phase BDEs (solid, straight line) are also shown.

kcal/mol. These values are in good agreement with available experimental ones[1] of 2 ± 0.5 kcal/mol.

Solvent Effect. Figure 3 illustrates the B3LYP/6-31+-G(,3pd) BDE$_{solv}$ variation of phenol, catechol, and guaiacol as a function of the seven solvents selected (solvent effect). Gas-phase BDEs are also shown for comparison. It is seen that the solvent effect is similar for phenol and catechol but different for guaiacol. On going from the group A to the group C solvents, BDEs$_{solv}$ of phenol and catechol increase significantly (by ca. 7.3−8.2 kcal/mol), with the solvent polarity, relative to the gas-phase (see also Table 5). On the contrary, there is a decrease of the BDEs$_{solv}$ of guaiacol with the solvent polarity. Although BDE$_{solv}$ in the group A solvents remains almost identical to the gas-phase value (Figure 3c), it decreases by ca. 1.7 and ca. 0.5 kcal/mol in the group B and C solvents, respectively. These latter data could account for a relatively easier tendency for hydrogen atom abstraction in both groups of solvents, in excellent agreement with the experiment.[62]
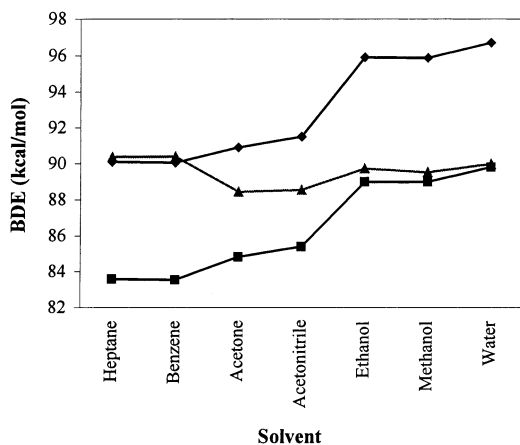
BDEs of 2-Mono- and 2,6-Disubstituted Phenols

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Figure 4. Substituent effect on the phenol (rhombs), guaiacol (triangles) and catechol (squares).

It is well-known that the main mechanism of action of phenolic antioxidants, in the nonpolar (group A) solvents, is the scavenging of free radicals by donating their phenolic hydrogen atom; the larger the BDE and/or Δ[BDE] the weaker the antioxidant activity. As it was stated in the Introduction, catechol was selected because it contains the structural unit that appears to be the main center responsible for the antioxidant activity of the flavonoids. The activities of two antioxidants, namely the monophenol (2,6-di-*tert*-butyl-4-methylphenol) and the flavonoid (3,5-di-*tert*-butylcatechol), were found[63] to decrease, on transferring from hexane to the HBA solvents. This is also the case with our theoretical results, indicating that the antioxidant activity of phenol and catechol decrease on going from hexane to the HBA solvents.

Guaiacol is expected to mimic the antioxidant behavior of the ubiquinol-0. The kinetic solvent effect, studied[62] in six solvents, differing in their HBA properties, on the hydrogen atom abstraction reaction from ortho-methoxy phenols was found to be smaller than for non-hydrogen bonded phenols. In addition, the small solvent effects make ubiquinol-0 a good antioxidant even in a polar environment. These results are also in excellent agreement with ours, showning that guaiacol (a) in all media presents lower solvent effects than monophenols and (b) exhibits its lower BDEs$_{solv}$, hence, its better antioxidant activity in the polar media. Consequently, our assumption made for a hydrogen atom transfer mechanism, for the reaction of the antioxidants under study, is correct for all solvents selected, not only for the group A ones, and/or our methodology describes the "bulk" solvent effects well in a wide spectrum of solvents.

Substituent Effect. In Figure 4, the substituent effect on the BDEs$_{solv}$ of phenol is shown. It is easily seen that, contrary to the significant OH effect on the absolute BDEs$_{solv}$ of phenol, that of OMe is low. Actually, the presence of the second OH group in catechol reduces BDEs$_{solv}$ of phenol in all media. Guaiacol shows a similar substituent effect to the OH group in the case of group C solvents only, and those in the group B and A solvents appear different. Hence, the presence and the nature of an ortho substituent play a key role in the BDEs$_{solv}$, in all media tested.

The substituent effect could be also studied with the aid of the Δ(BDE)$_{solv}$ values of Table 5. Calculated Δ(BDE)s$_{solv}$ for catechol, relative to phenol, range from -6.1 to -6.9 kcal/mol in all media tested. These values are very close to the experimental corresponding gas-phase one[12] (-7.1 kcal/mol). Hence, the substituent effect of the ortho-OH group in catechol is almost identical in both the gas and the liquid phases.

Calculated Δ(BDE)$_{solv}$ for guaiacol, being very small (ca. 0.3 kcal/mol) in the group A solvents, increase to be ca. -2.5 and -6.5 kcal/mol in the groups B and C, respectively.

Experimental studies have shown[62] that the presence of an ortho substituent is the main factor[64] in the solvent effect study, because it affects the phenolic OH−solvent interaction. Phenols with the same substituents in the ortho position would show the same solvent effect, whereas for different ortho groups, a significant solvent effect is expected. This is also in accordance with our theoretical results, because catechol and guaiacol, possessing different ortho groups, also present different solvent effects.

Summary and Conclusions

Gas-phase BDE study on phenol, catechol and guaiacol shows that the B3LYP/6-31+G(,3pd) level of theory provides very accurate Δ(BDE)s and absolute hydrogen bond enthalpies, once the absolute BDE has been approached, providing a strong evidence for the correctness of our method. Deviations of the absolute gas-phase BDEs do not exceed 0.72 kcal/mol, compared to experiment, and those of the relative ones do not exceed 0.24 kcal/mol. It also yields scaling factor values very close to one and could thus often be used directly without resorting to ZPE scaling, which is advantageous for the study of the BDEs.

Of the two continuum models, PCM and SCIPCM, used in the present study, the former only well describes the "bulk" solvent-effects, and it becomes essential to get the correct description of the interactions due either to non polar solvents and/or to polar H-bonded ones. This additional long-range field modifies both the structures and the BDEs$_{solv}$ of the solutes. Calculated BDEs$_{solv}$ are in very good agreement with the experimental ones, where available, depending on the solvent in which the compound is solvated. Solvent effects, depending on the E_N^T and/or α polarity parameter values of the solvent, are common for phenol and catechol and different for guaiacol. Calculated solvent effects are also in line with the experimental ones of known antioxidants, belonging to flavonoids and ubiquinols. Substituent effects in solution show that the presence and the nature of an ortho-substituent play a key role in the BDEs$_{solv}$ values. Phenols with different ortho groups, like catechol and guaiacol, show significant different solvent effects.

Overall the B3LYP/6-31+G(,3pd) procedure, provides a very cost-effective means of determining derived thermochemical quantities, like BDEs of hydroxy/methoxy ortho substituted phenols, in both gas and liquid phases. It could be also used as the basis set in the primary region of a locally dense basis set (LDBS) method, instead of a larger one, for the study of bigger antioxidant molecules. The accuracy in the BDE of the phenols achieved was based exclusively upon the derived data from the calculations; there was no need for further corrections regarding the ZPE values, the vibrational enthalpies, and the hydrogen exponents. It is relatively inexpensive, can be routinely used to give accurate estimates of experimental data, and shows no dramatic failures.

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