PCM Study of the Solvent and Substituent Effects on the Conformers, Intramolecular Hydrogen Bonds and Bond Dissociation Enthalpies of 2-Substituted Phenols

Alexandra T. Lithoxoidou and Evangelos G. Bakalbassis*

Laboratory of Applied Quantum Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, 541 24 Thessaloniki, Greece

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A PCM continuum model, at the DFT/B3LYP level, is used to study the solvent and substituent effects on the conformers, intramolecular hydrogen bond (HB) enthalpies, ($\Delta H_{\mathrm{intra}}$s), and O−H bond dissociation enthalpies, (BDEs), in 2-substituted phenols, 2-X-ArOH, in the liquid phase. Two electron-donating (edg) and three electron-withdrawing (ewg) substituents are chosen, involved in a variety of biochemical transformations. Seven solvents, differing in their H-bonding ability and polarity, are selected to model different environmental situations. Very good correlations are found between the computed R(O−H) and ν(O−H) values in solution for all non-HB 2-X-ArOH, showing that the former can be used as an universal molecular descriptor for the latter and vice-versa. In all 2-X-ArOH, the HB parent conformer is the most stable in all media, closely matching frequency experimental data in CCl_4. However, for all 2-X-ArO$^{\bullet}$, the most stable conformer either forms a "reverse"-HB or a HB is not formed, due to the long distance or steric effects. Changes in the stability, in solution, are observed for some of the 2-X-ArO$^{\bullet}$ conformers. The intramolecular HB-strength in solution, $\Delta H_{\mathrm{S,intra}}$, varies significantly with the size of the HB ring formed and the nature of the substituents. Reasonable correlations, derived between the two energetic parameters (BDE$_{\mathrm{aw,sol}}$ and $\Delta H_{\mathrm{S,intra}}$) and the solvent ($E_{\mathrm{N}}^{\mathrm{T}}$ and a), and/or molecular, [R(O−H) and ν(O−H)] ones, allow for an approximate estimation of the two former from the four latter. 2-X(edg) decrease BDEs (hence, increase the antioxidant efficiency of the solute, too) in all media; 2-X(ewg) present an opposite result. Moreover, an isodesmic reactions study affords total stabilization effect (TSE) values (identical to the Δ[BDE$_{\mathrm{aw}}$]s), which are mainly governed by the stabilization of the phenolic radical (SPR) than that of the parent molecule (SPP). Quantitative correlations between the two effects in the TSE in both the gas and the liquid phases are also given. Unlike in the protic solvents, the better stabilization of the radical than the parent species, derived for the 2-X(edg)-ArOH in the aprotic, apolar, and/or low polar solvents, could account well for their smaller BDE$_{\mathrm{sol}}$s. An effective antioxidant in solution should involve either one of the two edg in any one of the two latter solvents.

Introduction

Phenolic antioxidants (ArOH) are essential for foodstuff conservation and in sustaining life, because they inhibit radical-mediated oxidative damage by cutting off reactive species. The main mechanism of their action is considered to be the scavenging of free radicals by donating their phenolic hydrogen atom.[1] In addition, cleavage, formation, or both of an intramolecular hydrogen bond (HB) in a molecule, such as in 2-substituted phenols, 2-X-ArOH, as well as of an intermolecular one between the latter and the solvent, play a crucial role in a variety of biochemical transformations.

Despite the great importance of ArOH, only a few experimental studies exist, dealing with the estimation of their intramolecular HB enthalpies, $\Delta H_{\mathrm{intra}}$s. Moreover, DFT calculations, at the B3LYP/6-31G(d,p) level, were proven to be reliable for the computation of the gas-phase $\Delta H_{\mathrm{intra}}$s.[2,3] To the best of our knowledge, despite the detailed theoretical studies available,[2−4] concerning the geometrical aspects and energetics of the intramolecular HB in the gas phase, there is a lack of corresponding studies in solution. Moreover, although the vast majority of the computed $\Delta H_{\mathrm{intra}}$s determination in the literature refer to gas-phase reactions, most of the chemistry to which they are applied occurs in solution. However, 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.

Modeling of the solution environment is a growing area of interest within computational chemistry. The continuum reaction field models[5,6] represent simple and popular approaches to describe the solution environment and have been proven quite successful in a variety of applications.[7]

In recent studies,[8] the structure−activity relationships on phenolic antioxidants have been studied. A simple theoretical methodology was also established,[9] suitable for the accurate calculation of the absolute and relative gas- and liquid-phase phenolic O−H bond dissociation enthalpies, BDEs. It was also proven that the continuum model PCM was suitable for the estimation of the absolute and relative solution-phase BDEs (hereafter denoted as BDE$_{\mathrm{sol}}$s), as well as for the study of the "bulk" solvent effects of some simple phenolic molecules.

As far as the substituent effect on the BDE is concerned, it has been studied by many research teams,[10−12] in the gas phase. For para-substituted phenols, it was found[11] that, unlike electron-withdrawing substituents (hereafter denoted as ewg), electron-

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* To whom correspondence should be addressed. Phone: +302310997695. Fax: +302310997738. E-mail: bakalbas@chem.auth.gr.

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donating groups (edg) significantly reduce the BDE. Nevertheless, there are only a few theoretical studies[10,11,13,14] addressing substituent effects on ortho-substituted phenols. Suryan et al.[15,16] argued that the substituent effects on the phenol O−H bond strength are the same as for anisole O−CH_3 bond strength. This seems to be valid for para- and meta-substitution, but the assumption cannot be transferred to the case of ortho-substitution, also explained[10b] for the C−O BDE of 2-OHPhO-Me; in contrast to anisoles, intramolecular HB can be formed in phenols. To the best of our knowledge, theoretical studies in solution, on the substituent-effect on ortho-substituted phenols, are missing.

In the present study, the substituent and solvent effects on the five 2-X-ArOH, involving the edg, −OH (catechol) and −OMe (guaiacol), and the ewg, −NO_2, −CHO, and −COOH, are examined in the liquid phase. The rationale for selecting them is that they represent prototypal HB interactions, which may be found in biological systems. To model different environmental situations, seven dielectric media, ranging from strong polarity, viz., water, ethanol, and methanol (hereafter denoted as group C), via dipolar aprotic, acetonitrile and acetone (group B) to the nonpolar, *n*-heptane and benzene (group A), were selected.

The questions to which we address ourselves in this study are as follows: (a) Can our theoretical model “detect” the possible conformer stability changes of the 2-X-ArOH and 2-X-ArO$^\bullet$, occurring in solution? (b) Can our model estimate and/or predict the $\Delta H_{\mathrm{intra}}$s of the 2-X-ArOH in solution (hereafter denoted as $\Delta H_{\mathrm{S,intra}}$s), of which the experimental values are rare? (c) Can correlations be established between the DFT-computed $\Delta H_{\mathrm{S,intra}}$s and/or $\mathrm{BDE_{sol}}$s and the computed structural and/or energetic features or experimentally accessible parameters, to save experimental or computational work? (d) Can our method afford distinguishable solvent effects on the energetic data of the 2-X-ArOH, derived in different environments? (e) Can our method distinguish between the edg and ewg substituent effects in solution?

Method of Calculation

All calculations reported in the present study were carried out using density functional theory,[17] as implemented in the Gaussian 98 program suite.[18] Becke’s 3-Parameter hybrid functional combined with the Lee−Yang−Parr correlation functional, abbreviated as B3LYP level of density functional theory,[19] with the 6-31+G(,3pd), basis set were used,[9] along with five-component Cartesian d polarization functions.

Solvent effects were calculated using the polarized continuum model (PCM)[20] in its original dielectric formulation (D-PCM, within the UAHF[21] framework). The cavity was described by a different number of tessarae, with average area of 0.4 Å^2, depending on the solute and solvent. A wide spectrum of ϵ values was used, ranging from 0 (*n*-heptane) to 78.39 (water). The seven solvents tested, based upon their Dimroth and Reichardt’s,[22] $E_{\mathrm{N}}^{\mathrm{T}}$ and Kamlet−Taft[23,24] α polarity parameter values could be divided into the three, A, B, and C, groups mentioned above. More details on our method can be found in a recent paper.[9]

All structures were true minima on the calculated potential surface, verified by final frequency calculations that provide energy minima with certainty. UB3LYP were used for the geometry and vibrational frequency calculations of the radicals and the hydrogen atom. The method constitutes fully consistent calculation, because both the phenols and the respective radicals are calculated at the same level of theory.[9,25]

A frequency scale factor of[9,26] 0.9610 along with the ones of 0.9810 and 0.9985 for the DFT ZPEs and ΔH_{vib}, respectively, were calculated[9] in the gas phase. For the reasons described in that paper, we did not resort to ZPE and/or vibrational enthalpy scaling.

The $\langle S^2\rangle$ values calculated for all 2-X-ArO$^\bullet$ of the present study range from 0.78 to 0.79, being close to the expected value for a pure doublet wave function, 0.75. Therefore, the results of our DFT calculations are less affected by spin contamination in the liquid phase. These, in turn, could be reflected to the computed energies, affording accurate absolute and relative liquid-phase BDEs.

Solution-phase $\mathrm{BDE_{sol}}$s were estimated as described before.[9] The liquid-phase intramolecular HB enthalpy, $\Delta H_{\mathrm{S,intra}}$, of the 2-substituted phenols was derived by using the gas-phase origin of the parameter,[2] viz., by comparing the DFT enthalpies at 298 K for the intramolecular-HB conformer and the lowest-energy, fully optimized conformer, in which the hydroxyl group is pointing away from the substituent. This constitutes a reasonable procedure, because, within the framework of the PCM model, the cavity differences in both conformers are negligible, related to a H atom position change only. Moreover, the use of the unconventional basis set, 6-31+G(,3pd), resulted as a reasonable consequence of our detailed study[9] on the variation of $\mathrm{BDE_{sol}}$s on the basis set. Similar to the $\mathrm{BDE_{sol}}$ computation, the $\Delta H_{\mathrm{S,intra}}$ value is also the algebraic sum of enthalpies. Hence, it seems reasonable to apply our simple theoretical methodology to the liquid-phase $\Delta H_{\mathrm{S,intra}}$ calculation of 2-X-ArOH.

In both the gas and the liquid phase, all possible conformers of the phenols and the respective phenoxyl radicals under study (amounting to a total of 216 structures) were optimized, using tight convergence criteria. Moreover, a total of 35 ones corresponding to the C_6H_6 and X−C_6H_5 species, involved in the isodesmic reactions study in solution, were also considered.

All of the final conformers and their energies in the gas and the liquid phases are available as Supporting Information (Table S1).

Results and Discussion

Intramolecular Hydrogen-Bond Structures in Solution. In Table 1, selected gas- and liquid-phase structural parameters of the hydrogen-bonded and non-hydrogen-bonded fragments of the investigated phenols are tabulated. In particular, variations in solution, as well as those between the gas and the liquid phase in the O−H bond lengths, *R*(O−H), the *R*(OH···O) ones, the corresponding bond angles, and the O−H stretching frequencies, ν(O−H), are shown. Our gas-phase data is in close agreement with that of Korth et al.;[2] the corresponding deviations do not exceed 2.3%.

For non-hydrogen-bonded phenols, in the liquid phase, Table 1 shows that the *R*(O−H) is invariant with the nature of the substituent at the 2-position. For all phenols, the same *R*(O−H) was derived, relative to that of phenol (substituent effect), for each one of the three solvent groups; the only exception is that of the 2-X(ewg) ones in group C. In the corresponding ν(O−H) values, the substituent effect becomes noticeable on going from the gas phase (19 cm^{-1}) to group C (165 cm^{-1}). Moreover, there is a ν(O−H) decrease observed in the polar solvents (solvent effect), appearing larger in phenols with 2-X(ewg), due to the formation of an intermolecular HB with the solvent. Consequently, the more polar/protic the solvent the stronger the intermolecular HB and the smaller the ν(O−H) values in solution, hence, the weaker the free phenolic O−H

TABLE 1: Selected Structural Data[a] and O−H Stretching Frequencies[b] for the Intramolecular Hydrogen-Bonded and Non-Hydrogen-Bonded 2-X-ArOH in Both the Gas and the Liquid Phases

		intra-HB					non-HB		
	solvent[c]	*R*(O−H)	*ν*(O−H)	∠C−O−H	*R*(OH···O)	∠O−H···O	*R*(O−H)	*ν*(O−H)	∠C−O−H
phenol	gas-ph	0.966	3839.9	110.7			0.966	3839.9	110.7
	hept	0.967	3830.4	110.7			0.967	3830.4	110.7
	benz	0.966	3830.9	110.7			0.966	3830.9	110.7
	ac/ne	0.970	3763.0	110.7			0.970	3763.0	110.7
	ac/le	0.970	3754.9	110.7			0.970	3754.9	110.7
	eth	0.981	3497.3	110.1			0.981	3497.3	110.1
	meth	0.981	3490.6	110.0			0.981	3490.6	110.0
	wat	0.981	3478.3	110.0			0.981	3478.3	110.0
2-OH−phenol	gas-ph	0.969	3792.1	108.9	2.174	113.0	0.966	3841.9[d]	110.0
	hept	0.970	3781.6	108.9	2.169	112.9	0.967	3830.6	110.0
	benz	0.970	3780.4	108.9	2.166	113.0	0.967	3830.6	109.9
	ac/ne	0.971	3748.8	109.1	2.173	112.7	0.970	3765.1	109.8
	ac/le	0.971	3745.4	109.1	2.173	112.6	0.970	3757.0	109.8
	eth	0.978	3547.8	110.3	2.228	110.6	0.979	3554.4	108.8
	meth	0.979	3541.5	110.3	2.229	110.5	0.980	3549.0	108.7
	wat	0.979	3531.0	110.4	2.229	110.5	0.980	3538.9	108.7
2-OMe-phenol	gas-ph	0.970	3771.4	107.9	2.111	114.5	0.966	3838.5	109.7
	hept	0.971	3759.0	108.0	2.108	114.4	0.966	3828.8	109.7
	benz	0.971	3757.2	108.0	2.105	114.5	0.966	3839.4	109.7
	ac/ne	0.973	3723.1	108.3	2.112	114.0	0.970	3760.2	109.7
	ac/le	0.973	3719.6	108.3	2.112	114.0	0.970	3752.0	109.7
	eth	0.979	3535.8	109.3	2.141	112.2	0.982	3480.6	108.8
	meth	0.980	3528.5	109.3	2.143	112.2	0.981	3504.0	109.9
	wat	0.980	3515.7	109.3	2.145	112.0	0.982	3491.7	109.9
2-NO$_2$−phenol	gas-ph	0.988	3396.6	107.7	1.692	143.5	0.966	3827.1	110.5
	hept	0.988	3392.7	107.7	1.686	143.5	0.968	3803.1	110.3
	benz	0.988	3390.8	107.7	1.684	143.6	0.968	3799.6	110.2
	ac/ne	0.988	3389.1	107.8	1.684	143.6	0.972	3720.7	110.5
	ac/le	0.988	3387.5	107.8	1.683	143.6	0.973	3702.4	110.1
	eth	0.988	3383.8	108.1	1.684	143.2	0.986	3416.0	109.3
	meth	0.988	3383.4	108.1	1.684	143.2	0.987	3391.7	109.8
	wat	0.988	3383.0	108.2	1.685	143.0	0.987	3389.0	109.2
2-CHO−phenol	gas-ph	0.990	3367.1	108.3	1.740	145.5	0.967	3822.8	110.4
	hept	0.990	3345.0	108.1	1.724	146.0	0.968	3807.4	110.3
	benz	0.991	3339.3	108.0	1.720	146.2	0.968	3806.2	110.2
	ac/ne	0.991	3318.5	107.7	1.710	146.9	0.972	3730.5	110.0
	ac/le	0.991	3314.1	107.7	1.707	147.0	0.972	3721.3	110.0
	eth	0.992	3304.7	107.6	1.703	147.4	0.983	3454.1	109.4
	meth	0.992	3304.6	107.6	1.704	147.3	0.984	3446.4	109.4
	wat	0.992	3299.4	107.7	1.701	147.3	0.984	3431.9	109.3
2-COOH−phenol	gas-ph	0.986	3441.7	108.7	1.749	144.4	0.966	3824.2	110.2
	hept	0.987	3420.8	108.5	1.734	144.9	0.968	3809.3	110.1
	benz	0.987	3415.5	108.4	1.730	145.1	0.968	3808.4	110.0
	ac/ne	0.988	3389.6	108.1	1.716	145.8	0.971	3735.1	109.9
	ac/le	0.988	3385.9	108.1	1.713	145.9	0.972	3726.3	109.9
	eth	0.989	3353.1	107.7	1.690	146.8	0.983	3468.7	109.0
	meth	0.989	3353.5	107.8	1.692	146.6	0.983	3461.2	108.9
	wat	0.990	3348.4	107.9	1.690	146.5	0.984	3447.5	108.9

[a] All bond lengths are in Å, and bond angles are in degrees. [b] All stretching frequencies values are unscaled (cm^{-1}). [c] Abbreviations used are gas-ph = gas phase, hept = *n*-heptane, benz = benzene, ac/ne = acetone, ac/le = acetonitrile, eth = ethanol, meth = methanol, wat = water. [d] For the non-hydrogen-bonded 2-OH Phenol, the symmetric ν(O−H) values are given. The corresponding asymmetric ones are (cm^{-1}) gas, 3840.1; hept, 3828.6; benz, 3828.7; ac/ne, 3762.2; ac/le, 3754.1; eth, 3549.2; meth, 3543.7; wat, 3533.6.

bond, in agreement with the larger corresponding *R*(O−H) values. Contrary to Filarowski et al.[27] and similar to Korth et al.[2] in the gas phase, we failed to detect a linear correlation in the liquid phase between $\nu(\text{O−H})_{\text{non−HB}}$ and pK_a.

For the non-HB catechol, a regression coefficient, r^2 value of 0.9990 [$\nu(\text{O−H}) = -22907R(\text{O−H}) + 25981$, ($n = 7$), see Figure S1] is found for the relationship between *R*(O−H) and ν(O−H), in the seven solvents tested. Corresponding r^2 values for the 2-MeO, 2-NO$_2$, 2-CHO, and 2-COOH-phenols are 0.9983, 0.9996, 0.9980, and 0.9991, respectively; that of phenol is 0.9962. The very good correlations derived indicate that, for all of the non-HB 2-X-ArOH, *R*(O−H) could be used as an universal molecular descriptor for the determination of the ν(O−H) values in solution and vice-versa.

Unlike the above 2-X-ArOH conformers, in the intramolecularly HB ones, the substituent effect on *R*(O−H), presented mainly by the ewg, decreases on going from A to C group. A quite analogous effect is found for the ν(O−H) values. Moreover, similar to non-HB 2-X-ArOH, HB-ones show analogous but stronger solvent effects on the *R*(O−H) for the edg. However, solvent effects for the 2-X(ewg)-ArOH are almost insignificant, and its explanation will be given later in this section. The solvent effect could be due to the mutual participation of the O−H group of the solute in the formation of an intra- and intermolecular HB with the solvent. It should be also mentioned that all ν(O−H) values in Table 1 are unscaled. Nevertheless, close agreement between the calculated and the experimental ones[28] in CCl$_4$ (a group A solvent) is achieved,[29] by using a frequency scale factor of[9,26] 0.9610. It is obvious that the experimental values match better our scaled$_{\text{HB}}$ than the scaled$_{\text{non−HB}}$ ones. It is very likely then that the experimental conformers adopt in CCl$_4$ the HB instead of the non-HB configuration, in excellent agreement with our structural theoretical findings for group A (see also Figure 1).

The intramolecular HB *R*(OH···O) values vary significantly in solution with the size of the HB ring, ranging from 2.105 to

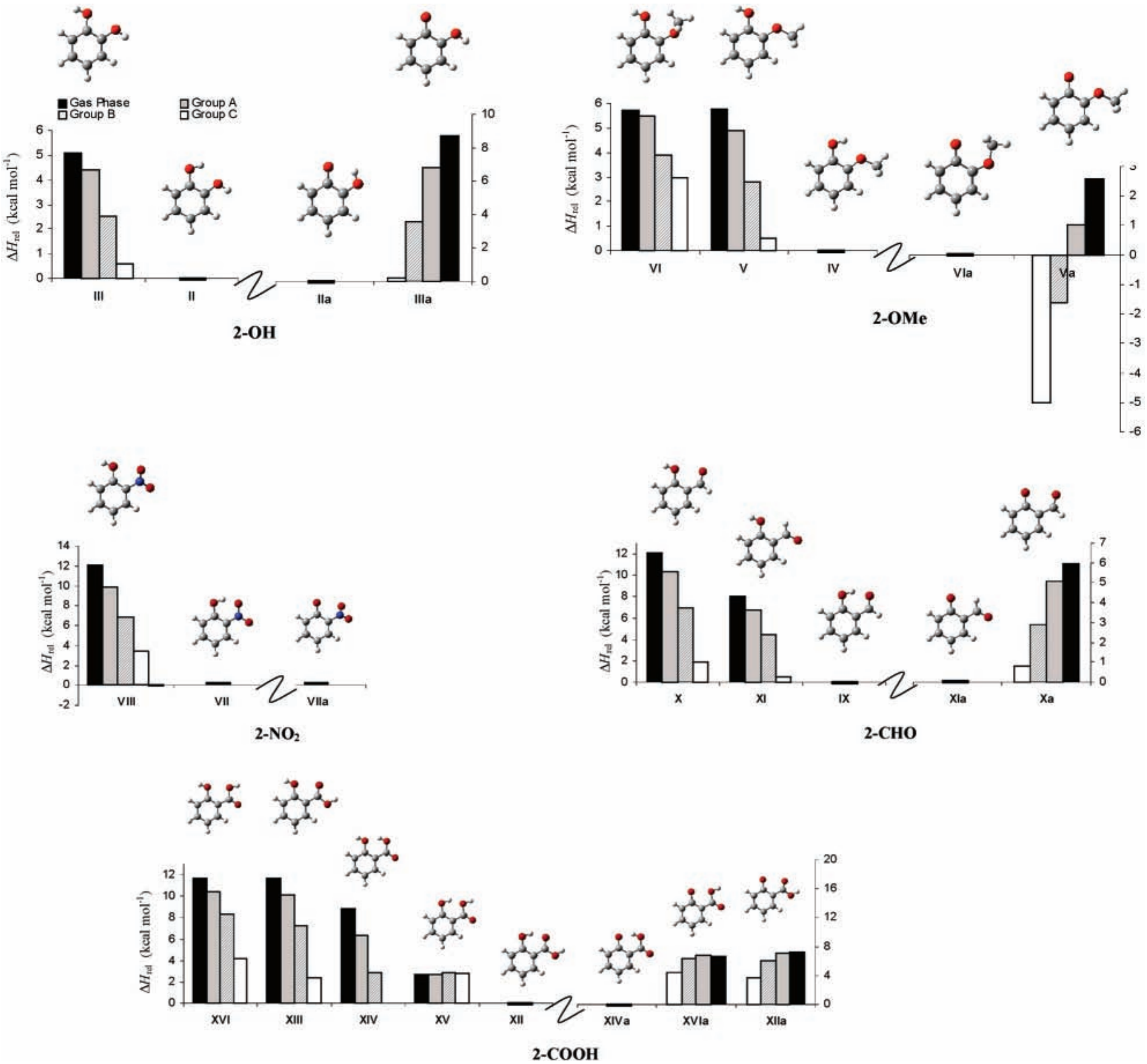


Figure 1. Relative enthalpies, ΔH_{rel} with respect to the most stable conformer of the 2-OH-, 2-OMe-, 2-NO$_2$-, 2-CHO-, and 2-COOH−ArOH, parent and radical conformers in each medium.

2.229 Å in the five-membered HB rings (involving edg) and from 1.683 to 1.749 Å in the six-membered ones (having ewg). Since the shorter the *R*(OH···O) the stronger the bond, it would be expected that the 2-NO$_2$ substituent would present the strongest intramolecular HBs in solution, accounting well for its identical *R*(O−H)s derived in both phases (see Table 1). These substituent effects on the intramolecular HB strength will be discussed in detail in the next section. In addition, a solvent effect in group C is also observed, resulting in (a) an increasing of the HB length in the five-membered rings, relative to the gas phase (by ca. 0.055 and 0.034 Å, for the 2-OH and 2-OMe, respectively) and (b) a decreasing in the six-membered one, (ca. 0.059, 0.039, and 0.007 Å for 2-COOH, 2-CHO, and 2-NO$_2$, respectively).

Unlike the non-HB 2-X-ArOH, the HB ones appear worse with regard to *R*(O−H) vs ν(O−H) relationships in the seven solvents tested, probably due to the HB effects on the phenolic O−H bond. In particular, contrary to catechol and guaiacol, exhibiting good correlations (r^2 values of 0.9969 and 0.9930, respectively), reasonable ones are found for both 2-COOH- and 2-CHO-ArOH (r^2 values of 0.9343, and 0.7997, respectively); 2-NO$_2$-ArOH shows a crude relationship. The good correlations for the 2-X(edg)-ArOH in solution could allow for an easy, fast, and accurate ν(O−H) calculation. Moreover, the role of the intramolecular HB on the ν(O−H) values determination could be examined by the *R*(OH···O) vs ν(O−H) relationships, appearing good (average r^2 values of ca. 0.9961) for all but the 2-NO$_2$−ArOH. Consequently, the role of the intramolecular HB is crucial in the determination of the ν(O−H) values, namely, in the phenolic O−H bond strength.

Enthalpies, $\Delta H_{S,intra}$, and Conformers. The global minimum conformers of the 2-X-ArOH under study possess an intramolecular HB, of which the liquid-phase bond-strength value, $\Delta H_{S,intra}$, has not been determined so far. However, to calculate only the substituent effect on the BDEs this additional enthalpic contribution has to be removed. Moreover, attempts should be also made to correlate the liquid phase, $\Delta H_{S,intra}$ of the 2-X-ArOH with (a) the physical parameters of the solvent and (b) the calculated structural parameters of the solute.

The investigation of the energetics of all parent and radical conformers in both the gas and the liquid phase is attempted prior to the examination of the $\Delta H_{S,intra}$ values; conformer

TABLE 2: Gas and Liquid Phase Intramolecular Hydrogen Bond Enthalpies,[a] ΔH_{Intra}, for the 2-X-ArOH, in kcal mol^{-1}

		gas phase		group A		group B		group C		
2-X[b]	exp	calc[c]	this work	hept[d]	benz	ac/ne	ac/le	eth	meth	wat
OH	−2.29[g]	−4.1	−5.1	−4.5	−4.3	−2.5	−2.5	−0.7	−0.6	−0.5
OMe	−2.0[h], −2.2[i]	−4.4	−5.8	−4.9	−4.9	−2.9	−2.7	−0.5	−0.7	−0.4
	−3.8[j], −4.1[k]	(−5.7)[e]	(−5.7)	(−5.3)	(−5.6)	(−4.0)	(−3.8)	(−3.1)	(−3.0)	(−3.0)
N***O***$_2$	−4.8[l],−6.2[k],−8.3[j]	−11.9	−12.0	−9.7	−9.9	−7.7	−6.1	−0.3	−3.4	0.5
	−6.65[g], −2.1[m]									
CH***O***	−7.09[g], −1.8[m]	(−9.2)	(−8.0)	(−6.7)	(−6.7)	(−4.6)	(−4.5)	(−0.7)	(−0.6)	(−0.3)
	−5.2[i],−8.1[k],−8.2[j]	−11.9	−12.1	−10.3	−10.3	−7.0	−6.8	−2.2	−1.9	−1.5
C***O***OH	−4.3[l]	−12.0	−11.7	−10.1	−10.1	−7.3	−7.1	−2.9	−2.3	−1.9
		(−11.4)	(−11.7)	(−10.2)	(−10.5)	(−8.4)	(−8.2)	(−4.6)	(−4.1)	(−3.8)
CO***O***H	−4.3[l]	(−7.9)	(−9.1)	(−7.3)	(−7.5)	(−4.5)	(−4.2)	(−0.6)	(−0.3)	(2.2)
		−7.3	−9.1	−7.5	−7.9	−5.6	−5.3	−2.3	−2.1	0.2
COOH	−4.3[l]	[−0.9][f]	[−2.9]	[−3.7]	[−4.2]	[−5.4]	[−5.5]	[−4.4]	[−4.4]	[−4.5]

[a] ΔH_{intra} is the difference between the most stable toward and away parent conformers and is given in the first line for each 2-X-ArOH. [b] The HB accepting atom of the substituent is given in bold italics. [c] Calculated data from ref 2. [d] See Table 1 footnote c. [e] For cases where, in the away conformer the substituent is rotated by 180°, relative to the HB toward one, the values are given in parentheses. [f] For cases where, in the away conformer a hydrogen atom of the substituent forms a HB to the phenolic oxygen, the values are given in square brackets. [g] Reference 30a,b. [h] Reference 30c. [i] Reference 30d. [j] Reference 30e. [k] Reference 28p. [l] Reference 30f. [m] Reference 30g.

TABLE 3: Gas and Liquid Phase Intramolecular Hydrogen Bond Enthalpies,[a] ΔH_{Intra}, for the 2-X-ArO$^\bullet$, in kcal mol^{-1}

	gas phase		group A		group B		group C		
2-X	calc[b]	this work	hept[c]	benz	ac/ne	ac/le	eth	meth	wat
OH	−9.6	−8.7	−6.6	−7.0	−3.7	−3.5	−0.5	−0.2	0.1
OMe	[−1.9][d]	[−2.6]	[−1.1]	[−1.0]	[1.4]	[1.8]	[4.8]	[5.0]	[5.3]
CHO	[−5.0][d]	[−6.2]	[−5.3]	[−4.9]	[−3.0]	[−2.8]	[−1.0]	[−0.8]	[−0.6]
COOH	−6.4	−6.6	−6.7	−7.0	−6.1	−6.5	−4.4	−4.4	−4.4
	(−7.7)[e]	(−7.2)	(−6.9)	(−7.1)	(−6.1)	(−5.8)	(−3.8)	(−3.7)	(−3.6)

[a] ΔH_{intra} is the difference between the most stable toward and away radical conformers. Unlike parent conformers, in the toward radicals a "reverse" HB exists between the hydrogen of the substituent and the phenolic oxygen. [b] See Table 2 footnote c. [c] See Table 1 footnote c. [d] For cases where, the two more stable radical conformers do not form a HB, ΔH_{intra} values express a rotation and are given in square brackets. [e] See Table 2 footnote e.

stability could change with the environment. Figure 1 represents the relative enthalpies, ΔH_{rel}, of all 2-X-ArOH parent and radical conformers derived in each medium, with respect to the most stable one (considered to be at the zero level). The most stable parent conformer of catechol is **II** in all media. Nevertheless, the stability of **III** increases on going from the gas phase to group C. The **IIa**, catechoxyl radical, is energetically more favorable than **IIIa** in all media, although their difference becomes meaningless in group C.

The guaiacol parent conformer, **IV**, is the most stable, and **VI** is the most unfavorable; **V** lies between in all media (see also Figure 1). It is worth mentioning that there is a change in the stability between the two 2-OMe-ArO$^\bullet$ conformers, in solution. In particular, **VIa** is more stable than **Va** in the gas phase and in group A, whereas the opposite holds true in groups B and C. The 2-NO_2-, 2-CHO-, and 2-COOH−ArOH show an analogous behavior (see Figure 1). In all 2-X-ArOH, the HB parent conformer is the most stable in all media. Moreover, with the exception of the **XI** conformer (in both phases) and the **XVI** one (in the gas phase), the conformation of the 2-substituent in the HB form is retained in the lowest-energy non-HB form, upon rotation of the phenolic OH group into the away position.

In all 2-X-ArO$^\bullet$, the most stable conformer either (i) forms a "reverse"[2]-HB between the hydrogen atom of the substituent and the phenolic oxygen atom [e.g., **IIa** (2-OH−ArO$^\bullet$) and **XIVa** (2-COOH−ArO$^\bullet$) respectively] or (ii) a HB is not formed, due either to the long distance or steric effects [e.g., **XIa** (2-CHO−ArO$^\bullet$) and **VIa** (2-OMe-ArO$^\bullet$, in the gas phase and in group A)]. There is only one, non-HB conformer, viz., **VIIa** (2-NO_2−ArO$^\bullet$), in which both a H atom is missing and the rotation of the substituent has no change on the conformation of the radical. There is also a solvent effect, regarding the stability of **XVIa** (2-COOH−ArO$^\bullet$), being more stable than **XIIa** in the gas phase and in group A, whereas the opposite holds true for groups B and C.

Table 2 shows the calculated $\Delta H_{\text{S,intra}}$ values for the parent phenols, and those for the phenoxyl radicals are given in Table 3. The correctness of the calculated $\Delta H_{\text{S,intra}}$ value depends on the conformational arrangement adopted by the away and toward phenolic conformers.[2] In the first line of each phenol in both tables, $\Delta H_{\text{S,intra}}$s are given, referring to the lowest-energy conformer of all species. Moreover, since some substituents examined possess two acceptor atoms and/or there are some additional rotational conformers, the data of all other possible HBs is also tabulated. For cases where in the away conformer a hydrogen atom of the substituent forms a reverse-HB to the phenolic oxygen, the values are given in square brackets. However, for cases where in the away conformer the substituent is rotated by 180° relative to the hydrogen-bonded toward one, the values are given in parentheses. For comparison, our calculated corresponding gas-phase data along with literature one is also summarized.

For the parent 2-X-ArOH (Table 2), our liquid-phase values match better with the experiment than our gas-phase larger ones. A possible rationale for the diverging experimental values, could be the different techniques and the media used in each case. Moreover, there is a gradual decreasing of the intramolecular HB strength with the polarity of the solvent; the more polar/protic the solvent the smaller the $\Delta H_{\text{S,intra}}$ values. This solvent effect was schematically depicted in Figure 1. It was shown[3,31] that 2-OCH_3−ArOH (involving a five-membered HB ring with an edg) in a strong HB accepting (HBA) solvent exists in the HB form, but the intramolecular HB is weakened because of the presence of an intermolecular HB between the solute and the solvent. All of these are in excellent agreement with our theoretical results in group C. However, for the 2-COOH−ArOH

TABLE 4: B3LYP/6-31+G(,3pd) BDE_{sol}s, Δ(BDE)s and Δ[BDE]s for Both the HB and Non-HB Phenols, Calculated in the Liquid Phase with the PCM Model[a]

AH	solvent[b]	BDE_{sol}[c]	Δ(BDE)[d]	Δ[BDE][e]	$BDE_{aw,sol.}$[c]	$\Delta(BDE_{aw.})$[d]	$\Delta[BDE_{aw.}]$[e]
phenol	gas-ph	88.53[f]	0				
	hept	90.10[g]	1.57				
	benz	90.06[h]	1.53				
	ac/ne	90.90	2.37				
	ac/le	91.51[i]	2.98				
	eth	95.91	7.38				
	meth	95.88	7.35				
	wat	96.71[j]	8.18				
2-OH−phenol	gas-ph	81.68[k]	0	−6.85[l]	85.35	0	−3.18[m]
	hept	83.60	1.92	−6.50[n]	85.79	0.44	−4.31
	benz	83.55	1.87	−6.51[n]	86.25	0.90	−3.81
	ac/ne	84.83	3.15	−6.07	86.06	0.71	−4.84
	ac/le	85.40	3.72	−6.11	86.44	1.09	−5.07
	eth	88.98	7.30	−6.93	88.79	3.44	−7.12
	meth	88.98	7.30	−6.90	88.58	3.23	−7.30
	wat	89.79	8.11	−6.92	89.24	3.90	−7.47
2-OMe-phenol	gas-ph	81.78	0	−6.75	84.37[o]	0	−4.16[p]
	hept	84.33	2.55	−5.77	85.44	1.07	−4.66
	benz	84.55[q]	2.77	−5.51	85.51	1.14	−4.55
	ac/ne	88.43	6.65	−2.47	85.54	1.17	−5.36
	ac/le	88.54	6.76	−2.97	85.81	1.44	−5.70
	eth	89.72	7.94	−6.19	89.18	4.81	−6.73
	meth	89.50	7.72	−6.38	88.85	4.48	−7.03
	wat	89.97	8.19	−6.74	89.55	5.19	−7.16
2-NO_2−phenol	gas-ph	103.33	0	14.80	91.29[r]	0	2.76[s]
	hept	103.33	0	13.23	93.62	2.33	3.52
	benz	103.57	0.25	13.51	93.63	2.34	3.57
	ac/ne	101.16	−2.17	10.26	93.50	2.21	2.60
	ac/le	101.49	−1.83	9.98	95.42	4.13	3.91
	eth	99.41	−3.92	3.50	99.09	7.80	3.18
	meth	99.15	−4.17	3.27	95.76	4.47	−0.12
	wat	99.39	−3.93	2.68	99.90	8.61	3.19
2-CHO−phenol	gas-ph	97.44	0	8.91	91.58	0	3.05
	hept	98.19	0.75	8.09	93.17	1.59	3.07
	benz	98.60	1.16	8.54	93.26	1.68	3.20
	ac/ne	97.77	0.33	6.87	93.74	2.16	2.84
	ac/le	98.26	0.82	6.75	94.32	2.74	2.81
	eth	98.63	1.19	2.72	97.44	5.86	1.53
	meth	98.48	1.04	2.60	97.37	5.79	1.49
	wat	99.10	1.66	2.39	98.22	6.64	1.51
2-COOH−phenol	gas-ph	95.74	0	7.21	90.60	0	2.07
	hept	96.02	0.28	5.92	92.59	1.99	2.49
	benz	96.04	0.30	5.98	92.98	2.38	2.92
	ac/ne	94.84	−0.90	3.94	93.62	3.01	2.72
	ac/le	95.17	−0.56	3.66	93.87	3.27	2.36
	eth	97.35	1.61	1.44	98.27	7.67	2.36
	meth	96.84	1.10	0.96	98.24	7.63	2.36
	wat	97.34	1.60	0.63	99.06	8.46	2.35

[a] Gas-Phase values are also presented (all values in kcal mol^{-1}). [b] See Table 1 footnote c. [c] BDE_{sol}s values are calculated with the most stable parent and radical conformers possessing intramolecular HB. $BDE_{aw,sol}$ refers to the ones calculated with the most stable away conformers, without any intramolecular HB. [d] Δ(BDE) has been estimated as $\Delta(BDE) = BDE_{sol} - BDE_{gas}$ for both the HB and non-HB (away) conformers. [e] Δ[BDE] has been estimated as $\Delta[BDE] = BDE_{sol,ArOH} - BDE_{sol,PhOH}$ for both the HB and non-HB conformers. [f] exp: 88.74 ± 0.55,[34] 88.19.[35] [g] exp: 89.36[34] (in isooctane). [h] exp: 88.3 ± 0.8,[36] 90.51[34] (PAC), 86.9[34] (Eq), 90.9 ± 1.3[37] (PAC). [i] exp: 95.0,[38] 92.9 ± 0.9,[37] 96.15.[34] [j] exp: 88.2 ± 0.3,[43] [k] exp: 81.64,[15] 81.17.[35] [l] exp: −7.17 ± 1.9,[34] −7.1.[15,16] [m] exp: −4.4.[39] [n] exp: −6.9.[40] [o] exp: 84.54.[15] [p] exp: −4.2,[15] −4.06 ± 0.96,[34] −3.9.[41] [q] exp: 83.16 ± 0.15.[36] [r] exp: 86.86.[35] [s] exp: −1.2 ± 1.9,[34] −1.3,[15,16] 2.61[34] (AM1).

involving a reverse-HB, there is a gradual increasing of the intramolecular HB with the polarity of the solvent. A substituent effect is also obvious in the $\Delta H_{S,intra}$ values. It is seen that, in both the gas and the liquid phase, 2-X(ewg) substitution results in stronger intramolecular HBs than the 2-X(edg) one, in close agreement with their calculated $R(OH\cdots O)$ values. Consequently, both the 2-X(edg) and/or 2-X(ewg) substitution as well as the size of the intramolecular ring formed (five- and/or six-membered one) affect the intramolecular HB strength in solution.

$\Delta H_{S,intra}$ values of the radicals (Table 3) refer to a reverse-HB formed between a hydrogen atom of the substituent and the phenolic oxygen atom. Similar to the parent molecules, the more polar/protic the solvent the smaller the $\Delta H_{S,intra}$ values of the radicals, except for the 2-MeO−ArO•. However, in the latter, $\Delta H_{S,intra}$ refers to an enthalpic contribution not associated with the pure donor−acceptor HB interaction (see Figure 1). Furthermore, in the **XIa** (2-CHO−ArO•, see Figure 1) despite the presence of a reverse-type enthaplic interaction between the H atom of the CHO group and the phenolic O atom, this does not correspond to a hydrogen bonding one, due to the long O•••H distance. Hence, $\Delta H_{S,intra}$s corresponding to the 2-OMe- and 2-CHO−ArO•, in which a HB is not formed, are presented in square brackets in Table 3, denoting a rotation. The opposite sign derived for the $\Delta H_{S,intra}$ of the guaiacoxyl radical, in groups B and C, is due to the away form, **Va**, lying lower in energy by ca. 1.6 and 5.0 kcal/mol, respectively, than the toward one, **VIa** (vide supra).

Moreover, **VIIa** is the only possible 2-NO_2−ArO•, accounting for the missing of the corresponding $\Delta H_{S,intra}$. Alike the 2-X-ArOH, solvent effect on the ΔH_{intra} is also obvious in the 2-X-ArO•. However, a substituent effect cannot be derived in the 2-X-ArO• conformers, because, as already mentioned, $\Delta H_{S,intra}$

in some of the radicals refers to an enthalpic contribution not associated with the pure HB interaction.

DFT-Computed BDEs in the Liquid Phase. Table 4 summarizes the DFT-calculated, absolute, and liquid-phased BDE_{sol}s along with the relative Δ(BDEs) [estimated as Δ(BDEs) $= BDE_{sol} - BDE_{gas}$] and Δ[BDEs], [estimated as $\Delta[BDEs] = BDE_{ArOH} - BDE_{PhOH}$] of the six phenols studied. In an attempt to eliminate the intramolecular HB additional enthalpic contribution from the BDE_{sol}s, two different values are incorporated in the table. The first one, BDE_{sol}, corresponds to the lowest energy conformers of the parent phenolic compound and the respective radical. $BDE_{aw,sol}$, derived from the most stable away conformers,[32] provides the "real" solvent effect on each 2-X-ArOH in each solvent, because the enthalpic contribution of the HB on the liquid-phase BDE value has been removed. Contrary to phenol, experimental liquid-phase BDEs are scarce for the 2-X-ArOH.

Comparisons between the available calculated and experimental BDEs (see Table 4, footnotes f−r) for the phenol and the 2-X(edg)-ArOH were made in a previous paper.[9] For the three 2-X(ewg)-ArOH, there are two gas-phase values for the 2-NO_2−ArOH only. Hence, to the best of our knowledge, all calculated absolute BDE_{sol}s and $BDE_{aw,sol}$s and relative ΔBDE_{sol}s and $\Delta[BDE_{aw,sol}]$s for all 2-X-ArOH are the first ever predicted.

Table 4 shows that both BDE_{sol}s and $BDE_{aw,sol}$s for all phenols considered appear different than their gas-phase ones. This difference, denoting an inherent solvent effect (implied also by the Δ(BDEs)), leads to larger values in all media, for all but the 2-NO_2−ArOH and 2-COOH−ArOH (in group B). Moreover, solvent effect on BDEs increases on going from group A to group C, appearing stronger for the HB conformers of the 2-X(edg)-ArOH than that of the non-HB ones (see also Figure S2a, illustrating the BDE_{sol} and $BDE_{aw,sol}$ variations of catechol as a function of the seven solvents selected). The opposite holds true for the 2-X(ewg)-ArOH (see Figure S2b). Experiment has shown[31] that the presence of an ortho substituent is the main factor[33] in the solvent effect study, since 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, in close agreement with our theoretical results, presented in Figure S2.

In addition, (a) most of theΔ(BDEs) of the HB conformer of the 2-NO_2−ArOH bear an opposite sign, relative to those of the other 2-X-ArOH, and (b) its $BDE_{aw,sol}$ in MeOH appears lower than expected. Moreover, with the exception of group C, the $BDE_{aw,sol}$s of the 2-X(edg)-ArOH appear higher than the BDE_{sol} ones, whereas the opposite holds true for the 2-X(ewg)-ArOH. This could imply that, in the former species, the presence of the intramolecular HB facilitates the H atom abstraction, whereas it becomes harder in the latter species. All of these can be easily seen in Figure S2, through the shift of either the gas-phase BDEs and/or group A and B ones. Consequently, PCM-calculated BDEs and Δ(BDEs) provide a secure and safe way for the study of both solvent and HB effects on the BDE_{sol}s. It is worth mentioning here that in group C a solvent effect of as much as 8 kcal/mol is observed. In the case of the simple phenol in water, Leopoldini et al.[42] calculated a O−H BDE for the simple phenol in water (97.1 kcal/mol) very closed to ours. Nevertheless, the difference between the experimental[43] and computed O−H BDE for the simple phenol in water is 8 kcal/mol.

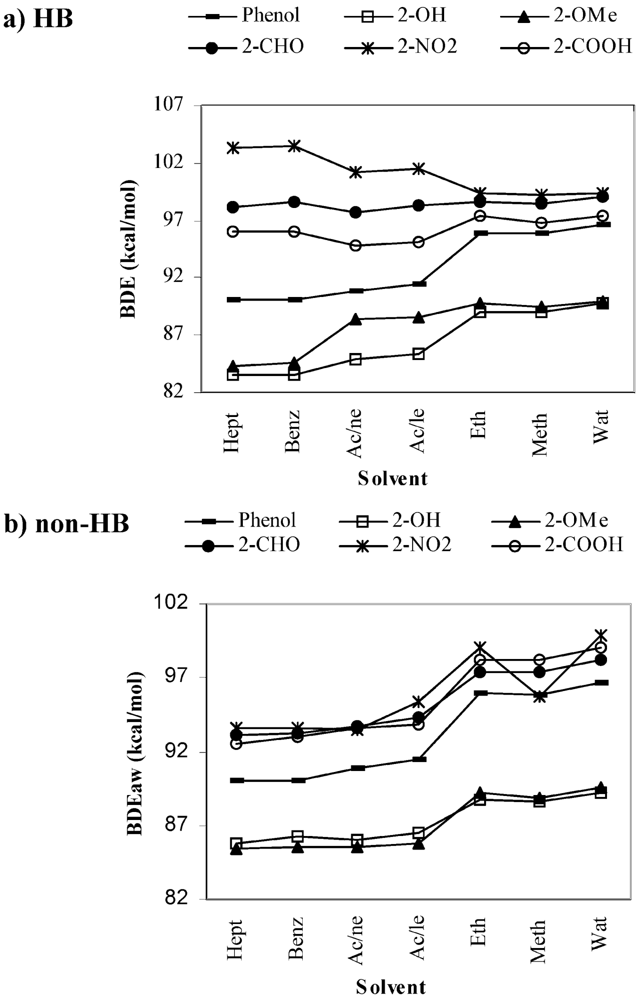


Figure 2. Substituent effect on the (a) BDE_{sol}s of phenol, and the five HB 2-X-ArOH, and (b) $BDE_{aw,sol}$s of phenol, and the five non-HB 2-X-ArOH.

It is well-known that the larger the liquid-phase BDEs and/or Δ(BDEs) the weaker the antioxidant activity. Figure 2a, (illustrating the BDE_{sol} variation of the phenol and the five HB 2-X-ArOH studied, as a function of the seven media) shows that 2-X(edg)-ArOH should present a relatively easier tendency for hydrogen atom abstraction than phenol, due to their lower than phenol calculated BDE_{sol}s in all solvents; the opposite holds true for the 2-X(ewg)-ArOH. Moreover, in the edg, the relative BDE_{sol} value-differences appear stronger in group B, and in the ewg, in groups A and B. The easiness and/or the difficulty in the hydrogen atom abstraction could be also derived on the basis of the $\Delta[BDE_{sol}s]$, implying also the substituent effect of each 2-X-group. The more negative the $\Delta[BDE_{sol}s]$, presented by the 2-X(edg), the easier the hydrogen atom abstraction; the more positive the $\Delta[BDE_{sol}s]$, presented by the 2-X(ewg), the harder the abstraction; 2-NO_2 group presents the hardest one. Figure 2b, showing the $BDE_{aw,sol}$ variation of the phenol and the five 2-X-ArOH as a function of the seven media, illustrates the real substituent effect. The relative BDE_{sol} value-differences between the 2-X-ArOH in each group of substituents have been reduced significantly. It is also seen that both edg present quite analogous substituent effects (almost identical $BDE_{aw,sol}$s) in every group of solvents, and this is also the case with the ewg, except for the 2-NO_2 in MeOH. It could be concluded then that the moderate relative BDE_{sol}s value-differences observed in Figure 2a are due to the relative differences in the intramolecular HB strength of the same compounds, in excellent agreement with

TABLE 5: Correlation Coefficient, *r* Values, between the $BDE_{aw,sol}$ and/or $\Delta H_{S,intra}$ and Solvent or Solute Parameters

		solvent parameters				solute parameters					
2-X		ϵ^{a}	$E_N^{T\ b}$	α^{c}	β^{d}	$\mu_{par}{}^{e}$	$\mu_{rad}{}^{f}$	R(O−H)	ν(O−H)	$\Delta\nu$(O−H)^{g}	R(OH···O)
H	$BDE_{aw,sol}$	0.735	0.937	0.994	0.789	0.944	0.915	0.992	−0.997		
OH	$BDE_{aw,sol}$	0.719	0.917	0.988	0.739	0.957	0.904	0.980	−0.978	−0.704	
	$\Delta H_{S,intra}$	0.760	0.962	0.928	0.915	0.998		0.932	−0.941	−0.925	0.923
OMe	$BDE_{aw,sol}$	0.688	0.898	0.988	0.739	0.919	0.898	0.981	−0.984	−0.929	
	$\Delta H_{S,intra}$	0.756	0.959	0.931	0.913	0.960		0.965	−0.950	−0.970	0.945
NO_2	$BDE_{aw,sol}$	0.775	0.851	0.878	0.631	0.932	0.808	0.853	−0.853	−0.853	
	$\Delta H_{S,intra}$	0.796	0.939	0.943	0.799	0.935			−0.945	−0.947	
CHO	$BDE_{aw,sol}$	0.754	0.944	0.995	0.776	0.954	0.938	0.989	−0.993	−0.993	
	$\Delta H_{S,intra}$	0.757	0.963	0.958	0.886	0.995		0.921	−0.956	−0.974	−0.937
COOH	$BDE_{aw,sol}$	0.727	0.935	0.993	0.788	0.958	0.881	0.997	−0.996	−0.996	
	$\Delta H_{S,intra}$	0.765	0.966	0.968	0.867	0.963		0.969	−0.994	−0.980	−0.993

[a] Dielectric constant of the solvent.[24] [b] Dimroth and Reichardt's parameter.[22] [c] Kamlet−Taft parameter[23,24] (measure of the hydrogen bond acidity). [d] Kamlet−Taft parameter[23,24] (measure of the hydrogen bond basicity). [e] Dipole moment of the parent compound, 2-X-ArOH. [f] Dipole moment of the radical, 2-X-ArO•. [g] $\Delta\nu$(O−H) is estimated as $\Delta\nu(O-H) = \nu(O-H)_{aw} - \nu(O-H)_{tow}$.

their $\Delta H_{S,intra}$s. Actually, as it was shown before, the 2-NO_2 substituent, due to both its shortest R(OH···O) and its identical R(O−H) values in both phases, should be considered as the strongest ewg; still, it shows one of the largest $\Delta H_{S,intra}$s, in accordance with its highest BDE_{sol}s.

The combination of the solvent and substituent effects could in turn lead to the choice of the optimum 2-X-substituent and group of solvents combination, for an effective antioxidant in solution. Figure 2b clearly shows that the latter should involve either one of the two 2-OH or 2-OMe groups in either one of the two aprotic groups of solvents A or B.

Correlation of the Molecular Descriptors. Table 5 shows the correlations derived between the two calculated, energetic parameters, $BDE_{aw,sol}$ and $\Delta H_{S,intra}$, and a series of experimental (solvent) and theoretical (molecular) parameters. Correlations of this type constituted one of the main targets of the present study.

Table 5 shows that reasonable correlations exist between the $BDE_{aw,sol}$s and/or $\Delta H_{S,intra}$s and the solvent and/or solute parameters. Nevertheless, they appear better for the energetic vs solute parameters, whereas some nonreasonable values, of as low as 0.631, appear for the energetic vs solvent parameters correlations. In particular, correlations derived between the $BDE_{aw,sol}$s and the solvent parameters are better for the E_N^T and/or *a* than the rest ones,[44] whereas 2-NO_2−ArOH shows the lowest values among all of them. Based upon the fairly good correlations derived for all but the 2-NO_2−ArOH, an approximate estimation of the $BDE_{aw,sol}$ values from the E_N^T and/or *a* solvent parameter ones could be attempted. For the same reason, this could be also the case with the $\Delta H_{S,intra}$s for all 2-X-ArOH.

The second group of correlations involves those between the same energetic parameters and a series of theoretical molecular descriptors of the solute [R(O−H), ν(O−H), $\Delta\nu$(O−H), R(OH···O), and the dipole moment values, μ, of both the parent compounds and the respective radicals]. All *r* values appear reasonable in this case, and only those related to the 2-NO_2 group and the μ values of the radicals appear relatively smaller. Moreover, *r* values for the ν(O−H), $\Delta\nu$(O−H), and R(OH...O) descriptors of the ewg are negative, implying that either (i) the larger the ν(O−H) and/or $\Delta\nu$(O−H) values the smaller the $BDE_{aw,sol}$s, hence, the easier the H-atom abstraction (thus, the more efficient the antioxidant activity of the solute, too), or (ii) contrary to the 2-X(edg), showing that the weaker the $\Delta H_{S,intra}$s the longer the R(OH···O), the two 2-X(ewg) ones show an opposite behavior in excellent agreement with the calculated data found in solution (see Tables 1 and 2). Moreover, correlations found between $BDE_{aw,sol}$s and/or $\Delta H_{S,intra}$s and the R(O−H) and/or ν(O−H) molecular parameters appear better than the rest, as a consequence of the excellent correlation found above between the two molecular parameters of the solutes. Hence, an approximate estimation of the $BDE_{aw,sol}$s and/or $\Delta H_{S,intra}$s values from the R(O−H) and/or ν(O−H) structural parameter values, for all but the 2-NO_2−ArOH, seems probable. This could be also the case for the approximate estimation of the two energetic parameters of all parent solutes from their μ parameter values. It should be stressed that both energetic parameters exhibit better correlations with the μ parameter values of the parent than with the radical ones. The worse correlations, however, found for the 2-NO_2−ArOH, relative to those of the rest 2-X-ArOH, could be also due to its identical R(O−H)s derived in all media (vide supra).

TABLE 6: Solvent Effect Stabilization of the Parent Phenols, SEP,[a] and of Phenoxyl Radicals, SER,[b] Relative to the Gas Phase,[c] in kcal mol^{-1}

		group A		group B		group C		
2-X		hept[d]	benz	ac/ne	ac/le	eth	meth	wat
H	SEP	−3.80	−1.55	−5.90	−3.19	−13.50	−15.65	−14.12
	SER	−3.17	−1.38	−4.61	−1.76	−7.34	−9.30	−7.42
OH	SEP	−4.76	−2.66	−9.29	−6.34	−20.10	−22.57	−21.15
	SER	−5.26	−3.12	−9.69	−6.80	−17.88	−20.33	−18.74
OMe	SEP	−4.50	−2.09	−7.49	−3.97	−16.55	−19.02	−17.07
	SER	−4.38	−2.30	−7.40	−4.08	−12.96	−15.53	−13.37
NO_2	SEP	−4.99	−2.71	−7.97	−5.82	−17.78	−17.15	−18.53
	SER	−3.60	−1.73	−6.83	−3.23	−11.20	−13.68	−11.40
CHO	SEP	−4.92	−2.75	−9.30	−6.09	−18.56	−21.18	−19.38
	SER	−4.27	−2.43	−8.22	−4.90	−13.92	−16.39	−14.22
COOH	SEP	−5.14	−2.87	−9.61	−6.14	−20.86	−23.69	−21.79
	SER	−4.10	−1.84	−7.68	−4.42	−14.40	−17.05	−14.82

[a] SEP has been estimated as SEP = $H_{ArOH,sol} - H_{ArOH,gas}$. [b] SER has been estimated as SER = $H_{ArO^{\bullet},sol} - H_{ArO^{\bullet},gas}$. [c] All parent and radical conformers used were the most stable non-HB ones. [d] See Table 1 footnote c.

Solvent Effects. The solvent effect stabilization of the parent phenols, SEP, and their radicals, SER, is attempted next. SEP and SER, given in Table 6, are estimated as the difference between the solvation enthalpies and the gas-phase ones, for each particular solute, namely

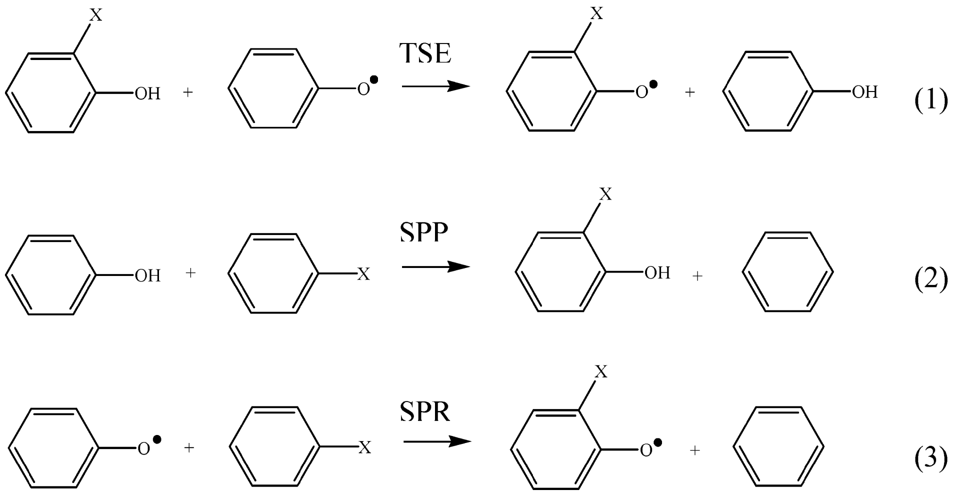
$$\mathrm{SEP} = H_{\mathrm{ArOH,sol}} - H_{\mathrm{ArOH,gas}} \qquad (1)$$

and

$$\mathrm{SER} = H_{\mathrm{ArO^{\bullet},sol}} - H_{\mathrm{ArO^{\bullet},gas}} \qquad (2)$$

The most stable non-HB conformers have been used in the study

SCHEME 1



of both solvent effects, in an attempt to avoid any possible intramolecular HB. The solvent effects of the moste stable HB ones are given in Table S2.[45]

In the case of phenol, SEP should correspond to the sum of the intermolecular solute−solvent interactions and the bulk solvent effect, whereas SER, due to the lack of the former in the phenoxyl radical,[9,34,46,47] should correspond to the latter only. It is seen that there is an increase of both SEP and SER values on going from group A to group C. The bigger SEP than SER values derived could further verify that the PCM model could describe well both kinds of solute−solvent interactions. However, SEP and SER in the case of 2-X-ArOH should have the same meaning, because, due to the presence of the 2-X substituent, solute−solvent interactions could not be excluded in the respective radicals. Moreover, SEP and SER values of all 2-X-ArOH (i) are all negative, implying that the solvent stabilizes both the parent and the radical of each phenol, (ii) increase on going from group A to C, indicating that the more polar/protic the solvent the better the stabilization of both species, owning to both the stronger solute−solvent interaction and the larger bulk effect, and (iii) appear different for solvents belonging in the same group. For instance, SEP and SER values in *n*-heptane are computed larger than those in benzene, suggesting that individual solvents of the same group, maintain their particular characters. Moreover, (iv) the greater SEP than SER values calculated in all media could account for a better stabilization for the parent than the radical conformer. The only exception is that of the 2-X(edg)-ArOH in groups A and B, in which the radicals appear more stabilized than (and/or equally to) the parents. This could further verify our previous findings that the 2-X(edg)-ArOH present the smaller $\mathrm{BDE}_{\mathrm{aw,sol}}$s, in groups A and B; hence, a H atom abstraction appears easier.

Substituent Effects. The substituent effect on the O−H BDEs can also be conveniently calculated by an isodesmic reaction (see Scheme 1, eq 1) giving the relative BDE of a substituted phenol with respect to the unsubstituted parent species. This effect, also referring to as the total stabilization effect (TSE), is comprised of contributions from both a parent-stabilization effect (PSE, hereafter denoted as SPP, stabilization of parent phenol, see Scheme 1, eq 2) as well as a radical stabilization effect (RSE, hereafter denoted as SPR, stabilization of phenoxyl radical, see Scheme 1, eq 3).[10b,c,11] For these quantities, in the liquid phase, it is

$$\mathrm{TSE} = \mathrm{SPR} - \mathrm{SPP} = \Delta[\mathrm{BDE}] \qquad (3)$$

TABLE 7: Stabilization of the Parent Phenols, SPP, and of Phenoxyl Radicals, SPR, Calculated in the Gas and the Liquid Phase, from the Isodesmic Reactions,[a] in kcal mol^{-1}

		gas	group A		group B		group C		
2-X		phase	hept[b]	benz	ac/ne	ac/le	eth	meth	wat
OH	SPP	4.43	4.36	4.15	3.90	3.98	4.96	4.97	4.81
	SPR	1.24	0.05	0.33	−0.95	−1.10	−2.16	−2.33	−2.66
OMe	SPP	4.41	4.28	4.02	3.86	3.72	3.92	4.17	4.04
	SPR	0.25	−0.38	−0.54	−1.51	−1.98	−2.82	−2.86	−3.12
NO_2	SPP	7.42	6.90	6.97	7.80	6.43	7.49	10.86	7.29
	SPR	10.18	10.43	10.54	10.40	10.35	10.67	10.73	10.49
CHO	SPP	4.82	4.22	4.13	3.21	3.12	3.37	3.31	3.07
	SPR	7.87	7.30	7.34	6.05	5.93	4.90	4.79	4.58
COOH	SPP	5.53	5.03	4.90	4.33	4.23	4.15	4.12	3.87
	SPR	7.60	7.52	7.82	7.04	6.59	6.51	6.47	6.22

[a] All parent and radical conformers used in the reactions were the most stable non-HB ones. [b] See Table 1 footnote c.

The substituent effect on the BDE is often discussed on the basis of the SPR.[48] However, the SPP cannot be ignored,[49,50] because substituents may introduce changes in the ground-state energy of the molecule and bond.[49a,51] Hence, another target of the present work is to average the contribution of both SPP and SPR on ΔBDEs of the phenols under study in several media and derive the influence of the solvent on the substituent trends.

Table 7 summarizes the SPP and SPR values, calculated by using the isodesmic reactions in both the gas and liquid phases, concerning the non-HB 2-X-ArOH, to be free of intramolecular HBs. It is found that, as would be expected, for each phenol, the total calculated effect TSE (=SPR − SPP) is identical to the $\Delta[\mathrm{BDE}_{\mathrm{aw}}]$ value (see also Table 4). It is also seen that the corresponding SPP and SPR values of both 2-X(edg)-ArOH and 2-X(ewg)-ArOH, but the 2-NO_2−ArOH, are close to each other in all of the media. The respective values of the latter are larger, possibly due to the stronger ewg character of the 2-NO_2, found before. Another similarity is that for each 2-X-ArOH the corresponding SPP and SPR values are almost the same in solvents of the same group; still, the gas-phase values are very close to the ones in group A, in close agreement with previous findings. Thus, the edg and ewg could be represented by their average SPP and SPR values in Figure 3, schematically depicting their effects on the 2-X-ArOH in the gas phase and in groups A, B, and C.

From Figure 3 and Table 7, it is seen that both edg and ewg at the 2 position destabilize the parent phenols (positive SPP values), in both the gas and the liquid phase. Moreover, the destabilization is stronger in the case of the ewg, with the

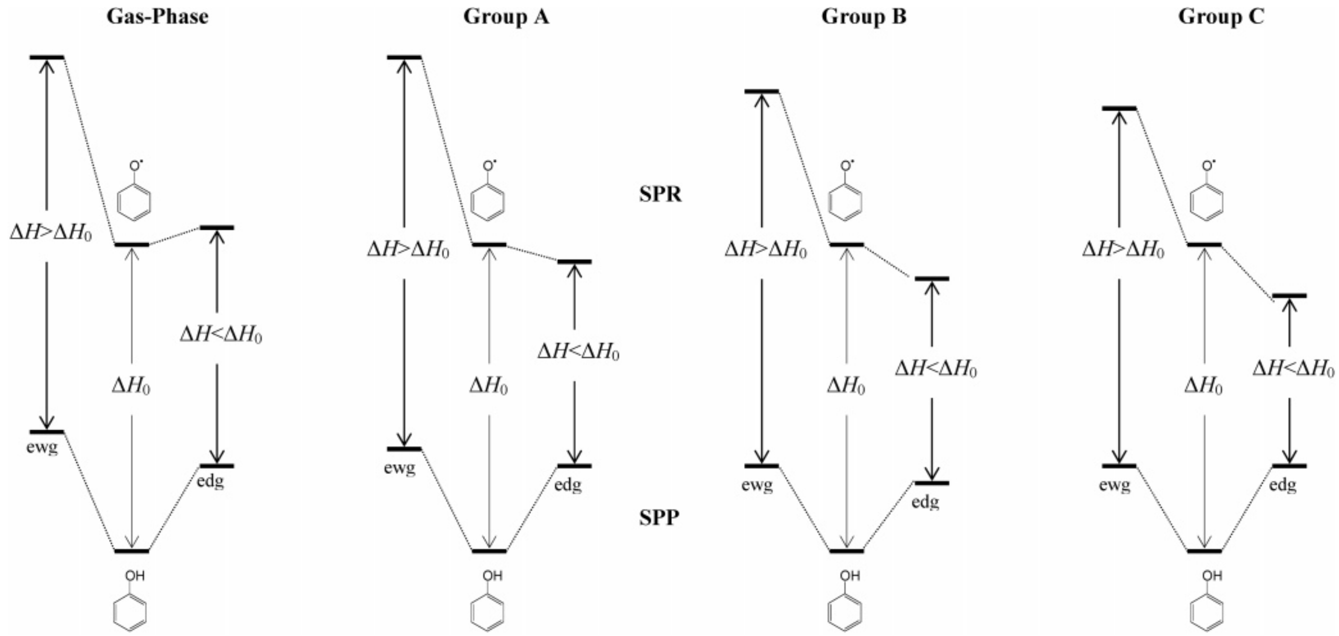


Figure 3. Schematic drawing of the ewg and edg SPP and SPR effects on the non-HB 2-X-ArOH and 2-X-ArO•, in all media.

exception of group C becoming equal. As far as the SPR values is concerned, it is found that the ortho edg stabilize the phenoxyl radicals (negative SPR values) in solution, whereas the ewg destabilize them by a greater amount (large positive SPR values). The only exception here is the small destabilization of the edg radicals observed in the gas phase. Moreover, in solution, on passing from group A to group C, the edg SPR increases, whereas the ewg radicals destabilization decreases. This latter is much stronger than that of the parents in both the gas and the liquid phase. Inspection of the TSE (= Δ[BDE]) values in the ortho substitution shows that the edg decrease the BDE (negative Δ[BDE]s), whereas the ewg increase it (positive Δ[BDE]s) relative to the unsubstituted ArOH, in all of the media. This conclusion is the same as that of the 4-substitution in the gas phase,[11] although the interactions, occurring in the 2 position, are quite different than those in the 4 position. However, it is shown that both SPP and SPR contributions of edg and ewg are decisive in the TSE and as has already been querying none of them could be eliminated. The decreased BDEs in the 2-X(edg)-ArOH are the combined result of the parents destabilization and the radicals stabilization, whereas the increased BDEs in the 2-X(ewg)-ArOH are the combination of the parents destabilization with the radicals stronger one.

Substituent effect can also be correlated well with Hammett-type σ^+ parameters. An excellent linear Hammett-type reaction has been found experimentally[52] for the para substitution. In the case of the non-HB 2-X-ArOH, a similar relationship between Δ[BDE] and the Brown substituent constant σ^+ requires an additional equation, that is

$$\sigma_0^+ = 0.66\ \sigma_P^{\ +} \qquad (4)$$

which has been originally proposed[53] for only three 2-X-substituents (Cl, MeO, and Me) but has been used[2] for a broad range of 2-X-compounds in the gas phase. In our study, despite the very few 2-X- groups studied, an effort will be made to investigate whether such a correlation exists, as a first reference to what happens in solution.

Table S3 summarizes the correlation coefficients, r values, between the $\Delta[\mathrm{BDE_{aw}}\mathrm{s}]$ of the selected 2-X-ArOH under study and σ_0^+ values, calculated by using eq 4, in both the gas and the liquid phase. With the use of the SPP and SPR vs σ_0^+ correlations, an answer to the question of which of the two effects has the maximum contribution on the total substituent effect, $\Delta[\mathrm{BDE_{aw}}]$, could be given. A reasonable relationship exists between the $\Delta[\mathrm{BDE_{aw}}]$ and the σ_0^+ in all media. The corresponding correlation for the SPR is also reasonable, whereas the one of the SPP is poor. Consequently, TSE is mainly governed by the SPR rather than the SPP effect.

A quantitative correlation between the two effects in the TSE can be derived, based upon a criterion established by Pratt et al.[10b,c] In particular, the slopes ρ^+ for the linear correlation of SPP and SPR with σ_0^+ of the substituent, in the gas phase, are -2.0 and -8.9, respectively. Hence, the SPR make a 4.5-fold greater contribution to the TSE than do SPP. The TSEs are well correlated by σ_0^+ ($\rho^+ = 6.9$ kcal/mol). In the liquid phase, ρ^+ values are 8.4 and 8.2 kcal/mol (*n*-heptane, benzene), 8.5 and 9.4 kcal/mol (acetone, acetonitrile), and 10.3, 8.9, and 10.8 kcal/mol (ethanol, methanol, and water) and are given for the first time. It is seen that, with the exception of group A, the values appear different for the solvents belonging to the same group; this conclusion was also derived in the solvent effect section. This, in turn, leads to diverged SPRs contributions to the TSEs, being 6.6- and 5.7-fold (group A); 5.4- and 8.7-fold (group B); and 9.7-, 4.2-, and 12.6-fold (group C), respectively, greater than do SPPs.

Conclusions

The PCM model well describes the bulk solvent effects, and it becomes essential to get (a) a reasonable description of the intramolecular HB interactions in solution, (b) the solvent, substituent, and HB effects on the $\mathrm{BDE_{sol}}$s, and (c) reasonable correlations between theoretical energetic parameters and experimental solvent ones. It could also lead to the choice of the most effective antioxidants in solution and save experimental work. Due to the small solvent effects derived in the apolar solvents, the use of the gas-phase results as an indicator for the free radical scavenging activity seems correct. Hence, our assumption made, regarding the possible H atom transfer antioxidant mechanism, also seems to be correct for the above media. Nevertheless, solvent effects become moderate in the polar and/or protic solvents and should not be ignored.

Supporting Information Available: Table S1, Sum of electronic and thermal energies for all stationary points. Table S2, Solvent effect stabilization of the parent phenols, SEP, and of phenoxyl radicals, SER, relative to the gas phase, for the most stable HB conformers. Table S3, Correlation coefficient, *r*, values, between $\Delta[\mathrm{BDE_{aw}}]$, SPP and SPR, and the σ_0^+, in the gas and the liquid phase. Figure S1, Correlation of DFT-computed phenolic OH vibrational frequencies and R(O−H) for the non-HB catechol in the seven solvents tested. Figure S2, Solvent effect on the $\mathrm{BDE_{sol}}$s and $\mathrm{BDE_{aw,sol}}$s of HB and non-HB conformers of (a) 2-OH−ArOH and (b) 2-CHO−ArOH. This material is available free of charge via the Internet at http://pubs.acs.org.

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(45) We agree with an anonymous referee that the behavior of the most stable HB conformer is of real interest for the solvent effect. However, our study cannot be based upon them, because, in the liquid phase, the intramolecular HB of a parent/radical phenol pair, could be different between the two species, in some phenols. For instance, although HB is of the same type in catechol's pair (**II**, **IIa**), it is different in guaiacol (**IV**, **VIa**) and in most of the rest 2-X-ArOH studied.

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