

Bond-dissociation enthalpies in the gas phase and in organic solvents: Making ends meet*

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Abstract: Solvent effects are responsible for the difference between gas- and solution-phase bond-dissociation enthalpies (BDEs), and are thus crucial for understanding reactivity in solution. While solvation effects can be negligible (e.g., in reactions involving carbon-centered radicals), they may be rather significant (e.g., when oxygen-centered radicals are formed). This paper reviews a number of models which have been proposed to deal with the difference between the solvation energetics of a radical and its parent molecule. It is concluded that the radical–solvent interaction may be larger than previously anticipated.

Keywords: thermochemistry; solvation; photoacoustic calorimetry; bond-dissociation enthalpy; quantum chemistry.

INTRODUCTION

McMillen and Golden said it best in their 1982 authoritative review on bond-dissociation enthalpies (BDEs) [1]: “In the short space available we refrain from reminding the reader of all the reasons that BDE information is fundamental to chemistry. There exist so many reviews and compilations of BDEs that we refer the still curious to (...) reviews such as those of Benson and Szwarc for intellectual succor if required!” [1–3]. To these we add several more modern reviews [4–6], and a recent account on the same subject by Blanksby and Ellison [7]. Notably, all the values presented in that vast body of work refer to molecules in the gas phase, and the database is expanding ever more rapidly thanks to the new quantum chemistry computational methods, which also deal with the isolated molecules [8]. However, most processes of interest to chemists and biochemists occur in the condensed phase, usually in solution, which immediately raises the question of how to relate all that available gas-phase data to the chemical problems in solution. Several studies involving BDE determination in solution also exist, Bordwell’s EC (electrochemical cycle) method [9], ESR (electron spin resonance) equilibration technique [10], and PAC (photoacoustic calorimetry) [11] being the more prolific. Nevertheless, much controversy has emerged concerning the so-called “solvent effect” on BDEs, responsible for the difference between the solution- and gas-phase values: Is it negligible? How strongly do radicals interact with the

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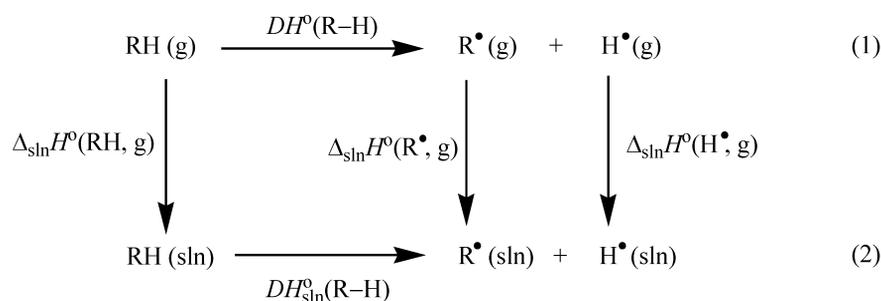
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solvent? How many solvent molecules do we need to model solvation? As Blanksby and Ellison stated less than four years ago, “there is clearly much work to be done in this area” [7].

For the past 10 years, we have been using PAC to determine BDEs in solution for a number of model compounds [12–22]. On the other hand, high-level quantum chemical (QC) studies have provided the BDEs of the isolated molecules and have also allowed us to test increasingly complex solvent models, aiming to bridge solution- and gas-phase data by quantifying the solvent effect [16,17,23–28]. In this overview, we describe the recent advances in solvation models when trying to make those ends meet, and strive to provide the answers to the questions raised above.

SOLVENT EFFECT ON BOND-DISSOCIATION ENTHALPIES

Taking as an example the R–H bond in an organic molecule, Scheme 1 presents the relationship between the gas-phase BDE, symbol $DH^\circ(\text{R–H})$, and solution BDE, denoted by $DH_{\text{sln}}^\circ(\text{R–H})$. By definition, $DH^\circ(\text{R–H})$ is simply the enthalpy of the homolysis reaction 1 in the gas phase, while $DH_{\text{sln}}^\circ(\text{R–H})$ is the enthalpy of the same reaction in a given solvent (reaction 2).



Scheme 1 Thermodynamic cycle relating solution- and gas-phase R–H BDE for an organic molecule.

The terms $\Delta_{\text{sln}}H^\circ(\text{X, g})$ bridging the two reactions are the solvation enthalpies of the parent molecule RH, its corresponding radical R^\bullet , and the hydrogen atom H^\bullet . The relationship between gas- and solution-phase BDEs is calculated using eq. 3, obtained from Scheme 1. This equation shows how to use the solvation enthalpy terms to account for the solvent effect.

$$DH^\circ(\text{R–H}) = DH_{\text{sln}}^\circ(\text{R–H}) + \Delta_{\text{sln}}H^\circ(\text{RH, g}) - \Delta_{\text{sln}}H^\circ(\text{R}^\bullet, \text{g}) - \Delta_{\text{sln}}H^\circ(\text{H}^\bullet, \text{g}) \quad (3)$$

The solvation enthalpy of a substance X, $\Delta_{\text{sln}}H^\circ(\text{X, g})$, is defined as the enthalpy associated with the dissolution of gaseous X in a given solvent, eq. 4.



Solvation enthalpies are commonly determined as the difference between two quantities (eq. 5): The first is $\Delta_{\text{sln}}H^\circ(\text{X, cr/l})$, the solution enthalpy of crystalline or liquid X in the solvent; the second quantity, $\Delta_{\text{sub/vap}}H^\circ(\text{X, cr/l})$, is the sublimation or vaporization enthalpy of X.

$$\Delta_{\text{sln}}H^\circ(\text{X, g}) = \Delta_{\text{sln}}H^\circ(\text{X, cr/l}) - \Delta_{\text{sub/vap}}H^\circ(\text{X, cr/l}) \quad (5)$$

Standard calorimetric techniques can be used to measure both terms in eq. 5 [29]. Alternatively, $\Delta_{\text{sub/vap}}H^\circ(\text{X, cr/l})$ can be obtained by a vapor pressure vs. temperature plot [29]. In either case, the final value of $\Delta_{\text{sln}}H^\circ(\text{X, g})$ can be known with an error smaller than ca. 1 kJ mol⁻¹. But while the application of eq. 5 is straightforward for many long-lived species, it is useless to evaluate solvation enthalpies of free radicals, simply because the available experimental techniques are not suited to deal with transient species. Nevertheless, in this case, solvation enthalpies can be assessed indirectly, by comparing gas-

and solution-phase BDEs for the same molecules and relating them with eq. 3. But this strategy alone takes us right back to the start, and to the questions raised in the Introduction.

Before making any advances, we need to look at eq. 3 in more detail. The most important feature is that we can do without an absolute value for the solvation enthalpy of the radical R^\bullet . Instead, we need the *difference* between its solvation enthalpy and that of its precursor RH, which is much easier to estimate than the individual quantities. The solvation of the H-atom is a separate and, in this context, less important subject, since it is expected that its enthalpy will be small in most solvents. Actually, it can be predicted using the hydrogen molecule as a suitable model [30–32], yielding $\Delta_{\text{sln}}H^\circ(\text{H}^\bullet, \text{g}) = 5 \pm 1 \text{ kJ mol}^{-1}$ for organic solvents [33]. We will now focus on the difference between the solvation enthalpies of a radical and its precursor, according to various models, the methods used to test those models, and the quality of the results they produce.

Is the difference between $\Delta_{\text{sln}}H^\circ(\text{RH}, \text{g})$ and $\Delta_{\text{sln}}H^\circ(\text{R}^\bullet, \text{g})$ negligible?

Not so long ago, the view that solvent effects on BDEs were negligible prevailed, mostly because many BDE values obtained in solution were identical to the corresponding gas-phase data, within the experimental uncertainties [9,34]. An accepted explanation for this fact was that most of the solution measurements had been carried out in nonpolar solvents, where the solvation terms in eq. 3 are expected to be small. One of the first works to test this assumption was that of Kanabus-Kaminska et al. [35], who used PAC to measure the C–H BDEs for a series of functionalized alkanes in a very polar and polarizable solvent: water. Comparison of their results with available gas-phase data showed that there is little or no difference between the solvation of the parent alkane and its corresponding radical. Although, in the light of current knowledge, that work should be reappraised [36], their conclusion of negligible differential solvation enthalpy was incorporated into much of the discussion about solvent effects ever since [37,38]. Recently, using a development of the PAC technique called time-resolved photoacoustic calorimetry (TR-PAC), we decided to test that hypothesis, by measuring the benzylic C–H BDE in toluene [14]. This represented an almost ideal test subject in this regard: the required TR-PAC experiment is of the most straightforward type that can be devised with this technique, allowing us to keep assumptions to a minimum.* Moreover, the gas-phase C–H BDE in toluene is well known, allowing the comparison between accurate solution- and gas-phase data. We have obtained $DH_{\text{sln}}^\circ(\text{C–H}) = 380.5 \pm 5.1 \text{ kJ mol}^{-1}$ in neat toluene, which yields $DH^\circ(\text{C–H}) = 375.5 \pm 5.2 \text{ kJ mol}^{-1}$ by using eq. 3 together with $\Delta_{\text{sln}}H^\circ(\text{H}^\bullet, \text{g}) = 5 \pm 1 \text{ kJ mol}^{-1}$ and the assumption $\Delta_{\text{sln}}H^\circ(\text{PhCH}_3, \text{g}) \approx \Delta_{\text{sln}}H^\circ(\text{PhCH}_2^\bullet, \text{g})$. This result is in perfect agreement with the gas-phase values recommended in recent reviews (e.g., $375 \pm 5 \text{ kJ mol}^{-1}$ and $375.7 \pm 2.5 \text{ kJ mol}^{-1}$) [5,7], with the latest gas-phase determination ($378 \pm 5 \text{ kJ mol}^{-1}$) [39], and with the result from a selection of the most accurate high-level computational procedures ($375 \pm 4 \text{ kJ mol}^{-1}$) [40]. In summary, our solution result corroborates the above hypothesis: the difference between $\Delta_{\text{sln}}H^\circ(\text{RH}, \text{g})$ and $\Delta_{\text{sln}}H^\circ(\text{R}^\bullet, \text{g})$ is indeed negligible, when R^\bullet is a carbon-centered radical.

Do radicals interact strongly with the solvent?

Phenolic compounds are important because some of them work as biological antioxidants [41], a role that is related to their low O–H BDE [42]. As antioxidants act in solution, not in the gas phase, solvent effects are especially important. A decade ago, the negligible differential solvation hypothesis was accepted for radical reactions in general [9], including those involving oxygen-centered radicals [43]. However, in 1995, Wayner et al. [37] reported PAC measurements of the phenol O–H BDE in several

*The reaction involved in this determination is too slow to be measured directly using classical PAC, but not with TR-PAC. However, it should be noted that we always favor the TR-PAC procedure because it is in itself less dependent on assumptions. For details, see ref. [14].

solvents, and found them to span almost 30 kJ mol⁻¹, increasing from isooctane (a nonpolar solvent) to acetonitrile (an aprotic and strongly polar solvent, $\mu = 3.95$ D). To understand these results, the authors proposed that, contrasting with the case of carbon-centered radicals, there will be a difference between the solvation of phenol and phenoxy radical, due to the ability of the parent phenol to form hydrogen bonds with the solvent. All else being equal, that difference will correspond to the enthalpy of the hydrogen bond thus formed. This assumption, which we call the “hydrogen bond only” (HBO) model for estimating solvation energetics, is represented by eq. 6, where the last member represents the hydrogen bond *formation* enthalpy (hence the minus sign) between phenol and the solvent S.

$$\Delta_{\text{sln}}H^\circ(\text{PhOH},\text{g}) - \Delta_{\text{sln}}H^\circ(\text{PhO}^\bullet,\text{g}) = -DH^\circ(\text{PhOH}\cdots\text{S}) \quad (6)$$

Using hydrogen-bond equilibria data to predict $DH^\circ(\text{PhOH}\cdots\text{S})$, together with eqs. 3 ($R = \text{PhO}$) and 6, Wayner et al. observed that the various solution results converge to an average value of 365.8 ± 4.0 kJ mol⁻¹ for the gas-phase PhO–H BDE, in very good agreement with the then accepted gas-phase value, 364.0 kJ mol⁻¹. This work paved the way for further studies in free-radical solvation energetics, making use of more general methods to estimate $DH^\circ(\text{PhOH}\cdots\text{S})$, namely, Drago’s electrostatic-covalent model (ECW) [44–46], as used by our group [12,13], and Abraham’s method [47,48], as applied by Snelgrove et al. [49]. Both procedures rely on a database of hydrogen bond acceptor and donor properties. Abraham’s method is somewhat more general (has a larger database), though it affords the Gibbs energy for hydrogen bonding, while the ECW model provides a direct estimate of its enthalpy. In practice, they afford similar results [13], with an estimated error of ± 1 kJ mol⁻¹. However, the accuracy of these methods in predicting solvent effects is only as good as the original hypothesis, the HBO model in this case (eq. 6).

The phenol O–H BDE in the gas phase has since then been revised as 371.3 ± 2.3 kJ mol⁻¹ [33], which is a weighted average of the results from several experimental gas-phase studies. More recently, another reassessment by Mulder et al. appeared in the literature (362.8 ± 2.3 kJ mol⁻¹) [50]. Although the two values almost overlap within the assigned uncertainties, the 8.5 kJ mol⁻¹ difference is rather significant if one wishes to evaluate solvent effects by comparison with solution data for PhO–H BDE. A detailed discussion of this matter is presented in a section before the Conclusion. Here it is enough to say that, based on the same data collected in that review [50], on our own PAC results [16,17] (which were missed by Mulder et al.), on all the latest high-level computational results [51,52], and on the ensuing discussion, we have strong reasons to favor the “high value” of 371.3 ± 2.3 kJ mol⁻¹.

Using TR-PAC, we have measured the PhO–H BDE in two cases also investigated by Wayner et al., benzene and acetonitrile. Table 1 summarizes our results and derived values using several solvation models (vide infra). Not surprisingly, using the HBO model [with $DH^\circ(\text{PhOH}\cdots\text{S})$, estimated through the ECW method, and $\Delta_{\text{sln}}H^\circ(\text{H}^\bullet,\text{g}) = 5 \pm 1$ kJ mol⁻¹], the gas-phase BDEs derived from our solution measurements are in keeping with those by Wayner et al., i.e., they are close to the recommended low value for gas-phase PhO–H BDE. This could mean that *both* the value of 363 kJ mol⁻¹ and the HBO model are correct. Yet, if one accepts that the gas-phase PhO–H BDE is 371 kJ mol⁻¹ or higher, then the HBO model should be questioned. In other words, the differential solvation enthalpy, $\Delta_{\text{sln}}H^\circ(\text{PhOH},\text{g}) - \Delta_{\text{sln}}H^\circ(\text{PhO}^\bullet,\text{g})$, may not correspond to the strength of the hydrogen bond between phenol and the solvent. To investigate this matter, we have resorted to quantum chemistry.

Table 1 Difference between the solvation enthalpies of phenol and its radical in benzene and acetonitrile, according to various models and theoretical procedures (see text). Data in kJ mol⁻¹.

Model ^a	Benzene		Acetonitrile	
	$DH_{\text{sln}}^{\circ}(\text{PhO}-\text{H}) = 380.5 \pm 5.4^{\text{b}}$	$DH^{\circ}(\text{PhO}-\text{H})^{\text{c}}$	$DH_{\text{sln}}^{\circ}(\text{PhO}-\text{H}) = 388.7 \pm 3.7^{\text{b}}$	$DH^{\circ}(\text{PhO}-\text{H})^{\text{c}}$
	$\Delta_{\text{sln}}H^{\circ}(\text{PhOH},\text{g}) - \Delta_{\text{sln}}H^{\circ}(\text{PhO}^{\bullet},\text{g})$		$\Delta_{\text{sln}}H^{\circ}(\text{PhOH},\text{g}) - \Delta_{\text{sln}}H^{\circ}(\text{PhO}^{\bullet},\text{g})$	
HBO	-8.7 ± 1.0	366.8 ± 5.6	-18.7 ± 1.0	365.0 ± 4.0
Microsolvation				
1 solvent molecule	-4.2	371.3	-10.7	373.0
2 solvent molecules	-4.2	371.3	-11.4	372.3
MC simulation				
With solvent relaxation	2.2 ± 4.9	377.7 ± 7.4	-2.5 ± 6.8	381.2 ± 7.8
Without solvent relaxation ^d	-4.9 ± 1.0	370.6 ± 5.6	-6.2 ± 0.2	377.5 ± 3.8
PCM	-0.7 ^e	374.1 ^f	-6.0 ^e	376.2 ^f

^aH-bond only (HBO): $\Delta_{\text{sln}}H^{\circ}(\text{PhOH},\text{g}) - \Delta_{\text{sln}}H^{\circ}(\text{PhO}^{\bullet},\text{g}) = -DH^{\circ}(\text{PhOH}\cdots\text{S})$; microsolvation: $\Delta_{\text{sln}}H^{\circ}(\text{PhOH},\text{g}) - \Delta_{\text{sln}}H^{\circ}(\text{PhO}^{\bullet},\text{g}) = DH^{\circ}(\text{PhO}^{\bullet}\cdots\text{S}) - DH^{\circ}(\text{PhOH}\cdots\text{S})$; MC: $\Delta_{\text{sln}}H^{\circ}(\text{PhOH},\text{g}) - \Delta_{\text{sln}}H^{\circ}(\text{PhO}^{\bullet},\text{g}) = \Delta E_{\text{SX}} + \Delta\Delta H_{\text{R}}$; polarized continuum model (PCM).

^bData from ref. [16].

^cGas-phase value calculated from solution result using eq. 3 with the corresponding estimate for $\Delta_{\text{sln}}H^{\circ}(\text{PhOH},\text{g}) - \Delta_{\text{sln}}H^{\circ}(\text{PhO}^{\bullet},\text{g})$ and $\Delta_{\text{sln}}H^{\circ}(\text{H}^{\bullet},\text{g}) = 5 \pm 1$ kJ mol⁻¹.

^dNeglecting the solvent relaxation term ($\Delta\Delta H_{\text{R}}$).

^eValues from ref. [60].

^fCalculated as in c, but with the PCM estimates for $\Delta_{\text{sln}}H^{\circ}(\text{H}^{\bullet},\text{g})$ in benzene and acetonitrile from ref. [60] (5.7 kJ mol⁻¹ and 6.5 kJ mol⁻¹, respectively).

A possible way of describing solvent effects makes use of the so-called “microsolvation” method, which considers that the solvated species can be modeled by a gas-phase complex, involving one molecule of the solute and a small number (usually 1 to 6) of solvent molecules [16,17,23,26–28]. The approach can be illustrated with the simplest case of the formation of a (1:1) solute–solvent complex [16,17]. According to this method, the interaction between PhOH and CH₃CN (represented by S) corresponds to the enthalpy of reaction 7, which, in the same manner as before, can be designated by $-DH^{\circ}(\text{PhOH}\cdots\text{S})$.



Computing the ground-state enthalpies of phenol, acetonitrile, and the phenol–acetonitrile complex*, we have obtained -23.1 kJ mol⁻¹ for the phenol–acetonitrile interaction, which is in fair agreement with the previous estimate of -18.7 kJ mol⁻¹, using the ECW method, and with theoretical and experimental data [53,54].** When the same exercise was carried out for the corresponding phenoxy radical (reaction 8), we obtained -12.4 kJ mol⁻¹ for the phenoxy–acetonitrile interaction.



The surprisingly high value for the interaction of PhO[•] with acetonitrile showed that it cannot be ignored, leading to a differential solvation of only -10.7 kJ mol⁻¹ (eq. 9), almost half of what the HBO model predicts using the ECW method.

$$\Delta_{\text{sln}}H^{\circ}(\text{PhOH},\text{g}) - \Delta_{\text{sln}}H^{\circ}(\text{PhO}^{\bullet},\text{g}) = DH^{\circ}(\text{PhO}^{\bullet}\cdots\text{S}) - DH^{\circ}(\text{PhOH}\cdots\text{S}) \quad (9)$$

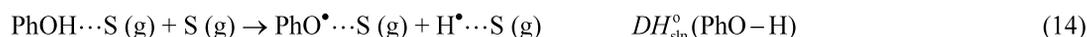
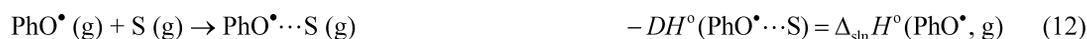
*We performed DFT calculations at the MPW1PW91/aug-cc-pVDZ level, see ref. [16] for details.

**The result of 23.1 kJ mol⁻¹ for the enthalpy of the hydrogen bond between phenol and acetonitrile can be compared with a recently calculated B3LYP result (24.6 kJ mol⁻¹; ref. [53]), with an experimental value by Sousa Lopes and Thompson (21.8 kJ mol⁻¹; ref. [54]), and with the literature evaluation used by Wayner et al. (19.7 kJ mol⁻¹; ref. [37]).

A simple explanation for the “strong” bond between the radical and acetonitrile is that while in the parent molecule the interaction is indeed dominated by the hydrogen bond with the solvent, in the radical there will be a strong dipole–dipole interaction with acetonitrile (phenoxy radical has a much larger dipole moment than phenol, 4.07 vs. 1.4 D, respectively) [16]. In the case of benzene, the computed differential solvation resulted in -4.2 kJ mol^{-1} , which is closer to the ECW prediction, but still about half of that value.

These microsolvation results and the derived $DH^\circ(\text{PhO}-\text{H})$ values in benzene and in acetonitrile are presented in Table 1. They clearly support the recommended high value for the gas-phase PhO–H BDE.

Accepting the microsolvation model, we can rewrite eq. 3 in terms of BDEs, eq. 15. This was made by using the reactions shown in Scheme 2.



Scheme 2 Relation between solution- and gas-phase O–H BDE in phenol according to the microsolvation model.

$$DH_{\text{sln}}^\circ(\text{PhO}-\text{H}) = DH^\circ(\text{PhO}-\text{H}) + DH^\circ(\text{PhOH}\cdots\text{S}) - DH^\circ(\text{PhO}^\bullet\cdots\text{S}) + \Delta_{\text{sln}}H^\circ(\text{H}^\bullet, \text{g}) \quad (15)$$

Scheme 2 indicates the general microsolvation procedure for evaluating the PhO–H BDE in solution using QC calculations. The enthalpy of the homolysis reaction 10, $DH^\circ(\text{PhO}-\text{H})$, can be derived from the ground-state energies of the species by using a high-level computational method. Alternatively, that quantity can be obtained with a lower-level computational method by using a suitable isodesmic and isogyric reaction. A lower-level computational method can also be used to estimate the enthalpies of reactions 11 and 12, $DH^\circ(\text{PhOH}\cdots\text{S})$ and $DH^\circ(\text{PhO}^\bullet\cdots\text{S})$, respectively [17]. The errors that may affect each one of these results will probably cancel when their difference is derived (eq. 9), which corresponds to an isodesmic and isogyric reaction, eq. 16.



It is clear from eq. 15 why solution BDEs are typically higher than the corresponding gas-phase values: the interaction of the parent compound with the solvent, $DH^\circ(\text{PhOH}\cdots\text{S})$, is stronger than in the case of the radical, $DH^\circ(\text{PhO}^\bullet\cdots\text{S})$. According to the microsolvation model, their difference is not as large as predicted by the HBO model. However, an important question remains: Is one solvent molecule really enough to accurately model solvation?

IMPORTANCE OF SIZE-DEPENDENCE ANALYSIS

For more complex systems, such as those involving more than one hydrogen bond donor group, additional solvent molecules will obviously be necessary even for the simple microsolvation model to work. These are to be included in eqs. 11 and 12, e.g., two for catechol [$1,2\text{-C}_6\text{H}_4(\text{OH})_2$], three for pyrogallol [$1,2,3\text{-C}_6\text{H}_3(\text{OH})_3$], etc. [17]. Note that in both these examples, the existence of intramolecular hydrogen bonds complicates the issue, especially if we are interested in quantifying the enthalpies of the

intramolecular H-bonds themselves [24]. This is an important subject but, for the general discussion of solvation intended here, it is still only the sum of the enthalpies of reactions 11 and 12 that is required, calculated as above. So, though more complicated, these are still cases where solvation is studied with only one solvent molecule per acceptor group.

What happens when we include solvent molecules in excess? Returning again to the more simple case of PhO–H BDE, we have applied the microsolvation approach by using two solvent molecules. The analog of eq. 11 for this case corresponds to the dissociation of the $\text{PhOH}\cdots(\text{S})_2$ cluster into phenol and the solvent dimer S_2 , optimized separately. Conversely, eq. 12 corresponds to the association of the solvent dimer with the phenoxy radical. Again we tested for the cases of benzene and acetonitrile. This study showed us the structure and nature of the interactions involved (*vide infra*) but, more importantly for now, that the enthalpic solvation effect calculated with one and two solvent molecules is essentially the same, as displayed in Table 1 [16]. However, this agreement may be fortuitous. The minimum number of solvent molecules to consider is difficult to predict, particularly for systems where cooperative polarization effects related to hydrogen bonding may significantly affect solute–solvent interactions, the classical example being hydration [23]. This implies the inclusion of as many solvent molecules as possible. Size-dependence analysis is therefore of crucial importance for assessing the reliability of the microsolvation approach. Yet, the inclusion of an increasing number of solvent molecules in the microsolvation approach based on high-level electronic structure calculations may lead to difficulties related to the presence of numerous isomers and prohibitive computational times.

Microsolvation is *not* solvation: The importance of statistical mechanics simulations

The most adequate procedure to model solvation is based on statistical mechanics Monte Carlo (MC) and molecular dynamics (MD) simulations [55,56]. Recall that microsolvation is based on the optimization of the structure of small aggregates through a QC method. Therefore, there is no thermal sampling, and surface effects are certainly relevant. Furthermore, some structures found in small clusters may not correspond to typical configurations of a liquid. This feature makes difficult any extrapolation of liquid-state properties based on optimized cluster structures. On the other hand, classical statistical mechanics simulations rely on the generation of a set of representative configurations (MC) or in a set of trajectories (MD) for a system with periodic boundary conditions at a given temperature, by using intermolecular potential models. This allows a more realistic description of the liquid properties.

Classical statistical mechanics simulations involve the construction or selection of an intermolecular interaction model. Although the construction of interaction models between closed-shell molecules has merited the attention of numerous studies, the interactions of radical species with closed-shell molecules are not very well understood. We have derived suitable Lennard–Jones parameters for modeling the interactions between phenol and phenoxy radical with benzene and acetonitrile, using a rigid geometry in all simulations [16]. The geometry of phenol and phenoxy radical were obtained from QC calculations. The coulombic interactions between the solutes (phenol or phenoxy) and the solvents (benzene or acetonitrile) were derived by fitting the charges of the solute to the electrostatic potential in the clusters with two solvent molecules described above. As a result, we predict the solute–solvent and solvent–solvent energies of the solution and the solvent–solvent energies in the pure liquid for systems with N (typically >200) solvent molecules. Table 2 reports the thermodynamic data obtained from MC simulations of the pure liquids and solutions. The solvation enthalpy of a substance X is derived from the data in that table, according to eq. 17.

Table 2 Thermodynamic properties of the pure liquids and solutions from MC simulations at $T = 298$ K and $p = 1$ atm.^a

	Pure benzene	Pure acetonitrile
N_S	216	500
	Phenol–benzene	Phenol–acetonitrile
E_{SX}	-84.5 ± 0.1	-111.0 ± 0.1
ΔH_R	39.3 ± 2.9	51.0 ± 5.0
$\Delta_{\text{sln}}H^\circ(\text{PhOH},\text{g})$	-47.7 ± 2.9	-62.5 ± 5.0
Exp. ^b	-50.6 ± 0.8	-59.4 ± 0.4
	Phenoxy–benzene	Phenoxy–acetonitrile
E_{SX}	-79.6 ± 1.0	-104.8 ± 0.2
ΔH_R	32.2 ± 3.8	47.3 ± 4.6
$\Delta_{\text{sln}}H^\circ(\text{PhO}^\bullet,\text{g})$	-49.9 ± 3.9	-60.0 ± 4.6

^a N_S is the number of solvent molecules. ΔH_R are solvent relaxation enthalpies. $\Delta_{\text{sln}}H^\circ(X,\text{g}) = E_{SX} + \Delta H_R - RT$ is the solvation enthalpy of the solute species X. Energy and enthalpy values are in kJ mol^{-1} .

^bExperimental value of $\Delta_{\text{sln}}H^\circ(\text{PhOH},\text{g})$ [16].

$$\Delta_{\text{sln}}H^\circ(X,\text{g}) = E_{SX} + \Delta H_R - RT \quad (17)$$

Here, E_{SX} is the solute–solvent energy and ΔH_R is the solvent relaxation enthalpy (i.e., the difference between solvent–solvent enthalpies in the solution and in the pure solvent). By including a large number of solvent molecules, the statistical mechanics method allows us to consider two important aspects of solvation not yet contemplated. First, the interaction between the solute and solvent (E_{SX}) takes into account long-range interactions, and not only specific (hydrogen bonds) and localized (small clusters) ones. Second, the solvent relaxation that is induced by the presence of the solute is also included (ΔH_R). In addition, periodic boundary conditions minimize surface effects, which are inherent to cluster calculations.

Although the classical statistical mechanics approach provides a much more realistic description of solvation, we must keep in mind that the quality of its results is strongly dependent on the reliability of the intermolecular potentials used. The construction of interaction models in liquid phase is not a trivial task. However, the usefulness of this approach was demonstrated by estimating the solvation of H_2 and of the H-atom. For such simple species, the interaction potentials are well known, so an MC simulation should afford accurate results. We have computed their solvation enthalpies in acetonitrile and obtained, through eq. 17, $\Delta_{\text{sln}}H^\circ(\text{H}_2,\text{g}) = 5.5 \pm 2.8 \text{ kJ mol}^{-1}$ and $\Delta_{\text{sln}}H^\circ(\text{H}^\bullet,\text{g}) = 5.8 \pm 3.5 \text{ kJ mol}^{-1}$ [16]. While an experimental value is not available for acetonitrile, $\Delta_{\text{sln}}H^\circ(\text{H}_2,\text{g})$ is remarkably constant, with an average value of $5 \pm 1 \text{ kJ mol}^{-1}$ for 10 typical organic solvents [33]. Therefore, the above results corroborate both the assumption that the solvation enthalpies of these species are similar and the value used before (cf. Table 1).

Returning to the main issue, according to the simulation approach the differential solvation between phenol and its radical is given by eq. 18, where $\Delta E_{SX} = E_{SX}(\text{PhOH}) - E_{SX}(\text{PhO}^\bullet)$ is the difference in the solute–solvent interaction energy, and $\Delta\Delta H_R = \Delta H_R(\text{PhOH}) - \Delta H_R(\text{PhO}^\bullet)$ is the difference in the solvent relaxation enthalpy.

$$\Delta_{\text{sln}}H^\circ(\text{PhOH},\text{g}) - \Delta_{\text{sln}}H^\circ(\text{PhO}^\bullet,\text{g}) = \Delta E_{SX} + \Delta\Delta H_R \quad (18)$$

The final results from MC simulations are also presented in Table 1. Again, they point to a very small difference between the solvation enthalpies of phenol and its radical. But the MC simulations allow a deeper analysis of this behavior.

As ΔE_{SX} is expected to be negative, whereas $\Delta\Delta H_R$ will be positive, these terms will partially cancel each other in eq. 18, as the results in Table 2 show. Furthermore, note that while solvent relaxation is sizable both for phenol and phenoxy radical, the differential relaxation enthalpy also nearly cancels ($\Delta\Delta H_R = 7.1 \pm 4.8 \text{ kJ mol}^{-1}$ in benzene and $3.7 \pm 6.8 \text{ kJ mol}^{-1}$ in acetonitrile), showing that the contribution of the solvent relaxation term to the solvation effect is small.

To investigate the importance of long-distance interactions (which, together with the solvent relaxation, was not contemplated in the previous models), we have looked into the differential solute–solvent interaction energy, ΔE_{SX} , as a function of the center-of-mass distance from the solute [16]. In benzene, this term converges at a rather small distance (7.7 Å), which further analysis showed to correspond to the first coordination shell, formed by 13 benzene molecules. On the contrary, considering all the solvent molecules within the first solvation shell in acetonitrile (at 7.0 Å), the differential solute–solvent interaction is far from the converged value, which is reached only near 17 Å and corresponds to 250 acetonitrile molecules. These results suggest that, while the solute–solvent interaction in benzene can be correctly estimated by considering only a few solvent molecules, the dipolar interactions between the polar solutes and polar solvent molecules in acetonitrile do extend to a long range, demanding the use of a very large number of solvent molecules to evaluate this term. In either case, considering only a single solvent molecule to model solute–solvent interactions seems a gross oversimplification.

How can microsolvation modeling and statistical mechanics simulations lead to similar results for the differential solvation?

Considering the above discussion and the results in Table 1, we will now try to explain why the microsolvation approach, which neglects both long-range interactions and solvent relaxation contributions, leads to a $DH^\circ(\text{Ph-OH})$ value in good agreement with experiment. The solvent relaxation enthalpy represents the most difficult calculation involved in the MC procedure due to its slow convergence, being itself a difference between two large and fluctuating numbers [16]. Since its contribution to the differential solvation in the present case is expected to be small, it may be safer to neglect it in our analysis.

Considering only the solute–solvent interaction term, which includes long-range interactions, MC and microsolvation results become very close to the ones derived from the microsolvation method (Table 1), as can be seen by comparing ΔE_{SX} results (i.e., neglecting $\Delta\Delta H_R$ in eq. 18). For benzene, we obtain $-4.9 \pm 1.0 \text{ kJ mol}^{-1}$ vs. -4.2 kJ mol^{-1} and, for acetonitrile, $-6.2 \pm 0.2 \text{ kJ mol}^{-1}$ vs. $-10.7 \text{ kJ mol}^{-1}$, respectively. As expected, the discrepancy is only noticeable for acetonitrile, but still small. In conclusion, while solvation demands a large number of solvent molecules to be genuinely described, the enthalpic solvation effect, which is a *difference* between the solvation enthalpies of the parent compound and its radical, can in some cases be reasonably estimated by considering one-to-one solute–solvent interactions.

Can continuum solvation models describe solvent effects on BDEs?

QC continuum reaction field models [57–59], a popular way of studying solvation, may have the advantage of providing substantial savings of computational time by comparison with the microsolvation or statistical mechanical approaches. A recent application of this approach to investigate solvent effects on BDEs was reported by Bakalbassis et al., who used the polarized continuum model (PCM) [59] to calculate $DH_{\text{sln}}^\circ(\text{PhO-H})$ in seven organic solvents, including benzene and acetonitrile [60]. Their results for the differential enthalpies of solvation in benzene and acetonitrile, included in Table 1, are in line with the results from the other models. It is also worth mentioning that the PCM prediction for the enthalpy of solvation of the H-atom in acetonitrile (6.5 kJ mol^{-1}), is in keeping with our MC result (5.8 kJ mol^{-1}). Moreover, the average of the PCM values for the enthalpies of solvation of H^\bullet (5.1 kJ mol^{-1}) matches the average value used throughout the present paper (5 kJ mol^{-1}).

It should be observed that continuum reaction field models take into account local polarization effects in an average way. Therefore, it is not clear how these simplified models correctly describe local effects such as hydrogen bond formation. A more attractive possibility is to include explicitly a small number of solvent molecules (as in the microsolvation model) and to add to this system a continuum model reaction field [25]. In such an approach, long- as well as short-range local interactions would be included.

THE ON-GOING CONTROVERSY AROUND THE O–H BOND DISSOCIATION ENTHALPY IN PHENOL

In this overview, the PhO–H BDE was used to assess the accuracy of the solvation models discussed but, as stated, it is still subject to some controversy. Based on a review of literature data, Mulder et al. recommend $362.8 \pm 2.9 \text{ kJ mol}^{-1}$ for the gas-phase PhO–H BDE [50], 8.5 kJ mol^{-1} lower than the previously recommended value of $371.3 \pm 2.3 \text{ kJ mol}^{-1}$ [33]. Their hard evidence relies on kinetic studies in the gas-phase and on theoretical methods. The kinetic studies involved the thermal decomposition of anisole and diphenyl ether and led to the respective activation enthalpies, which were identified with PhO–Me and PhO–Ph BDEs. From these results and standard enthalpy of formation data, quoted from the literature, the authors derived two values of PhO–H BDE in good agreement with each other (364.0 and $363.3 \text{ kJ mol}^{-1}$). However, this agreement rests on their choice of the standard enthalpy of formation of anisole. Instead of using the value recommended by Pedley [61], $-67.9 \pm 0.8 \text{ kJ mol}^{-1}$, Mulder et al. adopted an early value [62], $-76.7 \pm 0.9 \text{ kJ mol}^{-1}$. This choice was justified on the basis of group contributions. However, Pedley's recommendation is based on the combustion calorimetry results reported by Fenwick et al. [63] and also on their calorimetric measurements of the enthalpy of vaporization of anisole. Besides the well-known reputation of Arthur Head's group, from the National Physical Laboratory, this particular paper is a model of good practices on combustion calorimetry (e.g., it includes CO_2 analysis). Of course, any value can be questioned, but in the present case it would seem wiser to question, for example, the recommended standard enthalpy of formation of diphenyl ether or the activation enthalpy of its thermal decomposition. It remains to be said that using the kinetic result for anisole together with Pedley's value, one obtains $372.8 \pm 2.1 \text{ kJ mol}^{-1}$ for the gas-phase PhO–H BDE.

The second piece of evidence comes from the theoretical calculations. Mulder et al. reported values for the direct homolysis reaction of $364.4 \text{ kJ mol}^{-1}$ (CQS-QB3), $369.0 \text{ kJ mol}^{-1}$ (G3 and CBS-APNO), and $372.4 \text{ kJ mol}^{-1}$ [CCSD(T)/aug-cc-pVTZ]. It should be observed that G3, CBS-QB3, and CBS-APNO composite procedures are designed to reproduce atomization energies for a set of reference molecules and that they may exhibit significant deviations from experiment for a specific species, although the average value of deviations is smaller for the selected set of molecules. It seems, therefore, reasonable to assume that CCSD or CCSD(T) calculations may provide the most reliable estimates of the PhO–H BDE. A recent high-level calculation based on extrapolation of CCSD energies to infinite basis-set [64] led to $372.8 \text{ kJ mol}^{-1}$, in very good agreement with the Mulder et al. CCSD(T)/aug-cc-pVTZ result referred above. Although this procedure was latter disputed by DiLabio and Mulder [65], the latest and, to date, the highest-level calculation [basis-set extrapolated CCSD(T)] by Cabral and Canuto [51] yielded 382 kJ mol^{-1} , corroborating the previous conclusions and supporting the choice of the "high value" for the gas-phase PhO–H BDE.

To reduce the inherent deficiencies of the composite methods referred above, Mulder et al. [50] also used isodesmic reactions, namely, the H-atom transfer reaction between phenoxy and methanol. From the computation of this reaction enthalpy and the knowledge of the O–H BDE in methanol, the PhO–H BDE can be derived relative to a more accurate value. Using the experimental value of $437.6 \pm 2.9 \text{ kJ mol}^{-1}$ for the MeO–H BDE from ref [7], they obtained $361.5 \text{ kJ mol}^{-1}$ (CBS-QB3), $366.1 \text{ kJ mol}^{-1}$ (CBS-APNO) and $366.9 \text{ kJ mol}^{-1}$ (G3), results that are lower than the values obtained from the direct homolysis reaction and that they considered in good agreement with their recommended value of

$362.8 \pm 2.9 \text{ kJ mol}^{-1}$. However, they also recognized that these results depend on the choice of the “auxiliary” molecules in the isodesmic scheme, and more extensive error cancellation would be expected if the molecules and radicals involved had more similar characters. These calculations were recently reappraised by Da Silva et al. [52] who studied a series of isodesmic reactions using the G3, G3B3, and CSB-APNO composite procedures to address the issue. Starting with the same reaction and auxiliary value for the MeO–H BDE, these authors obtained an average PhO–H BDE of $368.0 \text{ kJ mol}^{-1}$ from the three procedures (results from the direct homolysis reaction yielded the average value of $370.3 \text{ kJ mol}^{-1}$). However, for a set of four extra isodesmic reactions they arrived at an average value of $372.4 \pm 4.1 \text{ kJ mol}^{-1}$, remarkably constant throughout the set. These authors also suggested that the deviation from this value for the reaction with MeOH might be due to the poorly known MeO–H BDE. Indeed, had they used the value of $440.5 \pm 2.1 \text{ kJ mol}^{-1}$ recommended by Ruscic et al. in the most recent critical evaluation of the energetics of a series of important organic radicals [66], they would have obtained an average value of $370.9 \text{ kJ mol}^{-1}$, in better agreement with the originally recommended “high value” of $371.3 \pm 2.1 \text{ kJ mol}^{-1}$ (as also would have Mulder et al.).

CONCLUSION

Solvent effects on the BDE of a molecule arise from the difference in solvation enthalpies between the molecule and the resulting radical (eq. 3). In the past, these effects were simply neglected, since it was expected that the solvation enthalpies were small. However, this simple assumption was challenged by several groups. During the last decade, we have tested some hypotheses and increasingly complex models to address this issue. The main conclusion from our study is that radicals may interact with the solvent as strongly as the parent compound. This similar interaction of radicals and their parent compounds with the solvent was suggested for carbon-centered radicals and confirmed by the TR-PAC determination of the C–H BDE in toluene. However, in the case of phenols and related compounds, it was proposed that the enthalpic solvation effect should be identified with the hydrogen bond enthalpy between the parent compound and the solvent (the HBO model). By finding that the interaction of the radical with the solvent is almost as strong, we demonstrated that the HBO model leads to an overestimation of the solvent effect, and the error increases with the polarity of the solvent. A more detailed analysis of the various factors at play sustains that the *differential* solvation enthalpy is indeed small, since they act in opposition (cf. eq. 18): (1) the solute–solvent interaction term is negative, whereas the solvent relaxation is positive; (2) while solvent relaxation is sizeable, it is similar for both the radical and its parent molecule; (3) the solute–solvent interaction is also of the same magnitude for both species. While MC simulations also demonstrate that a large number of molecules may have to be considered to describe solvation, the opposing factors should help canceling errors in the microsolvation model (using a single or a few solvent molecules).

For future work, we therefore favor, in a first step, the microsolvation approach through Scheme 2 and eq. 15 as a simple way of dealing with differential solvation. It is also expected that the accuracy of the results will not be strongly dependent on the theoretical level chosen, basically because the solvent effects are estimated from eq. 9, which corresponds to the isodesmic and isogyric reaction 16, thus assuring more accurate results thanks to error cancellation.* However, size-dependence analysis of the microsolvation approach and statistical mechanics simulations should be carried out, whenever possible, as complementary tools for investigating solvent effects on BDEs. In addition, it should be expected that ab initio MD simulations [67] will play a relevant role in the study of liquid-phase properties in the near future. They combine QC electronic structure calculations with the statistical mechanics approach, providing a promising route to model solvent effects.

*Besides the reported values obtained using density functional theory (DFT) calculations, we also tested a complete basis-set procedure (CBS-4M), and obtained similar results [17].

It remains to be said that the above discussion involving the solvation enthalpies of phenol and phenoxy radical, together with the PAC results, strongly support the recommended "high value" for the gas-phase PhO–H BDE, ca. 371 kJ mol⁻¹. However, we still feel that only a high-precision (less than ca. 1 kJ mol⁻¹) and accurate experimental gas-phase PhO–H BDE value will settle the controversy.

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