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REGULAR ARTICLE

Solvation enthalpies of neutral solutes in water and octanol

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Abstract The balance between electrostatic and non-electrostatic enthalpic contributions to the free energy of solvation of a series of neutral solutes in water and *n*-octanol is examined by means of continuum solvation calculations based on the Miertus–Scrocco–Tomasi (MST) method. The experimental data indicate that the solvation enthalpy of hydrocarbons is very similar in water and *n*-octanol, and that the enthalpic contribution measured for polar compounds is larger in water than in *n*-octanol. According to MST calculations, the different magnitude of the solvation enthalpy found for polar compounds in the two solvents can be largely attributed to the electrostatic contribution. Moreover, the results point out that there is close resemblance between the non-electrostatic components for both hydrocarbons and polar compounds in the two solvents. Finally, the results show the power of current continuum models like MST to dissect the total free energy of solvation in entropic and enthalpic contributions and suggest that new refinements of continuum solvation models should include not only the fitting to solvation free energies, but also their enthalpic components.

Keywords Solvation · Enthalpy of solvation · Water · Octanol · Continuum model · MST

1 Introduction

The free energy of solvation (ΔG_{sol}) is a key thermodynamic quantity to understand the influence of solvation on chemical processes. According to Ben-Naim [1], it can be defined as the reversible work required to transfer the solute from the ideal gas phase to solution at a given temperature, pressure and chemical composition. This definition is well suited for molecular formulations of the solvation problem, because it permits to relate ΔG_{sol} to the difference in the reversible works necessary to "build up" the solute both in solution and in the gas phase [2–5]. For practical applications, it is convenient to decompose ΔG_{sol} into separate, more manageable terms, which typically involves the separation between electrostatic (ΔG_{ele}) and non-electrostatic ($\Delta G_{\text{n-ele}}$) contributions (Eq. 1). The former accounts for the work required to assemble the charge distribution of the solute in solution, and the latter is typically used to account for cavitation (i.e., the work required to create the cavity that accommodates the solute), as well

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Dedicated to Professor Santiago Olivella on the occasion of his 65th birthday and published as part of the Olivella Festschrift Issue.

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as dispersion and repulsion interactions between solute and solvent molecules.

$$\Delta G_{\mathrm{sol}} = \Delta G_{\mathrm{ele}} + \Delta G_{\mathrm{n-ele}} = \Delta G_{\mathrm{ele}} + \Delta G_{\mathrm{cav}} + \Delta G_{\mathrm{vW}} \quad (1)$$

The partitioning scheme given by Eq. 1 has been largely adopted in the framework of quantum mechanical (QM) self-consistent reaction field (SCRF) continuum models [6–11], where the solvent is treated as a continuum polarizable medium characterized by suitable macroscopic properties. By means of a detailed parametrization of both electrostatic and non-electrostatic contributions, the most elaborate versions of QM-SCRF methods can estimate ΔG_{sol} with remarkable accuracy (<1 kcal/mol for water and generally around 0.5 kcal/mol for non-aqueous solvents). Inspection of both electrostatic and non-electrostatic components of ΔG_{sol} is valuable to gain insight, at least from a qualitative point of view, into the nature of the interactions between solute and solvent. However, since ΔG_{sol} is the experimentally measurable thermodynamic quantity, caution is necessary for a more quantitative analysis, because the adoption of a partitioning scheme, though convenient for practical reasons, neglects the mutual coupling between the different free energy components.

Besides the solvation free energy, knowledge of its enthalpic, ΔH_{sol}, and entropic, ΔS_{sol}, components is required to gain a comprehensive understanding into the physico–chemical basis of solvation. These quantities, which can be derived by using standard thermodynamic relationships (Eqs. 2, 3), provide a substantial reservoir of information about the interactions between solute and solvent molecules. Even though it can be anticipated that computation of ΔH_{sol} (and ΔS_{sol}) is more delicate than the prediction of ΔG_{sol}, which benefits from the enthalpy–entropy compensation, the availability of experimentally measured data for these magnitudes is valuable to calibrate the reliability of theoretical models to predict those thermodynamic quantities.

$$\Delta G_{\mathrm{sol}} = \Delta H_{\mathrm{sol}} - T\Delta S_{\mathrm{sol}} \quad (2)$$

$$\Delta H_{\mathrm{sol}} = \Delta G_{\mathrm{sol}} - T\left(\frac{\partial G_{\mathrm{sol}}}{\partial T}\right)_P \quad (3)$$

In this study we examine the suitability of the QM-SCRF MST [12–15] model to predict the enthalpic (and entropic) components of the free energy of solvation in water and *n*-octanol. To this end, we first describe the formalism used to determine the solvation enthalpy in the framework of the MST model. Then, the results determined for the solvation of a series of neutral solutes in water (partly presented in Ref. [16]) and *n*-octanol will be presented and analyzed in light of the available experimental data. Finally, the results will be used to examine the differential trends of the solvation in the two solvents.

2 Methods

2.1 The MST continuum method

In the MST model the free energy of solvation is determined as the sum of three contributions: electrostatic, cavitation, and van der Waals. Following the formalism of the polarizable continuum model (PCM) originally developed by Miertus, Scrocco, and Tomasi [17, 18], the electrostatic term (ΔG_{ele}) is determined by using a set of apparent charges spread over the cavity surface (Eq. 4), which accounts for the reaction field created in the solvent by the presence of the solute's charge distribution.

$$V_R = \sum_{j=1}^{M} \frac{q_j}{|r_j - r|} \quad (4)$$

where V_R is the perturbation operator used to couple the solute's charge distribution and the solvent reaction field, M is the total number of surface elements, j, into which the solute/solvent boundary is divided, and q_j is the apparent charge at the j surface element, which is centered at r_j.

The electrostatic contribution is determined as shown in Eq. 5, where the index sol means that the perturbational operator $\hat{V}_R^{\mathrm{sol}}$ is adapted to the fully polarized charge distribution of the solute in solution (given by the wavefunction Ψ^{sol}), and the index o stands for the gas phase environment.

$$\Delta G_{\mathrm{ele}} = \left\langle \Psi^{\mathrm{sol}} \middle| \hat{H}^{\mathrm{o}} + \hat{V}_R^{\mathrm{sol}} \middle| \Psi^{\mathrm{sol}} \right\rangle - \frac{1}{2}\left\langle \Psi^{\mathrm{sol}} \middle| \hat{V}_R^{\mathrm{sol}} \middle| \Psi^{\mathrm{sol}} \right\rangle - \left\langle \Psi^{\mathrm{o}} \middle| \hat{H}^{\mathrm{o}} \middle| \Psi^{\mathrm{o}} \right\rangle \quad (5)$$

The cavitation free energy is determined following Pierotti's scaled particle theory [19], where ΔG_{cav} is expressed as an expansion series in powers of the radius of the sphere which excludes the centers of the solute molecules from the solute, R_{MS} (i.e., the sum of the solute and solvent radii; Eq. 6). The expansion coefficients K_i ($i = 0$–3) are expressed in terms of properties of the solvent (the radius of the solvent molecule, R_{S}, and the numeral density, n_{S}), and of the solution (temperature, T, and pressure, P), as noted in Eqs. 7a–d, where $y = 4\pi R_{\mathrm{S}}^3 n_{\mathrm{S}}/3$.

$$\Delta G_{\mathrm{cav}} = K_0 + K_1 R_{\mathrm{MS}} + K_2 R_{\mathrm{MS}}^2 + K_3 R_{\mathrm{MS}}^3 \quad (6)$$

$$K_0 = RT\left[-\ln(1-y) + \frac{9}{2}\left(\frac{y}{1-y}\right)^2\right] - \frac{4\pi R_{\mathrm{S}}^3 P}{3} \quad (7a)$$

$$K_1 = -\frac{3RT}{R_S}\left[\frac{y}{1-y} + 3\left(\frac{y}{1-y}\right)^2\right] + 4\pi R_S^2 P \tag{7b}$$

$$K_2 = \frac{3RT}{R_S^2}\left[\frac{y}{1-y} + \frac{3}{2}\left(\frac{y}{1-y}\right)^2\right] - 4\pi R_S P \tag{7c}$$

$$K_3 = \frac{4\pi P}{3} \tag{7d}$$

Since Pierotti's theory was developed for solutes with spherical shape, its implementation to molecular-shaped cavities is performed by using the procedure proposed by Claverie [20] (Eq. 8) where the cavitation free energy of a given atom i is determined from the contribution of the isolated atom, $\Delta G_{\mathrm{cav},i}$, and a weighting factor, w_i, determined from the ratio between the solvent-exposed surface of atom i and the total surface of such an atom.

$$\Delta G_{\mathrm{cav}} = \sum_{i=1}^{N} w_i \Delta G_{\mathrm{cav},i} \tag{8}$$

where N is the number of atoms.

Finally, the van der Waals term (ΔG_{vW}) is computed using a linear relationship to the solvent-exposed surface of each atom, as noted in Eq. 9, where the atomic surface tensions, ξ_i, are determined by fitting to the experimental free energy of solvation. Accordingly, those surface tensions not only account for dispersion–repulsion interactions between solute and solvent, but also correct for the implicit assumptions introduced in the evaluation of the remaining components of ΔG_{sol}.

$$\Delta G_{\mathrm{vW}} = \sum_{i=1}^{N} \xi_i S_i \tag{9}$$

Molecular-shaped GEPOL cavities [21, 22] are used to define the solute/solvent interface for the calculations of electrostatic and non-electrostatic (cavitation, van der Waals) terms. In the last parametrization of the MST model, a dual-cavity strategy was used [23], so that non-electrostatic contributions are determined by using a van der Waals surface built up from Pauling's radii (in Å; polar hydrogen: 0.9, apolar hydrogen: 1.2, C and N: 1.5, O: 1.4, F: 1.35, S: 1.75, and Cl: 1.80), whereas the electrostatic term is determined by using a solvent-exposed surface created by scaling the atomic radii by a solvent-dependent factor, λ, which adopts values of 1.25, 1.50, 1.60, and 1.80 for the solvation of neutral compounds in water, octanol, chloroform, and carbon tetrachloride.

2.2 Enthalpy of solvation

The enthalpy of solvation can be represented by the addition of the electrostatic and non-electrostatic enthalpy components, as noted in Eq. 10, where each enthalpy component can a priori be determined by using the Gibbs–Helmholtz relationship (Eq. 3). Even though this partitioning scheme is arbitrary, it is convenient from a practical point of view as it reflects the partitioning scheme adopted for the solvation free energy, which is also expressed as the addition of electrostatic and non-electrostatic components (see Eq. 1), and permits to determine the electrostatic and non-electrostatic entropic terms by using expressions similar to that indicated in Eq. 2.

$$\Delta H_{\mathrm{sol}} = \Delta H_{\mathrm{ele}} + \Delta H_{\mathrm{n-ele}} = \Delta H_{\mathrm{ele}} + \Delta H_{\mathrm{cav}} + \Delta H_{\mathrm{vW}} \tag{10}$$

Since the electrostatic component of ΔG_{sol} depends on the permittivity of the solvent, ε, and on the cavity size, the electrostatic contribution to the enthalpy of solvation, ΔH_{ele}, can be determined as indicated in Eq. 11 [24–26], where V_{c} denotes the volume of the cavity. For n-octanol a value of -0.077 (K^{-1}) was adopted for the temperature dependence of the solvent permittivity, $\left(\frac{\partial \varepsilon}{\partial T}\right)_P$, whereas the temperature dependence of the cavity size, $\left(\frac{\partial V_c}{\partial T}\right)_P$, was evaluated using a thermal expansion coefficient of 8.27×10^{-4} (K^{-1}; values of -0.3554 and 2.56×10^{-4} were used for water) [16, 27]. Finally, the values of $\left(\frac{\partial G_{\mathrm{ele}}}{\partial \varepsilon}\right)$ and $\left(\frac{\partial G_{\mathrm{ele}}}{\partial V_c}\right)$ were estimated numerically from the ΔG_{ele} values calculated by varying both ε and λ (i.e., the scaling factor used to modulate the size of the cavity; see above). Numerical derivatives were performed by using increments of ±0.5 and ±1.0 for ε and of ±0.01 and ±0.05 for λ, and the results were found to be quite insensitive to changes in the increments used for derivative calculations.

$$\Delta H_{\mathrm{ele}} = \Delta G_{\mathrm{ele}} - T\left[\left(\frac{\partial G_{\mathrm{ele}}}{\partial \varepsilon}\right)_{\lambda}\left(\frac{\partial \varepsilon}{\partial T}\right)_{P} + \left(\frac{\partial G_{\mathrm{ele}}}{\partial V_{\mathrm{c}}}\right)_{\varepsilon}\left(\frac{\partial V_{\mathrm{c}}}{\partial T}\right)_{P}\right] \tag{11}$$

The non-electrostatic component of the solvation enthalpy ($\Delta H_{\mathrm{n\text{-}ele}}$) and entropy ($-T\Delta S_{\mathrm{n\text{-}ele}}$) can be determined by substracting the electrostatic enthalpy, ΔH_{ele}, and entropy, $-T\Delta S_{\mathrm{ele}}$, from the known experimental quantities.

2.3 Computational details

All calculations have been performed at the HF/6-31G(d) level using the standard MST protocol [12, 15], and the IEF version [28] of the MST mode [29]. The gas-phase geometry of the molecules was fully optimized and subsequently used for calculations in solution. Calculations were performed using a locally modified version of Gaussian-03 [30].

3 Results and discussion

A series of neutral, polar molecules, which include different series of monofunctional compounds, were chosen to determine the enthalpic contribution to solvation in water and *n*-octanol. Besides four hydrocarbons (hexane, heptane, octane, and cyclohexane), they include alcohols (2-methylpropan-2-ol, 1-butanol, and 2-butanol), ethers (diethylether, tetrahydrofuran, and tetrahydropyran), amines (propylamine, butylamine, pentanamine, diethylamine, dibutylamine), as well as water, morpholine, and piperidine. The free energy and enthalpy of solvation in water and *n*-octanol (see Table 1) were taken from the data compiled by Cabani et al. [31–33] For our purposes here, it is worth noting that the experimental data might be affected by the mutual solubility between water and octanol. However, this effect is expected to introduce only a moderate uncertainty (around 0.2–0.4 kcal/mol) in the solvation free energies [31, 34] and enthalpies of solvation [33, 35, 36].

Figure 1 represents the variation of the experimental values determined for the solvation free energies and enthalpies in water and *n*-octanol for the series of compounds. It is worth noting the different behavior found for the solvation free energies of hydrocarbons relative to polar compounds. Thus, whereas the transfer of hydrocarbons from the gas phase to water is unfavorable (ΔG_{sol} values ranging from 1.2 to 2.9 kcal/mol), transfer to *n*-octanol is favorable, as reflected in solvation free energies varying from −3.3 to −4.5 kcal/mol. Moreover, the solvation enthalpies of hydrocarbons in water and *n*-octanol are nearly identical, as noted in a root-mean square deviation (rmsd) of only 0.3 kcal/mol. On the other hand, for polar compounds there is a good correlation between the solvation free energies in water and *n*-octanol, as well as between the solvation enthalpies in the two solvents. The solvation free energies of polar compounds in water and *n*-octanol are generally rather similar (rmsd of 1.1 kcal/mol), though the solvation enthalpies exhibit a much larger difference (rmsd of 4.3 kcal/mol), they being notably lower (around 68%) in *n*-octanol relative to water.

Table 1 Experimental values of the solvation free energy and its enthalpic and entropic components (kcal/mol) in water and *n*-octanol

Compound	Water			*n*-Octanol		
	ΔG_{exp}	ΔH_{exp}	$-T\Delta S_{exp}$	ΔG_{exp}	ΔH_{exp}	$-T\Delta S_{exp}$
Hexane	2.5	−7.6	10.0	−3.3	−7.4	4.0
Heptane	2.6	−8.1	10.7	−4.1	−8.5	4.4
Octane	2.9	−9.5	12.4	−4.5	−9.6	5.1
Cyclohexane	1.2	−7.9	9.2	−3.7	−7.5	3.8
Water	−6.3	−8.9	2.6	−3.9	−9.7	5.8
2-Methylpropan-2-ol	−4.5	−15.3	10.8	−4.5	−11.2	6.7
1-Butanol	−4.7	−14.7	10.0	−5.3	−12.4	7.1
2-Butanol	−4.6	−15.0	10.4	−5.1	−11.8	6.7
Diethylether	−1.6	−11.2	9.6	−3.0	−5.9	3.0
Tetrahydrofuran	−3.5	−11.3	7.8	−3.9	−6.8	2.9
Tetrahydropyran	−3.1	−11.7	8.6	−4.3	−7.3	3.0
Propylamine	−4.4	−13.3	8.9	−4.7	−9.6	4.9
Butylamine	−4.3	−14.1	9.8	−5.4	−10.8	5.4
Pentanamine	−4.1	−14.9	10.8	−5.5	−12.0	6.5
Diethylamine	−4.1	−15.6	11.5	−4.8	−10.2	5.4
Dibutylamine	−3.3	−18.2	14.9	−5.4	−14.4	9.0
Morpholine	−7.2	−16.6	9.4	−6.0	−11.2	5.2
Piperidine	−5.1	−15.6	10.5	−5.5	−11.7	6.2

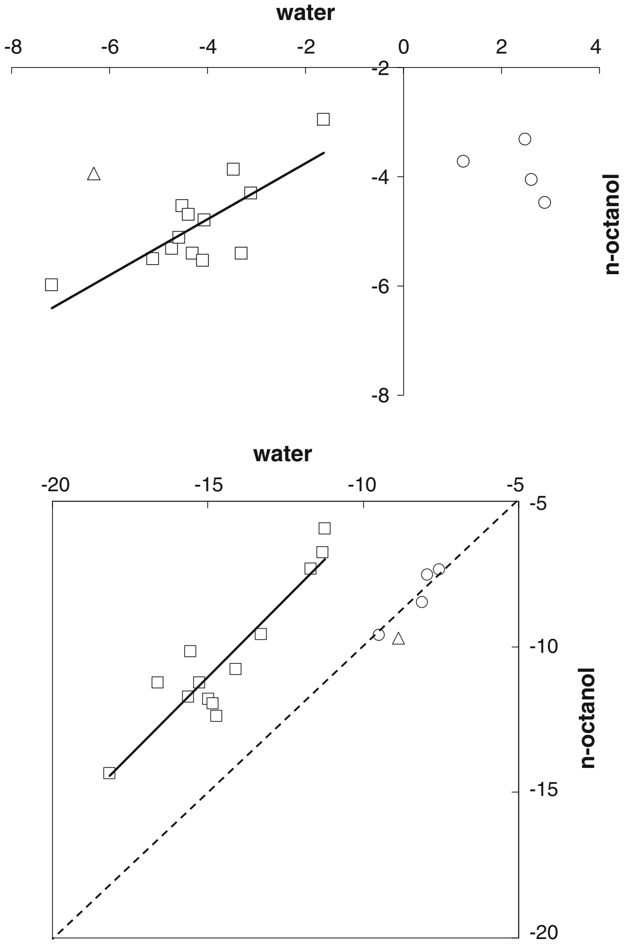

Fig. 1 Representation of (*top*) the solvation free energy and (*bottom*) its enthalpic component (kcal/mol) in water and *n*-octanol for the subset of hydrophobic (*open circle*) and polar (*open square*) compounds (water is shown as a *open triangle*). The *dashed line* represents the regression line with scaling factor of unity

The differential features associated with the solvation in water and *n*-octanol prompted us to explore the reliability of a continuum model to gain insight into the magnitude of the enthalpic contribution to the solvation free energy and to the balance between the electrostatic and non-electrostatic components (Eq. 10).

3.1 Free energies of solvation

Table 2 reports the electrostatic and non-electrostatic components of the free energy of solvation determined from MST calculations in water and *n*-octanol. The deviation between experimental and calculated free energies of solvation is generally small, as noted by mean-signed errors (mse) close to zero and rmsd values <1 kcal/mol, which compare with the statistical parameters obtained in the parametrization of the MST model for the two solvents [15, 29].

As expected, the electrostatic component of the solvation free energy in *n*-octanol is remarkably smaller (around 36%) than that found in water. In fact, the electrostatic term is the dominant contribution to the hydration free energy, it being on average ca. 145% of the experimental hydration free energy, whereas the contribution of this term to the solvation in *n*-octanol only amounts to around 50%. These findings point out that the non-electrostatic term has a positive contribution to the hydration of these molecules, which can be attributed to the cost of disrupting the structure of bulk water to create the solute cavity [37–39]. In contrast, the non-electrostatic term contributes to stabilize the solvation in *n*-octanol. These differential features are reflected in the balance between cavitation and van der Waals components for hydrocarbons (see Table 1): whereas cavitation is larger (in absolute value) than the van der Waals term in water, thus leading to an unfavorable hydration free energy (experimental values varying from 1.2 to 2.9 kcal/mol), the reverse trend is found in *n*-octanol (experimental values varying from −3.3 to −4.5 kcal/mol).

Table 2 Electrostatic and non-electrostatic components of the free energy of solvation (kcal/mol) in water and *n*-octanol

Compound	Water			*n*-Octanol		
	ΔG_{ele}	$\Delta G_{\text{n-ele}}$	ΔG_{sol}	ΔG_{ele}	$\Delta G_{\text{n-ele}}$	ΔG_{sol}
Hexane	0.0	2.6	2.5	−0.1	−2.9	−3.0
Heptane	−0.1	2.8	2.7	−0.1	−3.4	−3.5
Octane	−0.1	3.1	3.0	−0.1	−4.0	−4.1
Cyclohexane	0.0	1.7	1.7	−0.1	−3.4	−3.5
Water	−6.4	-0.3	−6.7	−4.6	−1.4	−6.0
2-Methylpropan-2-ol	−6.0	2.1	−3.9	−2.4	−2.0	−4.5
1-Butanol	−6.4	1.6	−4.8	−2.7	−3.0	−5.8
2-Butanol	−6.0	2.0	−4.1	−2.4	−2.4	−4.8
Diethylether	−3.9	3.2	−0.6	−1.3	−1.5	−2.8
Tetrahydrofuran	−5.0	2.4	−2.6	−1.9	−2.2	−4.1
Tetrahydropyran	−4.6	2.6	−1.9	−1.6	−2.7	−4.3
Propylamine	−6.2	1.5	−4.7	−2.4	−3.3	−5.7
Butylamine	−6.4	1.8	−4.6	−2.4	−3.8	−6.3
Pentanamine	−6.7	2.1	−4.6	−2.5	−4.4	−6.9
Diethylamine	−4.7	2.1	−2.6	−1.4	−2.9	−4.3
Dibutylamine	−5.9	3.3	−2.6	−1.5	−5.1	−6.6
Morpholine	−7.0	2.5	−4.5	−2.7	−3.3	−6.0
Piperidine	−4.8	1.5	−3.3	−1.4	−4.0	−5.4
mse			−0.5			0.2
rmsd			0.9			0.7

3.2 Electrostatic component of the solvation enthalpy

As noted above, the experimental enthalpies of solvation in water and *n*-octanol are nearly identical for hydrocarbons (Table 1). Since the ΔH_{ele} term is negligible for these compounds (Table 3), it can be concluded that the non-electrostatic contribution to the solvation enthalpy is similar in the two solvents. Based on this finding, it can a priori be expected that the non-electrostatic contribution determined for *uncharged* polar solutes must be similar in the two solvents, which in turn implies that the difference in the ΔH_{sol} values measured for *charged* polar compounds in water and *n*-octanol (see Table 1, Fig. 1) mainly arise from the electrostatic component of the solvation enthalpy.

Upon exclusion of water, which experimentally exhibits similar electrostatic enthalpies in water and *n*-octanol (see Table 1), the ratio $\Delta H_{\text{ele}}(\textit{octanol})/\Delta H_{\text{ele}}(\textit{water})$ amounts to

Table 3 Electrostatic component of the enthalpy of solvation (kcal/mol) in water and *n*-octanol

Compound	Water ($\lambda = 1.25$)	*n*-Octanol ($\lambda = 1.50$)	*n*-Octanol ($\lambda = 1.25$)
Hexane	0.0	-0.2	−0.1
Heptane	0.0	-0.2	−0.1
Octane	−0.1	−0.3	−0.2
Cyclohexane	0.7	−0.1	0.0
Water	−7.9	−9.0	−16.9
2-Methylpropan-2-ol	−7.8	−5.0	−11.6
1-Butanol	−8.3	−5.6	−13.5
2-Butanol	−7.8	−5.1	−12.3
Diethylether	−5.6	−2.9	−8.2
Tetrahydrofuran	−6.6	−3.8	−10.2
Tetrahydropyran	−6.0	−3.4	−9.2
Propylamine	−8.1	−5.5	−13.0
Butylamine	−8.6	−5.2	−13.7
Pentanamine	−9.0	−5.4	−14.1
Diethylamine	−6.5	−3.4	−10.3
Dibutylamine	−8.1	−3.3	−12.5
Morpholine	−9.0	−5.6	−13.7
Piperidine	−6.8	−3.1	−10.1

ca. 58%, which compares with the value of 68% found for the ratio between the solvation enthalpies in the two solvents (see above). Moreover, the ΔH_{ele} values in water amount on average to around 53% of the experimental hydration enthalpy, which compares with the ratio $\Delta H_{\mathrm{ele}}/\Delta H_{\mathrm{exp}}$ found for *n*-octanol (44%). In fact, there is a linear correlation between the ΔH_{ele} values determined for the series of polar organic compounds in water and *n*-octanol (see Fig. 2), they being on average 3.2 kcal/mol more favorable in water. Interestingly, this value is very close to the difference between the experimental ΔH_{sol} values in the two solvents (4.0 kcal/mol) supporting the assumption that the electrostatic response mainly determines the shift in the experimental solvation enthalpies observed for polar compounds. These findings can primarily be realized from the similar nature of the direct interactions formed between the solute's polar moieties and the H–O–X units (X: *H* and $(CH_2)_7CH_3$ for water and *n*-octanol) of the solvent in the first-solvation shell, and from the different magnitude of the solvent reaction field arising from the second and outer solvation shells, as expected from the different structure of the solvent molecules in water and *n*-octanol.

One of the features of the MST is that the boundary used to define the solute cavity depends on the nature of the solvent. The different sizes of the solvent-adapted cavities were obtained by comparison with atomistic simulations with explicit solvent and spectroscopic data, and are expected to capture the different nature of the solute/solvent interface depending on the molecular structure of solvent. The goodness of this procedure for defining the solute cavity becomes evident if ΔH_{ele} for *n*-octanol is computed with water-adapted cavities ($\lambda = 1.25$ instead of the *n*-octanol optimized value 1.50). In this case, the ΔH_{ele} values in *n*-octanol are larger (by ca. 55%) than the electrostatic enthalpies determined in water (see Table 3). This is clearly an artifactual result that disagrees with the hydrogen-bonding properties of water and *n*-octanol, and demonstrates not only the goodness of using the solvent-adapted cavity definition adopted in the MST model, but also the increase in information obtained when enthalpic considerations are introduced in the validation of a continuum model.

Comparison of the electrostatic components of the enthalpy and free energy of solvation in water and *n*-octanol for the polar compounds is shown in Fig. 3. In water ΔH_{ele} is found to be ca. 34% larger (in absolute value) than ΔG_{ele}, which means that the electrostatic component of the solvation entropy, $-T\Delta S_{\mathrm{ele}}$, is positive and disfavors hydration of polar solutes, as expected from the enthalpy–entropy compensation. For the series of compounds considered here, ΔS_{ele} amounts to around -6.4 cal K^{-1} mol^{-1}, which is around 19% of the experimental hydration entropy (average value of -33 cal K^{-1} mol^{-1}), indicating that the origin of the unfavorable hydration entropy is mainly due to non-

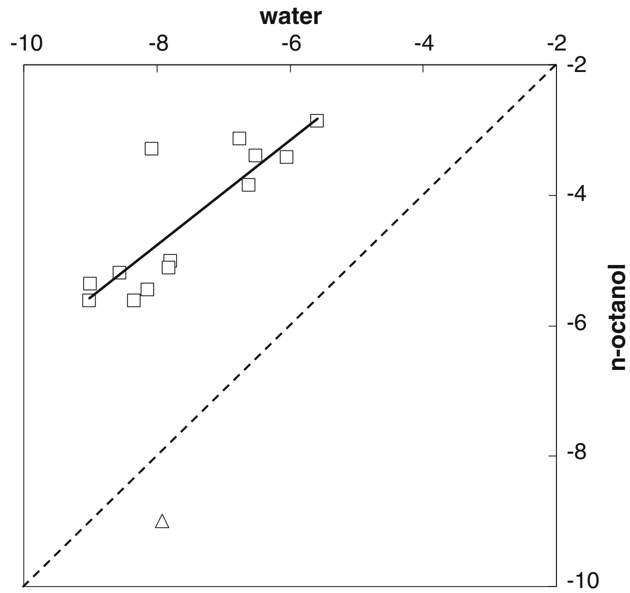

Fig. 2 Representation of the calculated electrostatic enthalpy of solvation (kcal/mol) for the series of polar compounds in water and *n*-octanol (water is represented as a *open triangle*). The *dashed line* represents the regression line with scaling factor of unity

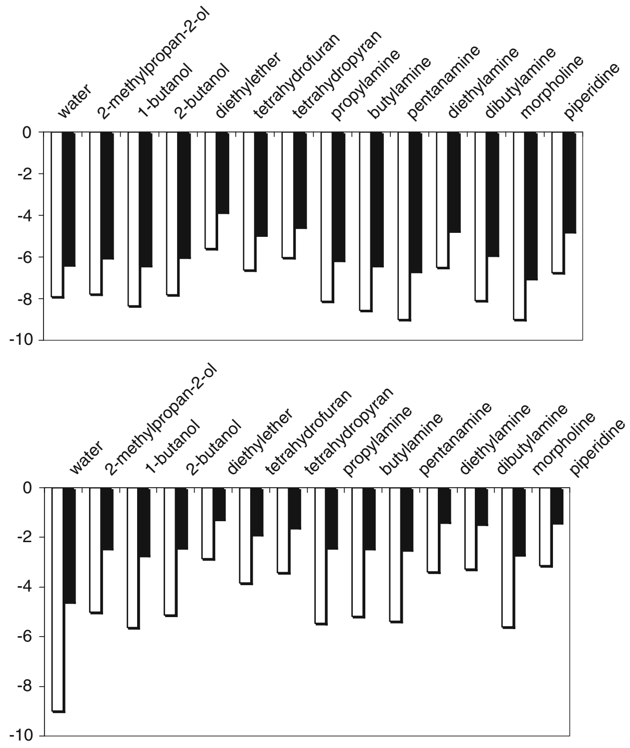

Fig. 3 Representation of the electrostatic enthalpy (*white*) and free energy (*black*) of solvation (kcal/mol) for the series of polar compounds in (*top*) water and (*bottom*) *n*-octanol

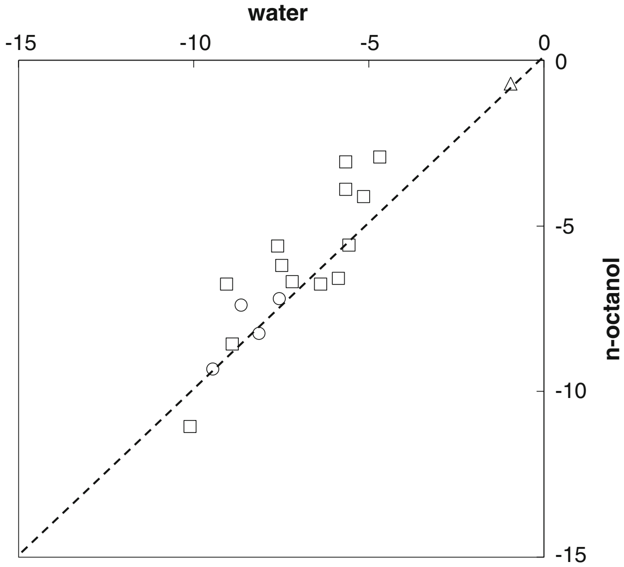

Fig. 4 Representation of the non-electrostatic component of the solvation enthalpy (kcal/mol) in water and *n*-octanol for the subset of hydrophobic (*open circle*) and polar (*open square*) compounds (water is shown as a *open triangle*). The *dashed line* represents the regression line with scaling factor of unity

Table 4 Non-electrostatic component of the enthalpy of solvation (kcal/mol) in water and *n*-octanol

Compound	Water	*n*-Octanol
Hexane	−7.6	−7.2
Heptane	−8.1	−8.3
Octane	−9.4	−9.3
Cyclohexane	−8.6	−7.4
Water	−1.0	−0.7
2-Methylpropan-2-ol	−7.5	−6.2
1-Butanol	−6.4	−6.8
2-Butanol	−7.2	−6.7
Diethylether	−5.6	−3.1
Tetrahydrofuran	−4.7	−2.9
Tetrahydropyran	−5.6	−3.9
Propylamine	−5.1	−4.1
Butylamine	−5.6	−5.6
Pentanamine	−5.9	−6.6
Diethylamine	−9.1	−6.8
Dibutylamine	−10.1	−11.1
Morpholine	−7.6	−5.6
Piperidine	−8.9	−8.6

electrostatic effects. Compared to hydration, the ΔH_{ele} term in *n*-octanol is around 110% larger (in absolute value) than ΔG_{ele}. Therefore, the electrostatic entropic component again destabilizes solvation in *n*-octanol, but ΔS_{ele} (-7.9 cal K^{-1} mol^{-1}, on average) amounts to ca. 45% of the experimental entropy of solvation (-18 cal K^{-1} mol^{-1}) for these compounds. At this point, it must be stressed that neat octanol is not a structureless liquid, but has a complex internal structure formed by variable-sized hydrogen-bonded aggregates comprising closed-loop ring clusters, packed inverted-micellar clusters and polymeric chains [40, 41], where the environment of a given solute is entirely dependent on the nature of the compound [41]. Thus, whereas apolar solutes reside in hydrophobic regions of the solvent surrounded by the hydrocarbon chains of *n*-octanol molecules, a sizable reorientation of solvent molecules must be promoted upon insertion of a polar group in apolar solutes, which makes the polar group to be buried in the more polar regions of the solvent forming hydrogen-bond interactions with hydroxyl groups of *n*-octanol molecules.

3.3 Non-electrostatic components of the solvation enthalpy

Figure 4 shows the comparison of the non-electrostatic enthalpic contributions to the solvation in water and *n*-octanol determined by substracting the electrostatic component from the experimental enthalpy of solvation (see Table 4). Clearly, by using this procedure, the non-electrostatic component of the solvation enthalpy necessarily includes any uncertainties associated with the computation of the electrostatic term.

Inspection of data in Table 4 shows that there is a close resemblance between the $\Delta H_{\text{n-ele}}$ values determined in the two solvents ($\Delta H_{\text{n-ele}}(\text{octanol}) = 1.05\Delta H_{\text{n-ele}}(water) + 1.1$; $r = 0.91$), which is in contrast with the differences found for the total enthalpies of solvation (see Fig. 1). Noteworthy, all the compounds, including hydrocarbons and water, are close to the ideal regression line with scaling factor of unity (see Fig. 4).

Comparison of the non-electrostatic components of the enthalpy and free energy of solvation in water and *n*-octanol is shown in Fig. 5. In water $\Delta H_{\text{n-ele}}$ is negative and much larger in absolute value than $\Delta G_{\text{n-ele}}$, which means that the non-electrostatic component of the solvation entropy, $-T\Delta S_{\text{n-ele}}$, is positive and disfavors hydration of *uncharged* solutes. For the series of compounds considered here, $\Delta S_{\text{n-ele}}$ amounts on average to -27.9 cal K^{-1} mol^{-1}, which is around fourfold larger than the average value found for ΔS_{ele} in water (see above). Moreover, $\Delta S_{\text{n-ele}}$ accounts for ca. 85% of the experimental hydration entropy, thus indicating that the origin of the unfavorable hydration entropy is mainly due to non-electrostatic effects, which in turn can be attributed to the reorganization of the water molecules associated with the creation of the solute's cavity.

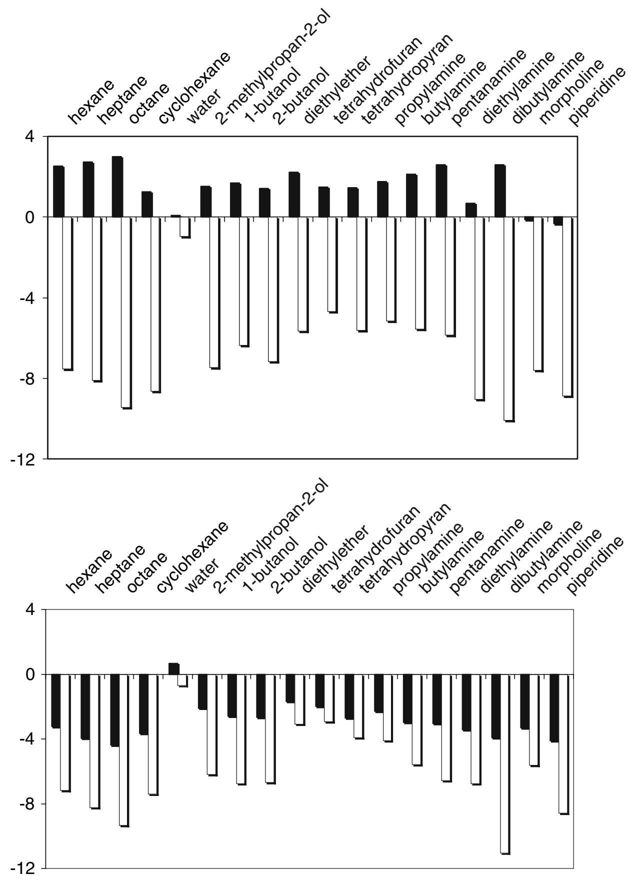

Fig. 5 Representation of the non-electrostatic enthalpy (*white*) and free energy (*black*) of solvation (kcal/mol) for the series of compounds in (*top*) water and (*bottom*) *n*-octanol

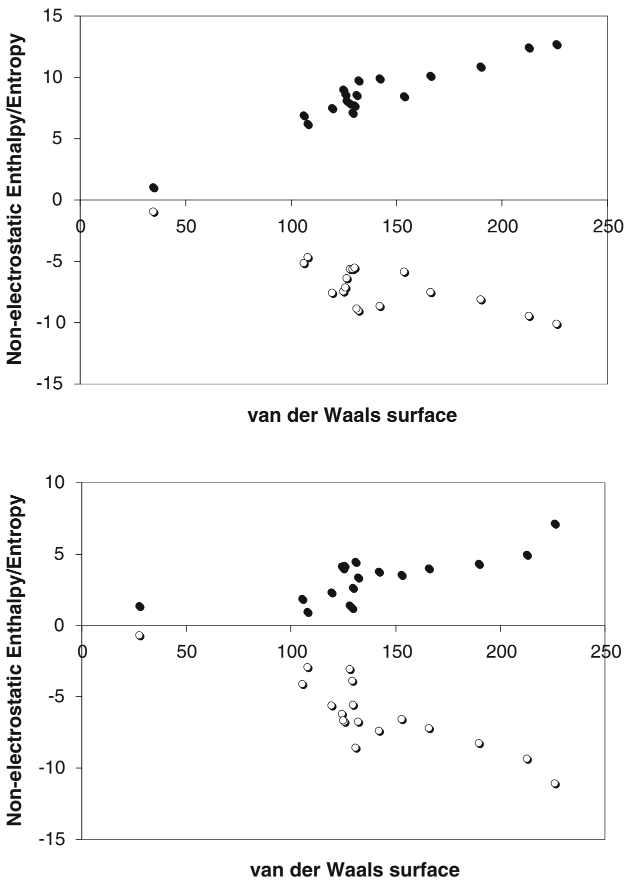

Fig. 6 Dependence of the non-electrostatic enthalpy (*white*) and entropy (*black*) of solvation (kcal/mol) on the van der Waals molecular surface for the series of compounds in (*top*) water and (*bottom*) *n*-octanol

With the only exception of water, $\Delta H_{\text{n-ele}}$ is favorable for the solvation in *n*-octanol, it being around 100% larger in magnitude than $\Delta G_{\text{n-ele}}$, which in contrast to the results found for aqueous solution makes a favorable contribution to the solvation in *n*-octanol. Accordingly, the non-electrostatic entropic component, $-T\Delta S_{\text{n-ele}}$, again destabilizes solvation in *n*-octanol, but $\Delta S_{\text{n-ele}}$ amounts on average to -9.8 cal K^{-1} mol^{-1}, which represents around 55% of the experimental entropy of solvation for these compounds. Overall, whereas $\Delta S_{\text{n-ele}}$ is the main contribution to the hydration entropy, both ΔS_{ele} and $\Delta S_{\text{n-ele}}$ contribute similarly to the solvation entropy in *n*-octanol.

Previous studies have shown that there is a linear dependence between the enthalpy of hydration of alkanes and their accessible surface area or related magnitudes [42–44]. Analysis of our results reveals the existence of linear relationships between $\Delta H_{\text{n-ele}}$ or $-T\Delta S_{\text{n-ele}}$ and the surface of the solute's van der Waals cavity (S_{vW}), which is used in MST computations for the calculation of the non-electrostatic contributions, indicating that both $\Delta H_{\text{n-ele}}$ and $-T\Delta S_{\text{n-ele}}$ increase with the size of the compounds (Fig. 6). The scaling coefficients of the regression equations reflect the similar magnitude of the non-electrostatic enthalpy in water and *n*-octanol (water: $\Delta H_{\text{n-ele}} = -0.049 S_{\text{vW}}$; $r = 0.80$; *n*-octanol: $\Delta H_{\text{n-ele}} = -0.045 S_{\text{vW}}$; $r = 0.86$), as well as the different magnitude of the non-electrostatic entropy in the two solvents (water: $-T\Delta S_{\text{n-ele}} = 0.061 S_{\text{vW}}$; $r = 0.94$; *n*-octanol: $-T\Delta S_{\text{n-ele}} = 0.024 S_{\text{vW}}$; $r = 0.76$). On the other hand, these findings suggest that, at least in a first approximation, one can assume that the non-electrostatic forces that mediate solvation of hydrocarbons and *uncharged* polar solutes are rather similar, which in turn support the assumption that the electrostatic work needed to charge up the solute in water and *n*-octanol is largely decoupled from the non-electrostatic interactions formed between *uncharged* solutes and solvent molecules.

Finally, the enthalpic and entropic components of the solvation free energy can be estimated by combining the electrostatic enthalpy and entropy (see Table 3, Fig. 3) to the non-electrostatic terms determined from the preceding regression equations. By using this computational strategy, a good correlation is found between the MST results and

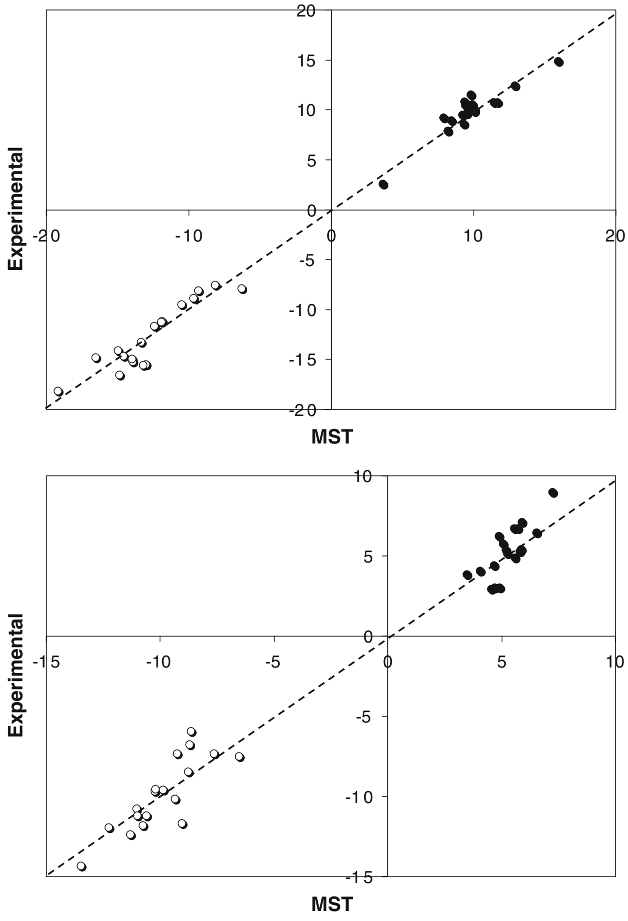

Fig. 7 Representation of experimental values of solvation enthalpies (*white*) and entropies (*black*; expressed as $-T\Delta S$) and the corresponding values obtained from MST computations for the series of compounds in (*top*) water and (*bottom*) *n*-octanol

the corresponding values determined experimentally (see Table 1), as noted upon inspection of Fig. 7.

4 Concluding remarks

The availability of computational procedures to determine the solvation free energy and its enthalpic and entropic components is necessary to gain a deeper understanding of the processes associated with the transfer of solutes from the gas phase into the bulk solvent. In this work we have examined the partitioning of the free energy and enthalpy of solvation in water and *n*-octanol within the framework of the MST version of the IEF-PCM continuum model. In particular, attention has been paid to the balance between the electrostatic and non-electrostatic contributions.

The results point out the relevant contribution played by electrostatic interactions to the hydration enthalpy of polar solutes. Nevertheless, even for these compounds the non-electrostatic term makes a significant contribution to the hydration enthalpy. The entropic contribution to the hydration is mainly associated with the non-electrostatic terms, which can be mainly attributed to the reorganization of the solvent molecules around the solute cavity. As expected from the nature the solvents the magnitude of the electrostatic enthalpy of solvation in *n*-octanol is smaller than that found for water. Interestingly, the ratio between the electrostatic enthalpies in water and *n*-octanol reflects the difference found in the corresponding values of solvation enthalpies in the two solvents.

The non-electrostatic enthalpic and entropic components of the solvation in water and *n*-octanol are linearly related with the size of the solutes, and this relationship holds for both hydrocarbons and the *uncharged* polar molecules examined here. In other words, for practical purposes the "neglect" of coupling between electrostatic and non-electrostatic components, though not physically rigorous, does not seem to introduce a dramatic artifact in simulations.

Finally, the present results suggest that calibration of solvation models would largely benefit not only by considering experimental solvation free energies, but also their enthalpic and entropic components. Hopefully, an integrated description of these thermodynamic quantities would yield more balanced and accurate models, which will be valuable to gain a more comprehensive understanding of the forces that mediate solvation of solutes in diverse solvents.

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