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Fast Computation of Solvation Free Energies with Molecular Density Functional Theory: Thermodynamic-Ensemble Partial Molar Volume Corrections

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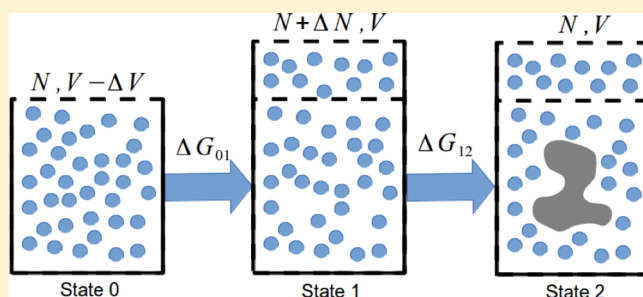
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Supporting Information

ABSTRACT: Molecular density functional theory (MDFT) offers an efficient implicit-solvent method to estimate molecule solvation free-energies, whereas conserving a fully molecular representation of the solvent. Even within a second-order approximation for the free-energy functional, the so-called homogeneous reference fluid approximation, we show that the hydration free-energies computed for a data set of 500 organic compounds are of similar quality as those obtained from molecular dynamics free-energy perturbation simulations, with a computer cost reduced by 2–3 orders of magnitude. This requires to introduce the proper partial volume correction to transform the results from the grand canonical to the isobaric-isotherm ensemble that is pertinent to experiments. We show that this correction can be extended to 3D-RISM calculations, giving a sound theoretical justification to empirical partial molar volume corrections that have been proposed recently.

SECTION: Molecular Structure, Quantum Chemistry, and General Theory



Solvation free energy (SFE) is one of the main physical quantities in solution chemistry. Many important characteristics, such as dissociation constants, partition coefficient (log P), which are necessary for describing most of the processes in physical chemistry and biochemistry are expressed through the SFE. Despite the importance of that physical quantity, determination of SFE is often problematic. Experimental determination of SFE is often complicated. It can require essential time and resources, especially if SFE is calculated for low soluble and low volatile substances.^{1,2} This increases the importance of the numerical SFE calculations. SFE calculation methods can be separated into two classes: (i) explicit solvent methods (simulations),^{3,4} and (ii) implicit solvent methods.⁵ As for the advantages of the simulation methods we can name their relatively high accuracy (however, one should remember that accuracy of the simulations greatly depend on the force-field and partial charges determination).^{4,6,7} One of the disadvantages of the explicit solvent methods is their high demands to the computational resources, which make them inapplicable in some practical applications where the speed is critical.

Among the most common implicit solvent methods are the continuum electrostatics models, which are based on solutions of the Poisson–Boltzmann equation for the charges inside the molecular cavity inside the dielectric continuum.^{5,8} This type of methods allows one to perform the calculations much faster

than it is done in the simulations. However, accuracy of implicit solvent methods is often not enough for accurate prediction of the SFE; that is why in practice the methods with empirical corrections are often used. Many of methods of this type, such as COSMO-RS or SM6/SM8, allow one to calculate SFE with a high accuracy for some classes of simple compounds.^{9–13} However, for the compounds with complicated structure these methods often fail to give a good correspondence to experiments.^{14,15}

On the other hand, the numerical methods that have emerged in the second part of the last century from liquid-state theories,^{16,17} including integral equation theory in the reference interaction-site model (RISM) approximation^{18–23} or in the molecular picture,^{24–26} classical density functional theory (DFT),^{16,27–29} or classical fields theory,^{30,31} become methods of choice for many physical chemistry or chemical engineering applications.^{32–35} They can be used as evolved implicit solvent methods to predict the solvation properties of molecules at a much more modest computational cost than molecular dynamics (MD) or Monte Carlo (MC) simulations, while retaining the molecular character of the solvent. There have been a number of recent efforts in that direction using 3D-

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RISM,^{36–41} lattice field theories^{42,43} or Gaussian field theories.^{31,44–46} Another important class of approaches relies on classical DFT in the molecular^{47–57} or interaction site⁵⁸ representation, or constructed from the statistical associating fluid theory (SAFT).⁵⁹

3D-RISM in the hyper-netted chain (HNC) or Kovalenko–Hirata (KH) approximation is certainly the method that has been pushed the furthest in that direction to date, with recent application to the high-throughput prediction of organic molecules solvation free-energies,^{60–63} and the development of highly efficient multigrid algorithms for that purpose.^{64–66} Unfortunately, it turns out that SFEs calculated that way systematically overestimate the experimental values, and display a very poor correlation.^{67,68} It was found that the accuracy can be considerably improved by including an empirical partial molar volume (PMV) correction,^{60–62,68} i.e., a term of the form $an_0\Delta V + b$, where a and b are adjustable energetic parameters, n_0 denoting the water density. Truchon et al. have proposed very recently a rationalization of these PMV corrections using a physically motivated form of the factor a , but with yet an adjustable multiplicative parameter.⁶³

Toward similar goals, a molecular density functional theory (MDFT) approach to solvation has been introduced recently.^{47–55} It relies on the definition of a free-energy functional depending on the full six-dimensional position and orientation solvent density. In the so-called homogeneous reference fluid (HRF) approximation, the (unknown) excess free energy can be inferred from the angular-dependent direct correlation function of the bulk solvent, which can be predetermined from molecular simulations of the pure solvent.^{69,70} This is equivalent to a second-order Taylor expansion of the excess free-energy around the homogeneous liquid density. In a recent work,⁵⁴ we introduced an even simplified version of MDFT for water, that can be derived rigorously for simple point charge representations of water such as SPC or TIP4P, involving a single Lennard-Jones interaction site and distributed partial charges. In that case we showed that the functional can be expressed in terms of the particle density $n(\mathbf{r})$ and site-distributed polarization density $\mathbf{P}(\mathbf{r})$, and it requires as input three simple bulk physical properties of water, namely the density structure factor, and the k -dependent longitudinal and transverse dielectric susceptibilities. Those quantities can be inferred from experiments, or from molecular dynamics simulations of the selected point-charge model in bulk conditions.^{71,72}

In refs 50, 51, and 53–55, MDFT was applied to the solvation structure and solvation thermodynamics of molecular solutes in acetonitrile and water. For water, it was shown that the inclusion of three-body corrections beyond the straight HRF approximation was necessary to accurately describe the hydration free-energy of hydrophobes,^{53,55} or the water structure around chemical groups giving rise to strong hydrogen bonding to the solvent.⁵⁴ In the same context, Wu and collaborators have recently applied their interaction-site DFT approach to the high-throughput prediction of the solvation free-energies of neutral organic molecules.⁷³ They showed that excellent correlation to experimental or MD results can be reached using an isotropic hard-sphere bridge corrections (as in refs 56–58 from the same group; see also refs 53 and 55). Here, keeping in mind all possible refinements, we go back to the straight HRF approximation for the same problem, and rather focus on the application of our theory to the computation of SFEs in the proper thermodynamic

ensemble corresponding to the experimental conditions. Doing so, we are able to draw a link between our theoretical approach and the empirical PMV corrections proposed in 3D-RISM calculations, since the HRF approximation in classical DFT is equivalent to the HNC approximation in integral equation theories.

Sketch of the Theory. In molecular density functional theory, the solvent molecules are considered as rigid entities with position \mathbf{r} and orientation Ω (in terms of three Euler angles θ, ϕ, ψ) and are described by an atomistic force field. The solute, described within the same atomistic force field as a collection of Lennard-Jones sites carrying partial charges, creates at each point in the solvent an external microscopic potential $v(\mathbf{r}, \Omega)$. The system is then characterized by the position and orientation-dependent inhomogeneous solvent density $\rho(\mathbf{r}, \Omega)$ and by a free-energy functional $\mathcal{F}[\rho] \equiv \mathcal{F}[\rho(\mathbf{r}, \Omega)]$, which can be written as¹⁶

$$\mathcal{F}[\rho] = kT \int [\rho(1) \ln(\Lambda_{\text{rot}} \Lambda^3 \rho(1)) - \rho(1)] d1 + \int \rho(1) v(1) d1 + \mathcal{F}^{\text{exc}}[\rho] \quad (1)$$

In short notations, (1) stands for (\mathbf{r}_1, Ω_1) , and $d1 = d\mathbf{r}_1 d\Omega_1$. The first term is the ideal free-energy, with Λ being the de Broglie thermal wavelength. With respect to the standard expression for isotropic particles,^{16,27,28} the additional term $\Lambda_{\text{rot}} = (2\pi\hbar)^{3/2} (J_x J_y J_z)^{-1/2} kT^{-3/2}$, where J_x, J_y , and J_z are moments of inertia of the molecule about the principal axes, accounts for the inclusion of the orientational degrees of freedom.⁷⁴

$\mathcal{F}^{\text{exc}}[\rho]$ is the excess free energy functional, which accounts for particle effective interactions in the liquid. In the HRF approximation,^{47,48} the excess free energy functional is represented by the first two terms of the Taylor series expansion around the homogeneous liquid state at the density $\rho_0 = n_0/8\pi^2$ (n_0 the particle number density), i.e.,

$$\mathcal{F}^{\text{exc}}[\rho] = \mathcal{F}^{\text{exc}}[\rho_0] + \int \left. \frac{\delta \mathcal{F}^{\text{exc}}}{\delta \rho(1)} \right|_{\rho_0} \Delta \rho(1) d1 + \frac{1}{2} \int \Delta \rho(1) \left. \frac{\delta^2 \mathcal{F}^{\text{exc}}}{\delta \rho(1) \delta \rho(2)} \right|_{\rho_0} \Delta \rho(2) d1 d2 \quad (2)$$

where $\Delta \rho(1) \equiv \rho(1) - \rho_0$, and by definition, $\delta^2 \mathcal{F}^{\text{exc}} / \delta \rho(1) \delta \rho(2) |_{\rho_0} \equiv -kT c(12)$ where $c(12)$ is the angular dependent two-particle direct correlation function of the pure solvent. The HRF approximation can be shown to be equivalent to the HNC approximation in integral equations. This can be most easily realized when the solute is itself a solvent molecule, the so-called test particle limit (or Percus trick).¹⁶

The correct thermodynamic ensemble to be considered in classical DFT is the grand-canonical ensemble in which the chemical potential of the solvent, μ_0 , is imposed. One thus has to deal with the grand-potential

$$\Theta[\rho] = \mathcal{F}[\rho] - \mu_0 \int \rho(1) d1 \quad (3)$$

The value of the chemical potential is imposed, for example, by direct contact with a huge reservoir at constant density ρ_0 . The relation between μ_0 and ρ_0 is obtained from the requirement that, in the absence of external perturbation, the density in the

system should be the uniform density ρ_0 , i.e., $\delta\Theta/\delta\rho(1)|_{\rho_0} = 0$, yielding

$$\mu_0 = \mu_0^{\text{id}} + \mu_0^{\text{exc}} = k_B T \ln \Lambda_{\text{rot}} \Lambda^3 \rho_0 + \left. \frac{\delta \mathcal{F}^{\text{exc}}}{\delta \rho(1)} \right|_{\rho_0} \quad (4)$$

$\delta \mathcal{F}^{\text{exc}}/\delta \rho(1)$ is here independent of the particle coordinates due to homogeneity of the fluid in the absence of the external potential.

For a given solute creating a potential $v(1)$, the grand-canonical solvation free-energy is obtained by minimizing the functional $\Delta\Theta[\rho] = \Theta[\rho] - \Theta[\rho_0]$, which, according to 1–4 amounts to the following expression that we used in all of our previous works; see Supporting Information for derivation.

$$\Delta\Theta[\rho] = kT \int \left(\rho(1) \ln \left(\frac{\rho(1)}{\rho_0} \right) - \Delta\rho(1) \right) d1 + \int \rho(1) v(1) d1 - \frac{kT}{2} \int \Delta\rho(1) c(12) \Delta\rho(2) d1 d2 \quad (5)$$

Such functional form insures that $\rho(\mathbf{r}, \Omega) = \rho_0$ far from the solute where $v(\mathbf{r}, \Omega) = 0$. Its minimization yields the inhomogeneous equilibrium density of the solvent in the presence of the solute and the solute grand-canonical solvation free-energy, $\Delta\Theta_{\text{MDFT}}$. The latter is evaluated with respect to the homogeneous fluid at the same chemical potential μ_0 (thus staying all the way in contact with the reservoir at constant density ρ_0) and at the same constant volume V . This corresponds to the transition between state 1 and state 2 in Figure 1. In the initial state, the system contains $N + \Delta N =$

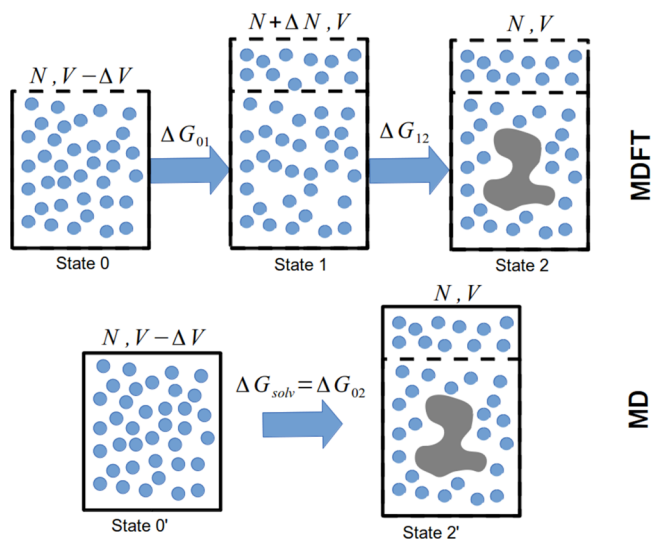


Figure 1. Thermodynamic scheme for the computation of the solvation free energy using the MDFT in the grand-canonical ensemble (top) or the molecular dynamics free energy perturbation method in the isobaric-isotherm ensemble (bottom). In the thermodynamic limit, states 0 and 0' and states 2 and 2' are equivalent, which motivates eqs 11 and 16 in the text.

$\int_V n_0 d\mathbf{r} = n_0 V$, whereas in the final one it contains $N = \int_V d\mathbf{r} n(\mathbf{r})$, where the number density is defined by $n(\mathbf{r}) = \int d\Omega \rho(\mathbf{r}, \Omega)$.

For a given solute model, this solvation free-energy should be compared to either the known experimental values, or to the results of explicit molecular simulations, both generally determined in the isobaric-isotherm ensemble with a constant

number of solvent molecules, N , and a constant pressure, P . To be consistent between theoretical approaches, let us recall how free energies can be computed in simulations. There are several methods based on the MD or MC simulations for calculating the free energy differences between two given states. Commonly used are the free-energy perturbation,⁷⁵ thermodynamic integration^{3,76} and Bennett acceptance ratio^{77–79} methods. The common feature of all these methods is that in addition to the simulations in the initial and final states, one needs to perform the simulations in a series of intermediate states. In the case of free-energy perturbation calculations, the following standard scheme may be used, as in ref 6: A cubic box is considered, the solute placed at the center, and the remaining space is filled with solvent particles, which amount to a fixed number N ; the simulation box volume is further released to accommodate for the imposed pressure. We denote as V the volume of the box after the relaxation; this corresponds to state 2' in Figure 1. The solute–solvent interactions are then progressively turned off, and the corresponding thermodynamic work is estimated. The system comes to state 0' in Figure 1, which corresponds to the uniform fluid in a volume $V - \Delta V$, with a homogeneous density $n_0 = N/(V - \Delta V)$ corresponding to that of the chosen solvent model. The free-energy of this transformation is just the inverse of the solute Gibbs SFE, ΔG_{solv} , to be compared with the experimental value.

It is clear then from this overall scheme that the MDFT solvation process should be evaluated using the same reference state, the uniform fluid of density n_0 in a volume $V - \Delta V$, state 0 in Figure 1, which is identical to state 0' in the thermodynamic limit with negligible particle number and volume fluctuations. To be compared with ΔG_{solv} , the free-energy difference computed by minimization, ΔG_{12} , should be corrected by the free energy difference between state 1 and 0 in Figure 1, ΔG_{01} , involving a volume change from $V - \Delta V$ to V at constant density, i.e.,

$$\Delta G_{\text{solv}} = \Delta G_{02} = \Delta G_{01} + \Delta G_{12} \quad (6)$$

This expression can be rewritten in terms of Helmholtz free energy

$$\Delta G_{\text{solv}} = \Delta F_{01} + \Delta F_{12} - W_{01} - W_{12} = \Delta F_{01} + \Delta F_{12} \quad (7)$$

where ΔF_{01} and ΔF_{12} are Helmholtz free energy changes and W_{01} and W_{02} are the pressure mechanical works of the system in the transitions $0 \rightarrow 1$ and $1 \rightarrow 2$, respectively. The second equality stems from the fact that the pressure works exactly compensate between the solvent expansion in $0 \rightarrow 1$ and its compression by the solute insertion in $1 \rightarrow 2$. See the Supporting Information for complete proof. As detailed there too, injection of the zero density $\rho = 0$ in eq 2 with the condition that $\mathcal{F}_{\text{exc}}[\rho = 0] = 0$, and use of eqs 1–4 gives access to the value of the Helmholtz free energy in the volume V at constant, uniform position and orientation density ρ_0

$$F_V[\rho_0] = -P_0 V + \mu_0 N_0 = - \left(n_0 kT - \frac{kT}{2} n_0^2 \hat{c}_s(k=0) \right) V + \mu_0 N_0 \quad (8)$$

equalities that defines the homogeneous pressure P_0 , and where $N_0 = n_0 V$. $c_s(r_{12}) = \int d\Omega_1 d\Omega_2 c(\mathbf{r}_{12}, \Omega_1, \Omega_2)$ represents the spherical component of the solvent direct correlation function, and $\hat{c}_s(k=0) \equiv \int c_s(|\mathbf{r}|) d\mathbf{r}$. Obviously, the corresponding Gibbs free energy is given by $G_V[\rho_0] = \mu_0 N_0$. The above equation leads to

$$\Delta F_{01} = \mu_0 \Delta N - n_0 kT \Delta V + \frac{kT}{2} n_0^2 \hat{c}_S(k=0) \Delta V \quad (9)$$

Furthermore, going from the grand-canonical to canonical ensemble yields

$$\Delta F_{12} = \Delta \Theta_{\text{MDFT}} + \mu_0 (-\Delta N) \quad (10)$$

and we finally get using eqs 6 and 7

$$\Delta G_{\text{solv}} = \Delta \Theta_{\text{MDFT}} - n_0 kT \Delta V + \frac{kT}{2} n_0^2 \hat{c}_S(k=0) \Delta V \quad (11)$$

One can easily relate the volume increase ΔV in $0 \rightarrow 1$ to the particle number variation in $1 \rightarrow 2$, $\Delta N = N - N_0$, i.e.,

$$\Delta V = -\frac{1}{n_0} \Delta N = \frac{1}{n_0} (N_0 - \int d\mathbf{r} n(\mathbf{r}_1)) \quad (12)$$

This defines ΔV as the *partial molar volume* of the solute at infinite dilution in the considered solvent.

We note that eq 11 is only valid for the case when the solute has a fixed position and the bulk density is kept unchanged in the process $0 \rightarrow 1 \rightarrow 2$. However, in experiments, and in most simulations, the solutes are not fixed and they can be considered as forming a homogeneous solution (at infinite dilution) with the solvent. This fact does not change the energy itself, but it does affect the chemical potential of water.

It can be easily realized that if the solute is released and the whole volume is accessible to the solvent, its ideal chemical potential becomes

$$\mu_2^{\text{id}} = kT \ln \Lambda^3 \frac{\Lambda_{\text{rot}} N}{\Phi V} \neq kT \ln \Lambda^3 \frac{\Lambda_{\text{rot}}}{\Phi} \frac{N}{V - \Delta V} = \mu_0^{\text{id}} \quad (13)$$

whereas the excess chemical potential is unaffected (here $\Phi = \int d\Omega = 8\pi^2$). Along this line, since the Gibbs free energy in state 0 is $G_0 = \mu_0 N$, the Gibbs free energy in state 2 can be written as

$$\begin{aligned} G_2 &= \Delta G_{\text{solv}} + \mu_0 N \\ &= \Delta G_{\text{solv}} + \mu_2 N + (\mu_0 - \mu_2) N \\ &= \Delta G_{\text{solv}} + \mu_2 N + n_0 \Delta V kT \end{aligned} \quad (14)$$

We have used the fact that $\mu_0^{\text{id}} - \mu_2^{\text{id}} = NkT \ln(V/(V - \Delta V)) \approx n_0 \Delta V kT$. The relation is strict when $V \rightarrow \infty$. On the other hand, the system with a released solute can be regarded as a homogeneous binary mixture, so that the following relation holds true:

$$G_2 = \sum_{i=1}^2 \mu_i N_i = \mu_{\text{solute}} + \mu_2 N \quad (15)$$

Up to the solute kinetic energy, which cancels out in free-energy differences regardless, the value of G_2 in eqs 14 and 15 should be the same, so that using eq 11

$$\mu_{\text{solute}} = \Delta \Theta_{\text{MDFT}} + \frac{kT}{2} n_0^2 \hat{c}_S(k=0) \Delta V \quad (16)$$

Note that the correction term can be recast in terms of the solvent isothermal compressibility using the relation $n_0 \hat{c}_S(k=0) = 1 - 1/n_0 kT \chi_T$.¹⁶

Equations 11 and 16 constitute the main results of this paper. The $n_0 kT \Delta V$ term that distinguishes those two equations is reminiscent of the standard state volume correction discussed,

e.g., in ref 80. Equation 16 is the one to be used when comparing the MDFT calculations to experiments, as will be done below.

All the above derivation stems naturally in a classical DFT context, in which the starting fundamental quantity is the free energy defined in the grand-canonical ensemble. As mentioned in the introduction, there have been much efforts in 3D-RISM approaches to correlate the deviation observed between the computed SFE and experimental or MD results to empirical partial molar volume corrections. Since such integral equation approaches are developed in a grand-canonical framework by imposing the solvent density far from the solute, it can be proved under certain restrictions that the partial molar volume term derived above should apply *mutatis-mutandis* to the 3D-RISM calculations. This requires one to extract the spherical component of direct correlation function, $\hat{c}_S(k)$, from a preliminary 1D-RISM calculation (see the Supporting Information). Our DFT approach thus gives a sound theoretical justification to the empirical corrections that were proposed to date and provides a theoretical value to the ΔV -coefficient that should be used. In a very recent publication, Truchon et al.⁶³ proposed a so-called cavity correction term that looks formally at first sight very similar to ours in eq 16. It is in fact quite different in nature: it involves the solute–solvent direct correlation function instead of the solvent–solvent in our formulation, and it requires an empirical multiplicative factor that is not present in our case. Moreover, as discussed above, our equation applies to a mobile solute. It is not clear how the two approaches can be related.

As an application of the MDFT formalism described above, and test of eq 16, we have computed the hydration free-energies of a series of 504 organic compounds, for which both experimental and molecular dynamics free-energy perturbation (MD-FEP) data are available from the work of Mobley et al.⁶ We used as input the structures and partial atomic charges from the Supporting Information of this paper. This data set was used recently as a test case for interaction-site DFT⁷³ and 3D-RISM⁶³ approaches.

Briefly, the procedure was as follows (with more details in the Supporting Information): Each molecule was placed at the center of a cubic box with dimension 40 Å, and MDFT minimizations were performed using the direct correlation function of TIP3P water⁸¹ (the model used in ref 6) and the functional form and algorithms described in ref 54. The position and orientation water density $\rho(\mathbf{r}, \Omega)$ was represented on a 3D grid with 100^3 points for positions, and an angular grid for orientations; we used a Lebedev grid of six orientations for the water molecular axis orientations (angles θ, ϕ), plus a two-angle regular grid for the rotation around the molecular axis (angle ψ from 0 to π). We used the functional and the minimization method described in ref 54. Each minimization takes 5–10 min on a single CPU core and requires ~2 Gb of memory. Eight out of the 504 molecules turned out to give divergent results and were discarded from the statistics. This failure is attributed to the shortcomings of the HRF approximation for molecules with very high local field. This could be corrected by three-body correction terms in the functional, that we do not consider in this paper. All calculations below were organized with the MolDB workflow system.⁸² Statistical processing was performed with GNU Octave.⁸³

In Figure 2 the results of the MD simulations and of the MDFT calculations, using $\Delta G_{\text{MDFT}} = \mu_{\text{solute}}$ in eq 16, are

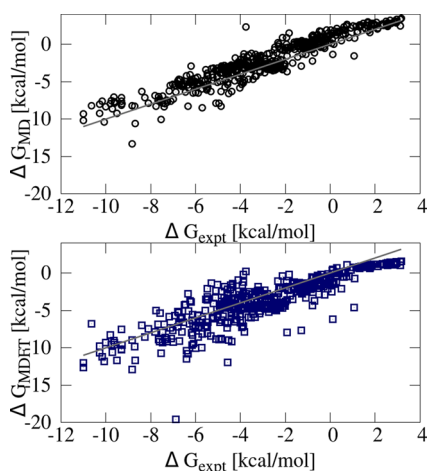


Figure 2. MDFT results, converted to the *NPT* ensemble (bottom) and MD results (top) correlated to experimental results.

compared to the experimental solvation free energies. Different water model were investigated (see Supporting Information for details); we display here the results for the TIP3P model, consistent with the MD simulations. We observe an evident correlation of the MDFT calculations with experimental data (correlation coefficient $r \approx 0.9$). The root-mean-square deviation (RMSD) of the MDFT results is 1.8 kcal/mol, which is 0.5 kcal/mol larger than that of the MD simulations (1.25 kcal/mol). The higher dispersion of the results ($\sigma_{\text{MDFT}} = 1.6$ kcal/mol instead of $\sigma_{\text{MD}} = 1.1$ kcal/mol) points, again, to the shortcomings of the HRF approximation; see Supporting Information for more details. It should be noted also that employing the fixed-solute ensemble correction of eq 11 instead of eq 16 for a free solute, and despite a relative difference of only $\sim 10\%$, leads to significantly worse results. Referring to the proper standard state therefore appears to be essential.

For comparison, 3D-RISM calculations were also carried out for the same set of molecules. We employed the multigrid 3D-RISM method of Sergiievsky et al.,⁶⁵ that is available online.⁸⁴ The calculations were performed on a rectangular grid with a step size of 0.2 Å. The buffer (minimal distance from the solute to the boundary of the calculation box) was set to 15 Å. As conventionally done to avoid charge superposition effects, we used a modified SPC-E model (MSPC-E) with additional LJ parameters for the hydrogens ($\sigma_{\text{H}} = 1.1$ Å, $\epsilon_{\text{H}} = 0.046$ kcal/mol). In the calculations we used the total site–site correlation functions of water calculated previously by Fedorov and Kornyshev with the dielectrically consistent RISM technique.⁸⁵ To improve the convergence of the algorithm, we have separated the short- and long-range parts of the potentials and have treated them separately by using the Ng procedure.⁸⁶

The HNC closure was used in the calculations. At the end of the calculation, we invoked eq 16 to convert the results to the *NPT* ensemble. The required function $c_s(r)$ was in this case expressed as a sum of site–site functions (consistent with the RISM assumptions). The same definition of the PMV as in eq 12 was used, with the water density replaced by the oxygen density.

The 3D-RISM calculations converged for 439 of the 504 molecules. This rather high divergence rate points to the known divergences of the pure HNC closure, and it can be normally improved by using of the Kovalenko–Hirata (KH) closure.

However, we found it more consistent here to stick to the HNC closure, which is fully compatible with the HRF approximation used for DFT. These 439 molecules were used for analysis. The results are compared to the experimental data in Figure 3.

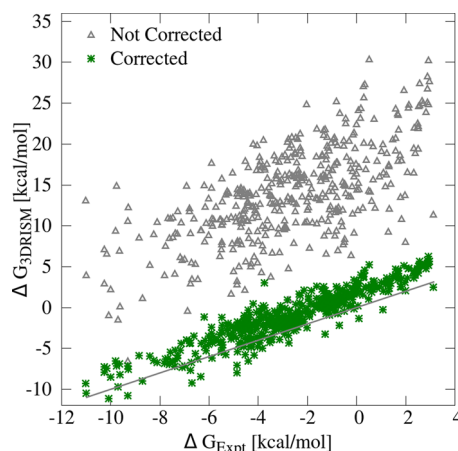


Figure 3. 3D-RISM solvation free energies with and without ensemble correction compared to experimental results.

We note first that the results without the ensemble correction of eq 16 are very dispersed and poorly correlated to the experimental results. This is consistent with previous findings.^{67,68} It is also consistent with what is obtained with MDFT when the ensemble correction is omitted (see Figure 1 of the Supporting Information); the rigorous DFT approach tells us, however, that this correction term has to be there. The RMSD of the 3D-RISM calculations appears slightly higher than that in MDFT (2.39 kcal/mol). We note, however, that most of this error is due to the systematic error ($M \approx 1.9$ kcal/mol), and that the standard deviation is close to that obtained with MDFT ($\sigma_{\text{3D-RISM}} = 1.45$ kcal/mol). The relatively big systematic shift of the 3D-RISM results (the factor b in the empirical correction of Palmer et al.⁶¹) can be explained by the imperfect solvent properties used in the calculations (extracted from a preliminary RISM study of the bulk solvent) and, obviously, by the shortcomings of the RISM approximations. For the MSPC-E water model, we find that the factor $a = (kT/2)n_0\hat{c}_s(k=0)$, multiplying the partial molar volume term $n_0\Delta V$ in eq 14, amounts to -3.26 kcal/mol, compared to the coefficient $a = -3.31$ kcal/mol determined empirically by Palmer et al.⁶¹ for the same water model. See the Supporting Information for all the details.

In conclusion, we have shown that the computation of solvation free energy with classical DFT, moreover in the framework of the HRF approximation (equivalent to the HNC approximation in integrals equation approaches), should include a partial molar volume correction accounting for the change of ensemble from μVT to *NPT*. The proportionality factor is found to depend on $\hat{c}_s(0)$, the value of the Fourier-transformed isotropic direct correlation function at $k = 0$. This PMV correction was shown to be directly extendable to the 3D-RISM theory, with a $\hat{c}_s(k)$ extracted from a consistent 1D-RISM description of the solvent. Although of related appearance, it has a different nature than the one proposed recently by Truchon et al.⁶³

Using this PMV correction, we have computed the solvation free-energies for the data set of 504 organic molecules studied

by Mobley et al.⁶ using both MDFT and 3D-RISM with an HNC rather than KH closure. Since both methods rely on a related set of approximations, they are found to yield an accuracy that is similar compared to experimental results, and only slightly worse than that obtained with much more costly MD-FEP simulations. Similar, if not slightly better agreements were found for the same data set using interaction-site DFT with a hard-sphere bridge functional⁷³ or 3D-RISM with cavity corrections.⁶³ The agreement appears even significantly better in ref 63 for the nonpolar component of the free energy. In those previous studies, however, a single parameter was used to optimize the results (reference hard-sphere radius or multiplicative factor). In contrast, the present approach is completely parameter-free. Therefore, it inherits more visibly the effects of the approximations, but it stands as a better starting point to further improve the theory.

There is still much room and work to be done to improve the applicability and accuracy of the liquid-state theoretical methods. Certain improvements should be common to DFT and RISM, such as accounting for solute flexibility, which is naturally incorporated in MD-FEP methods, or accounting for solvent and solute polarizability. Other improvements should go separately in each approach. In integral equations, it is desirable to improve upon the HNC or KH closures that are limits of the theory nowadays. In DFT, it has been shown that the free-energy functional can be substantially improved by adding three-body correction terms, either using a hard-core reference^{52,55} or accounting for the nonadditive character of H-bonding interactions.⁵⁰ We have to determine how those further corrections will add to the most basic one introduced in this paper: referring to the correct thermodynamic ensemble when comparing to experiment.

■ ASSOCIATED CONTENT

● Supporting Information

Grand potential with respect to uniform density; Gibbs free energy of the uniform fluid; pressure in the homogeneous reference fluid approximation; pressure of the inhomogeneous fluid; mechanical work of the solvent in the solvation process; energy components in different states; chemical potential of a non-fixed solute; equivalence of the free energy calculation in 3DRISM and MDFT; comparison of MDFT NPT and μVT results to the experimental ones; comparison of the theoretical and empirical corrections; test of the numerical errors associated with grid discretization; calculations of polar/nonpolar components with different water models; and list of compounds used in the calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

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