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Octanol–Water Partition Coefficient from 3D-RISM-KH Molecular Theory of Solvation with Partial Molar Volume Correction

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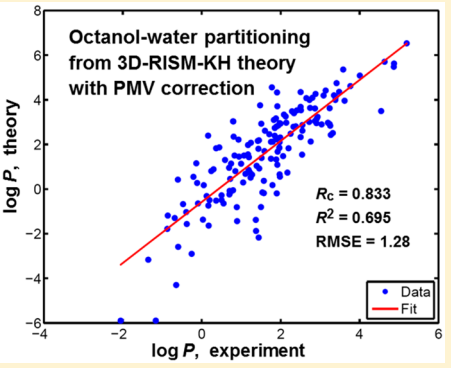
Supporting Information

ABSTRACT: The octanol–water partition coefficient is an important physical–chemical characteristic widely used to describe hydrophobic/hydrophilic properties of chemical compounds. The partition coefficient is related to the transfer free energy of a compound from water to octanol. Here, we introduce a new protocol for prediction of the partition coefficient based on the statistical-mechanical, 3D-RISM-KH molecular theory of solvation. It was shown recently that with the compound–solvent correlation functions obtained from the 3D-RISM-KH molecular theory of solvation, the free energy functional supplemented with the correction linearly related to the partial molar volume obtained from the Kirkwood–Buff/3D-RISM theory, also called the "universal correction" (UC), provides accurate prediction of the hydration free energy of small compounds, compared to explicit solvent molecular dynamics [Palmer, D. S.; et al. *J. Phys.: Condens. Matter* **2010**, *22*, 492101]. Here we report that with the UC reparametrized accordingly this theory also provides an excellent agreement with the experimental data for the solvation free energy in nonpolar solvent (1-octanol) and so accurately predicts the octanol–water partition coefficient. The performance of the Kovalenko–Hirata (KH) and Gaussian fluctuation (GF) functionals of the solvation free energy, with and without UC, is tested on a large library of small compounds with diverse functional groups. The best agreement with the experimental data for octanol–water partition coefficients is obtained with the KH-UC solvation free energy functional.



INTRODUCTION

The octanol–water partition coefficient characterizes hydrophobic (lipophilic)/hydrophilic properties of chemical compounds.[1,2] For dilute solutions it is defined as the ratio of molar concentrations of a compound in octanol and water, $P_{o/w} = [C_o]/[C_w]$. In practice, it is more common to use the logarithm of the molar concentration ratio because of the large range of changes of the partition coefficient. As the equilibrium constant, the partition coefficient is directly related to the transfer free energy of a compound from water (polar solvent) to octanol (nonpolar solvent):

$$-k_B T \log P_{o/w} = \Delta G_o - \Delta G_w \quad (1)$$

The partition coefficient is one of the most important physicochemical characteristics used in pharmacology, environmental studies, and food industry. In pharmacology, the partition coefficient is used to predict distribution of drugs within the body. It is a crucial parameter that defines drug-likeness of a compound. The partition coefficient, along with other descriptors, defines the efficiency of a drug crossing the blood brain barrier and reaching the central nervous system.[3]

Because of the practical importance, many theoretical methods have been developed to predict the partition coefficient.[4−13] These methods range from the phenomenological approaches based on different descriptors such as quantitative structure–activity relationship (QSAR) models[8−10,14,15] to the sophisticated approaches based on first-principles calculations of the transfer free energy between different solvents, including explicit solvent molecular dynamics (MD) simulations[12,13] and calculations based on different solvation models with account for quantum-mechanical effects.[16−24] While the first group of approaches provides fast prediction of the partition coefficient, which is of paramount importance for virtual screening of large sets of compounds (e.g., drug candidates in rational drug design), the first-principles calculations provide a more reliable prediction of the partition coefficient (especially beyond the scope of a training set used to parametrize phenomenological models) which is transferable in some cases. This second group comprises a large number of approaches mostly based on continuum solvation. This includes the molecular mechanics point-charge based Poisson–Boltzmann/solvent area (PBSA) solvation model[16,17] and its approximation by the generalized Born/solvent area (GBSA) solvation model[18,19] as well as solvation models developed in the context of quantum-mechanical (QM) self-consistent reaction field calculations such as the conductor-like

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screening model (COSMO) and conductor-like screening model for real solvent (COSMO-RS),[20] the Miertus–Scrocco–Tomasi (MST) solvation model,[21,22] and the SM8, SM8AD, and SMD solvation models by Truhlar and co-workers.[23,24] The GBSA/PBSA methods are commonly used for postprocessing of ensembles of conformations generated in molecular dynamics (MD) simulations, which can be important for large flexible compounds. Note that QM based solvation model calculations require significant computational resources, which is frequently unfeasible for screening large libraries of compounds in drug design applications.

A major drawback of the continuous solvation methods is their inability to treat specific solute–solvent and solvent–solvent interactions such as hydrogen bonding, and their nontransferability (reparametrization is required for a new solvent composition and possibly thermodynamic conditions). In principle, these difficulties can be avoided by using all-atom explicit solvent MD simulations. However, such simulations are computationally demanding and cannot be used in most practical applications such as virtual screening in rational drug design.

As alternative to explicit solvent MD simulations is the statistical-mechanical method of integral equation theory of molecular liquids in different versions[25] that can be used to calculate the solvation free energy as well as the solvation structure. In the context of prediction of the partition coefficient, the performance of the self-consistent field (SCF) coupling of the reference interaction site model (RISM) molecular theory of solvation and the Hartree–Fock method (RISM-SCF) was assessed recently for 16 organic compounds in water and chloroform.[6]

Over the past decade, the statistical-mechanical, three-dimensional reference interaction site model with the Kovalenko–Hirata closure relation (3D-RISM-KH molecular theory of solvation)[26,27,30] has been successfully employed to study a wide range of problems, from chemistry in solution in a wide range of thermodynamic conditions[26−34] to functioning of biomolecular systems under physiological conditions.[29,31,35−55] Importantly, the 3D-RISM-KH theory provides a quantitative description of the solvation thermodynamics in various solvents, both polar and nonpolar, at different solvent compositions and thermodynamic states. It accounts for the specific solute–solvent and solvent–solvent interactions such as hydrogen bonding and solvation entropic effects related to hydrophobicity. Recently, it was shown that the 3D-RISM-KH theory supplemented with the solvation free energy correction based on the partial molar volume of the compound (also obtained from the 3D-RISM-KH theory) provides the hydration free energy for a large diverse set of compounds with an accuracy comparable to that of much more computationally demanding explicit solvent MD.[55] To the best of our knowledge, there were no systematic studies of the performance of the 3D-RISM-KH theory for prediction of the solvation free energy on a large set of compounds in nonpolar solvents.

The goal of the present study is to demonstrate the predictive capability of the 3D-RISM-KH theory for calculation of the transfer free energy between water and octanol (the octanol–water partition coefficient). This is the first study of the performance of the 3D-RISM-KH theory to predict the solvation free energy in a nonpolar solvent and the octanol–water partition coefficient for a large diverse set of compounds. We compare the 3D-RISM-KH results with the experimental data and with those obtained from the GBSA continuum solvation model.

COMPUTATIONAL METHODS

3D-RISM-KH Molecular Theory of Solvation. The 3D-RISM-KH theory is based on the rigorous statistical-mechanical foundation and provides comprehensive information on microscopic solvation structure and thermodynamics in complex solvents. The 3D-RISM-KH theory can accurately and efficiently predict the solvation free energy ΔG_{solv} for water and octanol and thus log $P_{o/w}$ for all library compounds.

The solvation structure of a solute macromolecule can be described by the probability density $\rho_\gamma g_\gamma(\mathbf{r})$ of finding atomic site γ of a solvent molecule at 3D space position $\mathbf{r}$ around the solute. Here, ρ_γ is the number density of bulk solvent, and $g_\gamma(\mathbf{r})$ is the 3D density distribution function. The latter describes the solvent density enhancement when $g_\gamma(\mathbf{r}) > 1$ or depletion when $g_\gamma(\mathbf{r}) < 1$ relative to the average bulk density (where $g_\gamma(\mathbf{r}) \to 1$).

The distribution functions can be obtained from the 3D-RISM integral equation[26,29,56−59]

$$h_\gamma(\mathbf{r}) = \sum_\alpha \int d\mathbf{r}' c_\alpha(\mathbf{r} - \mathbf{r}')\chi_{\alpha\gamma}(r') \tag{2}$$

where $h_\gamma(\mathbf{r})$ and $c_\gamma(\mathbf{r})$ are the 3D total and direct correlation functions for solvent site γ, respectively, and the summation runs over all interaction sites on all solvent species. The 3D total correlation function has the meaning of normalized density correlation and is related to the 3D density distribution function as $h_\gamma(\mathbf{r}) = g_\gamma(\mathbf{r}) - 1$.[25] The 3D direct correlation function is formally defined as a solution to eq 2. Outside the solute repulsive core, it has the asymptotics proportional to the 3D solute–solvent site interaction potential, $c_\gamma(\mathbf{r}) \sim -u_\gamma(\mathbf{r})/(k_BT)$, where k_BT is the Boltzmann factor times the solvent temperature. Inside the repulsive core, $c_\gamma(\mathbf{r})$ is related to the solvation free energy. The radially dependent site–site susceptibility of solvent $\chi_{\alpha\gamma}(r)$ is an input to the 3D-RISM integral eq 2 and can be obtained from the dielectrically consistent RISM theory for site–site radial correlation functions (DRISM).[60,61]

To be solved, the 3D-RISM integral eq 2 for the 3D total and direct correlation functions has to be complemented with another relation called a closure which also involves the 3D interaction potential $u_\gamma(\mathbf{r})$ between the whole solute molecule and solvent site γ specified with a molecular force field. The exact closure has a nonlocal functional form that can be presented as an infinite diagrammatic series in terms of multiple integrals of the total correlation function.[25] However, it is computationally intractable and in practice is replaced with amenable approximations which should analytically ensure asymptotics of the correlation functions and features of the solvation structure and thermodynamics to properly represent the solvation physics. In the current study, we use the closure relation proposed by Kovalenko and Hirata (KH approximation).[26,29,31] It provides an accurate description of the solvation structure and thermodynamics in biomolecular systems[29,31,35−55] as well as various association effects in complex liquids and electrolyte solutions.[26−34] The 3D version of the KH closure reads

$$g_\gamma(\mathbf{r}) = \begin{cases} \exp(-u_\gamma(\mathbf{r})/(k_BT) + h_\gamma(\mathbf{r}) - c_\gamma(\mathbf{r})) & \text{for } g_\gamma(\mathbf{r}) \le 1 \\ 1 - u_\gamma(\mathbf{r})/(k_BT) + h_\gamma(\mathbf{r}) - c_\gamma(\mathbf{r}) & \text{for } g_\gamma(\mathbf{r}) > 1 \end{cases} \tag{3}$$

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It couples in a nontrivial way the hypernetted chain (HNC) and mean spherical approximation (MSA) closures.[25] The former is applied to the spatial regions of solvent density depletion $g_\gamma(\mathbf{r}) < 1$, including the repulsive core of the solute−solvent interactions, and the latter to the regions of solvent density enrichment $g_\gamma(\mathbf{r}) > 1$, such as association peaks, while keeping the right asymptotics of $c_\gamma(\mathbf{r})$ peculiar in both HNC and MSA. (The distribution function and its first derivative are continuous at the joint boundary $g_\gamma(\mathbf{r}) = 1$ by construct.)

The site−site susceptibility of pure solvent breaks up into the intra- and intermolecular terms

$$\chi_{\alpha\gamma}(r) = \omega_{\alpha\gamma}(r) + \rho_\alpha h_{\alpha\gamma}(r) \tag{4}$$

where the intramolecular correlation function $\omega_{\alpha\gamma}(r) = \delta_{\alpha\gamma}\delta(r) + (1 - \delta_{\alpha\gamma})\delta(r - l_{\alpha\gamma})/(4\pi l_{\alpha\gamma}^2)$ represents the geometry of solvent molecules with site−site separations $l_{\alpha\gamma}$ specified by the molecular force field, and $h_{\alpha\gamma}(r)$ is the radial total correlation function between solvent sites α and γ. Prior 3D-RISM-KH calculations, $h_{\alpha\gamma}(r)$ are obtained from the DRISM theory[60,61] with the KH closure (DRISM-KH approach),[29,34] for all species of solvent which may include ions, cosolvent, and ligands at a given concentration.

The solvation free energy ΔG of a solute in (multicomponent) solvent can be obtained in a closed analytical form by analytically performing Kirkwood's thermodynamic integration by using the 3D-RISM-KH integral eqs 2 and 3:[26,29]

$$\Delta G_{\mathrm{KH}} = k_\mathrm{B}T \sum_\gamma \rho_\gamma \int \mathrm{d}\mathbf{r}\left[\frac{1}{2}h_\gamma^2(\mathbf{r})\Theta(-h_\gamma(\mathbf{r})) - \frac{1}{2}h_\gamma(\mathbf{r})c_\gamma(\mathbf{r}) - c_\gamma(\mathbf{r})\right] \tag{5}$$

where $\Theta(x)$ is the Heaviside step function. To properly describe the electrostatic interactions in solution with polar molecular and ionic species, the electrostatic asymptotics of all the correlation functions (both the 3D and radial ones) are separated out and treated analytically in the convolution of both the 3D-RISM-KH and DRISM-KH integral equations, as well as in the integral for the solvation free energy (5).[29,30,34]

Further to the solvation free energy, the 3D-RISM-KH theory also provides other thermodynamic functions in an analytical form, including the Kirkwood−Buff/3D-RISM expression for the partial molar volume (PMV) of the solute macro molecule expressed in terms of the 3D direct correlation function[35−37,54]

$$\bar{V} = k_\mathrm{B}T\chi_T\left(1 - \sum_\gamma \rho_\gamma \int \mathrm{d}\mathbf{r}\, c_\gamma(\mathbf{r})\right) \tag{6}$$

where χ_T is the isothermal compressibility of pure solvent which is obtained from DRISM-KH calculations[26] along with the solvent susceptibility.

The solvation free energy expression given by eq 5 is directly related to the functional form of the KH closure to the 3D-RISM-KH integral equations, eqs 2 and 3. It can be derived by the analytical integration of the thermodynamics charging formula for the solvation free energy with the KH expression (3) for the 3D distribution function. In practice, the 3D-RISM-KH theory can be used with a different functional of the solvation free energy. In particular, Chandler and co-workers derived the so-called Gaussian fluctuation (GF) free energy functional based on the assumption of Gaussian fluctuations for the solvent, which is similar to the HNC functional form but without the h_γ^2 term.[62,63] The solvation free energy calculated from the GF functional using the site−site correlation functions obtained from the RISM-HNC integral equations was generally in reasonable agreement with experiment and in better agreement than those obtained with the HNC functional.[64,65] In the context of 3D-RISM theory, the GF functional reads[45,46]

$$\Delta G_{\mathrm{GF}} = k_\mathrm{B}T \sum_\gamma \rho_\gamma \int \mathrm{d}\mathbf{r}\left[-\frac{1}{2}h_\gamma(\mathbf{r})c_\gamma(\mathbf{r}) - c_\gamma(\mathbf{r})\right] \tag{7}$$

The GF functional using the 3D correlation functions obtained from the 3D-RISM-KH theory could provide the hydration free energy in better agreement with experiment in some cases.[46,55]

Recently, Fedorov and co-workers[55] found that the correction to the solvation free energy functional constructed as a linear function of the PMV calculated in the form (6) using the correlation functions from the 3D-RISM-KH theory

$$\Delta G_{\mathrm{UC}} = \Delta G + \alpha(\rho\bar{V}) + \beta \tag{8}$$

significantly improves the agreement between the calculated and experimental data for hydration free energies of a set of small neutral compounds. The constants α and β in eq 8 were obtained from the linear regression analysis. This partial molar volume correction technique, also called the "universal correction" (UC), was parametrized with the GF functional on a training set of 65 molecules and tested on a set of 120 molecules.[55] Recently, the UC correction to the KH functional has also been parametrized for the hydration free energy on a large set of 504 organic molecules.[66] In the same study, another correction to the KH functional based on the Ng modified free energy functional[67] was introduced and demonstrated to accurately predict the hydration free energy of the same set of 504 compounds.[66]

In the current study, we assess the performance of different functionals and corrections to predict the solvation free energies of a large set of compounds in nonpolar solvent (1-octanol) as well as in water. This includes the KH functional (5) and the GF one (7), both with and without the UC. Below we shall call the UC form (8), depending on the free energy functional used, as the KH or GF functional with the UC (KH-UC or GF-UC).

Library of Compounds. To compare theoretical predictions on the water−octanol transfer free energy, a library of compounds with available experimental data on both hydration free energies and solvation free energies in octanol is needed. In this study, we adopt a diverse library of small compounds containing a large set of molecules (172 molecules) which was used in the previous theoretical studies on the hydration free energies and partition coefficients.[5,7]

Some molecules from this library have structural similarity with the proteins amino acid side chains and backbone, which is important for extending the current protocol to biomolecular systems. These include alkanes, aromatic hydrocarbons, nitrogen in heterocyclic compound, hydroxyl groups, carboxylic groups, amine groups, sulfur groups, and amide groups. The library also includes alkenes, alkynes, halogen compounds, ether, aldehydes, ketone, ester, amide, nitrile, and phosphor groups.

Structure Preparation and Force Field Parameters Used in Free Energy Calculations. The three-dimensional structures of 1-octanol as well as all library compounds were built with the Avogadro[68,69] and then optimized with the AMBER12 molecular dynamics package.[70] Energy minimization was performed with 1000 steepest descent steps followed with 4000 conjugate gradient minimization steps using the

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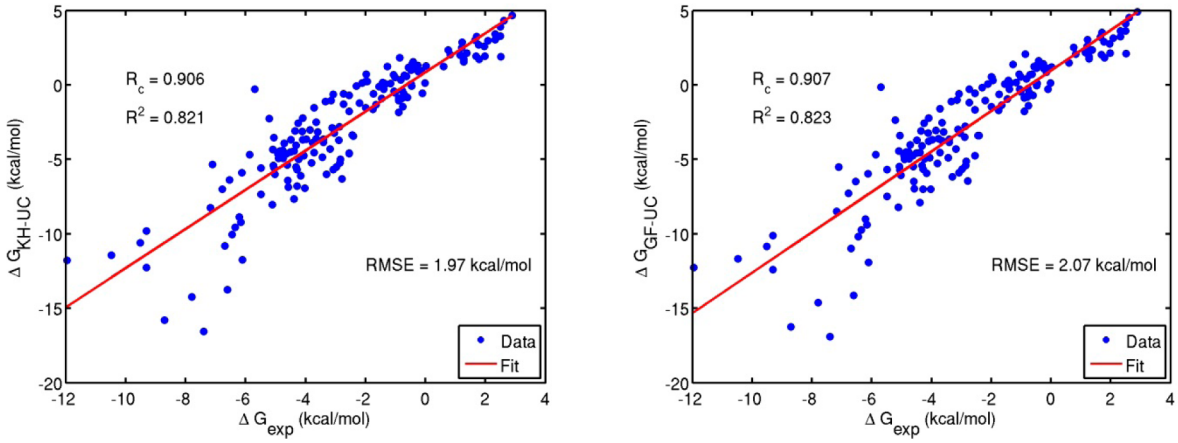

Figure 1. Hydration free energies obtained from the KH (left panel) and GF (right panel) free energy functionals with the UC using the correlation functions from the 3D-RISM-KH theory. A comparison against experimental data[5,7] for the library compounds.

generalized Born implicit solvation model (igb = 1). The dielectric constant was set to $\varepsilon = 78.5$ for water and $\varepsilon = 9.86$ for octanol. No periodic boundary was used, and the cutoff distance for nonbonded interactions was set to 999.9 Å. The van der Waals parameters for all library compounds and for 1-octanol were taken from the general Amber force field (gaff).[70,71] The atomic partial charges were calculated using the AM1-BCC method implemented in the Antechamber program from the Amber Tools 12 package.[72] The optimized structures were used in both the 3D-RISM-KH and GBSA calculations with the same force field parameters.

3D-RISM-KH Calculations. The 3D-RISM-KH integral equations (2) and (3) were solved on a uniform rectangular 3D grid of 128 × 128 × 128 points in a cubic box of size 64 × 64 × 64 Å^3 large enough to accommodate the compound molecule along with sufficient space of 2−3 solvation shells around it. The 3D-RISM-KH equations were converged to a relative root-mean-square tolerance of 10^{-4} adequate for free energy accuracy better than 0.1% by using the modified direct inversion in the iterative subspace (MDIIS) accelerated numerical solver.[27,29,30] It was shown that such a setup provides hydration structure of proteins very close to that obtained in explicit solvent MD simulations.[47] The site−site susceptibility functions of bulk solvent given by eq 4 were obtained from the DRISM-KH theory for both water and octanol solvents. The SPC/E water model[73] was used for the water solvent at temperature $T = 298.15$ K, density $\rho = 0.997$ g/cm^3, and dielectric constant $\varepsilon = 78.5$. The force field parameters for 1-octanol solvent molecules were assigned as discussed in the previous section. In the calculation of the bulk solvent susceptibility of octanol, the nonpolar hydrogens were merged with respective carbon atoms (similarly to procedures in constructing united atom force fields). The octanol solvent had temperature $T = 298.15$ K, density $\rho = 0.824$ g/cm^3, and dielectric constant $\varepsilon = 10.3$.

GBSA Calculations. GBSA calculations of the hydration free energy and the solvation free energy in octanol for the library compounds were performed with the *sander* program from the AMBER12 molecular dynamics package.[70] The protocol and the force field parameters used for structure optimization described in the previous subsection were employed for the free energy calculations as well.

RESULTS AND DISCUSSION

Hydration Free Energy from the 3D-RISM-KH Theory. There is a very good agreement between the experimental data and the hydration free energies for the library compounds obtained by converging the 3D-RISM-KH integral equations (2) and (3) for the 3D correlation functions of water solvent around a compound molecule which are then entered into the free energy functional, either the KH functional (5) or the GF one (7), and into the UC expression (8) added to each of the functionals (Figure 1). We note that the use of UC is crucial to obtain a consistent agreement with the experimental data for the hydration free energy (for the hydration free energy without UC, see Figure S1 of the Supporting Information). The linear coefficients in the UC expression (8) parametrized for the hydration free energy calculated with the KH and GF solvation free energy functionals are displayed in Table 1. Note that the UC coefficients appear different with the two functionals which give different hydration free energies with root-mean-squared errors (RMSEs) of 22.84 and 15.22 kcal/mol for KH and GF, respectively (see Figure S1 of the Supporting Information and Table 1). However, the corrected hydration free energies come out in good agreement with experiment for both the KH-UC and GF-UC functionals (Figure 1 and Table 1). The KH-UC functional provides marginally better results for RMSEs while GF-UC gives slightly better correlations between the calculated and the experimental

Table 1. Linear Coefficients in the Universal Correction (UC) (8) to the Kovalenko−Hirata (KH) and Gaussian Fluctuation (GF) Solvation Free Energy Functionals (5) and (7) for the Two Solvents[a]

functional	α (kcal/mol)	β (kcal/mol)	RMSE (kcal/mol) with UC (without UC)
		water	
KH	−4.58	0.340	1.975 (22.84)
GF	−3.16	0.894	2.07 (15.22)
		octanol	
KH	0.083	−0.939	1.03 (1.37)
GF	19.81	2.932	1.25 (5.08)

[a]The RMSE between the calculated solvation free energies (with and without UC) for the library compounds and experimental data[5,7] are shown for illustration.

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hydration free energies (1.975 kcal/mol and 0.905 for KH-UC, and 2.07 kcal/mol and 0.907 for GF-UC). The coefficient of determination from linear regression fit (R^2) is around 0.82 in both cases (Tables S1 and S2 in the Supporting Information). The accuracy of the solvation free energy obtained from the 3D-RISM-KH theory supplemented with UC in this way is comparable with the results of explicit solvent MD simulations.[55]

As noted in ref 55, the PMV term corrects for the overestimation of hydrophobicity by the KH, HNC, and GF solvation free energy functionals. The correction was introduced following the observation that the PMV strongly correlates with the difference between the calculated and experimental values the hydration free energy, rather than with the calculated or experimental values themselves (ref 55 and Figures S2 and S3 of the Supporting Information).

Solvation Free Energy in Octanol from the 3D-RISM-KH Theory. For the partition coefficient calculations, the solvation free energies of the compounds in octanol need to be predicted alone with their hydration free energies with comparable accuracy. The good performance of the 3D-RISM-KH theory in prediction of the solvation free energy of various molecular species in different nonpolar solvents was demonstrated previously.[32−34] Here, we assess the following four approaches to the solvation free energy: the KH and GF functionals, each with and without the UC. We compare the results of these calculations with experimental data for the present large set of diverse compounds.

First, we calculate the solvation free energies for the library compounds by entering the 3D correlation functions of octanol solvent around a compound molecule obtained from the 3D-RISM-KH integral equations (2) and (3) into the KH and GF solvation free energy functionals (5) and (7) without the UC (Figures S4 of Supporting Information). In contrast to the hydration free energy calculations, the KH functional provides an excellent agreement with the experimental data even without the UC (RMSE is 1.37 kcal/mol, the correlation coefficient is 0.897, and the coefficient of determination is 0.805). Interestingly, for the octanol solvent the KH functional performs much better than the GF one (RMSE is 5.08 kcal/mol, the correlation coefficient is 0.788, and the coefficient of determination is 0.621). It is worth noting that the GF functional without the UC performs better in hydration free energy calculations.

A considerably better performance of the 3D-RISM-KH theory with the KH free energy functional in the case of solvation in octanol compared to hydration can be explained by cancellation of errors in the calculation of the solvation structure. It is well-known that the 3D-RISM (as well as RISM) integral equation theory with the HNC closure relation considerably overestimates the hydration free energy of hydrophobic solutes. A part of this inconsistency is due to the shortcoming of the HNC closure overestimating the overlap of the repulsive core (usually from the Lennard-Jones potential) of the solute molecule with those of solvent molecules approaching it. This is typical of the NHC closure in any version (radial site−site, 3D site, or 6D molecular, as well as radial atomic) of integral equation theory of liquids and can be largely mitigated by introducing a bridge correction to the closure, for example, in the Verlet functional form for the solute atomic charges set to zero[74] or other forms and parametrizations obtained from an available accurate solution for a reference system.[25] The remaining major part of the hydration free energy inconsistency in the 3D-RISM-HNC theory comes from the overestimation of the entropy decrease (ordering) of water solvent in the hydrophobic hydration shell compared to bulk water.[75] With a local form of closures to RISM theory, this is related to the so-called issue of improper-diagram-related inconsistency of RISM treatment for auxiliary sites, that is, sites with small repulsive cores located inside larger repulsive cores. In the context of the water model, these are the positively charged hydrogen sites with no repulsive core located inside the negatively charged oxygen site with the spherical repulsive core that largely determines the entire molecular shape. As a remedy, a bridge correction adding the missing effective repulsion to solute−water correlations in the 3D-RISM-HNC equations was proposed in an empirical form optimized to reproduce the hydration free energy on a training set of compounds.[76] Alternatively, such a bridge correction was derived heuristically as an effective interaction obtained by averaging the repulsion between the hydrophobic solute and water solvent cores over solvent molecular orientations around each of its interaction sites weighted with the corresponding solvent site distribution functions $g_\gamma(\mathbf{r})$.[75] Notice also that such an empirically derived construct is related to the solvation entropy estimate in the form $-T\Delta S = k_B T \sum_\gamma \rho_\gamma \int d\mathbf{r}\, g_\gamma(\mathbf{r}) \ln g_\gamma(\mathbf{r})$. This repulsive bridge correction counters the overestimation of water ordering around a hydrophobic solute in the (3D-)RISM-HNC approach and thus refines the hydration free energy as well as its entropic component and provides their correct dependence on the hydrophobic solute size.[75] Almost the same overestimation of the hydrophobic hydration free energy is peculiar to the 3D-RISM-KH theory, too, as the KH closure (3) treats the solute−solvent repulsive core region in the HNC approximation. In fact, the use of the UC expression (8) for the hydration free energy[55] or the Ng-modified free energy functional for the hydration free energy[66] is similar to applying the repulsive bridge correction over the whole solvation shell which for a hydrophobic solute appears to be proportional to its PMV. As distinct from the case of hydration, for solvation in octanol the orientational averaging of the solute−solvent correlation functions applied within the 3D-RISM-KH theory, in particular over octanol molecular orientations around the hydroxyl oxygen, produces considerable effective repulsion due to the overlap of their long hydrophobic tail with the solute repulsive core. As a result, the performance of the 3D-RISM-KH theory in reproducing the solvation free energy appears to be much better for such solvent.

To understand whether the UC can improve the agreement between calculated and experimental data for the solvation free energy in octanol, we calculated the PMV for the library compounds in octanol using the 3D-RISM-KH theory, estimated the correlations of the PMV with the calculated and experimental values of the solvation free energy, and performed the linear regression analysis for the solvation free energy vs PMV data (Figures S5 and S6 and Tables S1 and S2 in the Supporting Information). There are strong and moderate anticorrelations of the PMV with the solvation free energies from the GF and KH free energy functionals (the correlation coefficients are −0.927 and −0.693, respectively). Note that for hydration there is a positive correlation of the PMV with the calculated data for both the KH and GF functionals, but not with the experimental one (Figures S2 and S3 of the Supporting Information). Also, for octanol solvent there is a weak anticorrelation (correlation coefficient −0.601) of the

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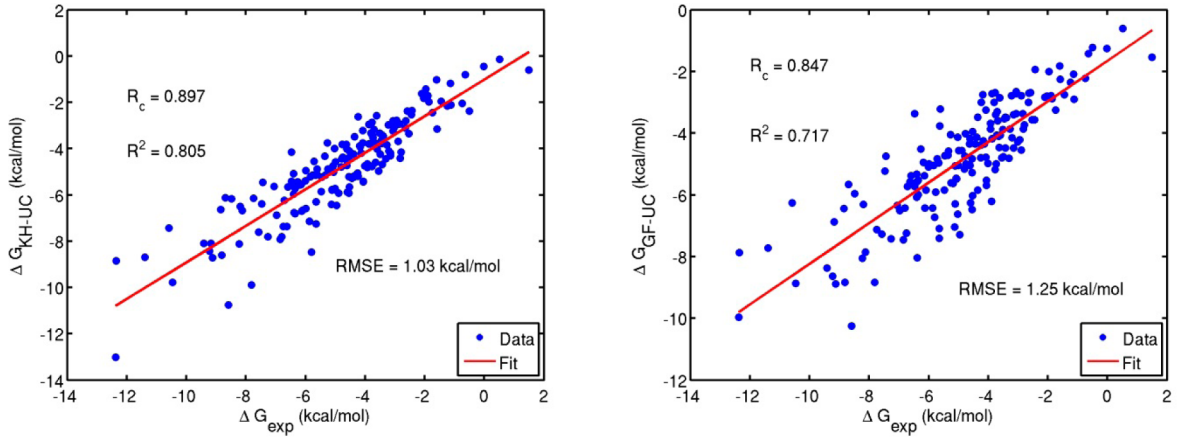

Figure 2. Solvation free energy in octanol obtained from the KH (left panel) and GF (right panel) free energy functionals with the UC using the correlation functions from the 3D-RISM-KH theory. A comparison against experimental data for the library compounds.

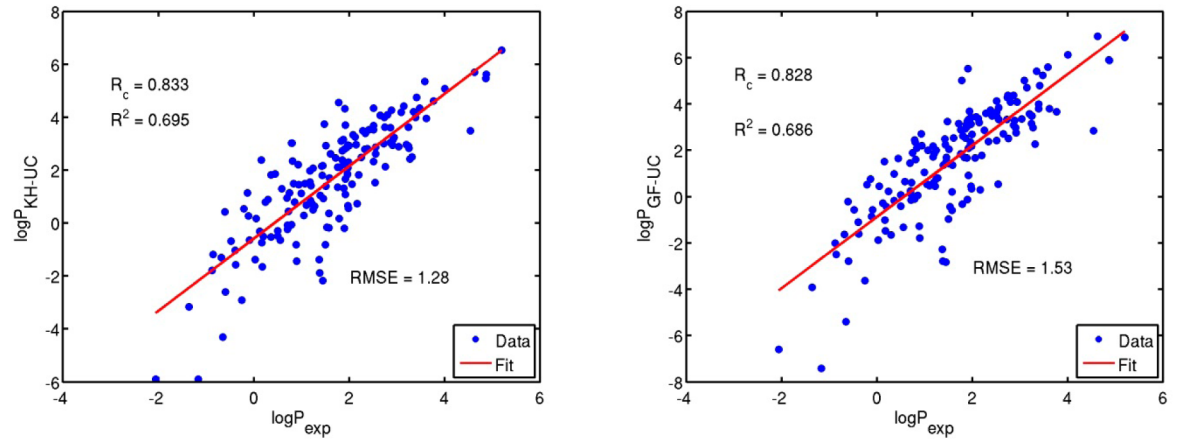

Figure 3. Logarithm of the octanol−water partition coefficient obtained from the KH (left panel) and GF (right panel) free energy functionals with the UC using the correlation functions from the 3D-RISM-KH theory. A comparison against experimental data for the library compounds.

PMV with the experimental data compared to the almost decorrelated data in the case of hydration. Also, in contrast to hydration, the PMV is completely decorrelated with the difference between the experimental and calculated solvation free energies in octanol for the KH functional with the UC (Figure S5). Therefore, the UC does not improve the correlation between the experimental data and the solvation free energy calculated with the KH functional and only slightly improves the correlation for the GF functional (Figure 2, Table 1, and Figure S4). At the same time, the UC use significantly reduces RMSE in the case of the GF functional (1.25 and 5.08 kcal/mol with and without the UC, respectively) and provides clear improvements for the KH functional (RMSE of 1.03 kcal vs 1.37 kcal/mol without the UC). The linear coefficients in the UC expression (8) parametrized for the solvation free energy in octanol calculated with the KH and GF functionals are presented in Table 1. The UC coefficients are of a much smaller magnitude for the KH functional compared to the GF one since the former provides a much better prediction of the solvation free energy in octanol even without the UC. Thus, we can conclude that for the solvation free energy in octanol the KH functional provides superior performance compared to the GF functional, with the best result (based on RMSE) obtained with the UC.

The octanol molecule is characterized with a higher degree of flexibility, compared to that of the water molecule. The results for the solvation free energy in octanol presented in Figure 2 were obtained for rigid solvent molecules in the most stable conformation (solvent model 1), the approximation commonly used in practice. To assess the effect of octanol molecule flexibility on the solvation free energy, we repeated the calculations but with all the octanol solvent molecules in another distinct representative conformation (solvent model 2). [Note that a solvent model affects the solute−solvent correlations in eqs 2 and 3 through the bulk solvent site−site susceptibility (eq 4).] To select a representative conformation, we performed implicit solvent molecular dynamics simulations of bulk octanol at the same thermodynamics conditions as in the free energy calculations. The force field parameters are described in the Computational Methods section. As solvent model 2 for further analysis, we selected an octanol conformation with the largest root-mean-square deviation of atomic positions (RMSD = 1.88 Å) from the minimum-energy structure of solvent model 1. For illustration, we make a comparison of the partial molar volumes and the solvation free energies of the library compounds obtained for these two octanol solvent models in Figures S7−S9 of the Supporting Information. The RMSD between the solvation free energies for solvent model 1 presented in Figure 2 and those for solvent model 2 obtained from the KH functional with the UC term (Figure S9) is only 0.105 kcal/mol (2.2% of the average value over the library compounds). Interestingly, it is much smaller

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than the RMSD between the results from the KH functional without the UC (Figure S8) amounting to 0.171 kcal/mol (or 4.5%). Note that the octanol solvent molecule flexibility much stronger affects the PMVs (Figure S7). For the library compounds, the RMSD between the PMVs calculated with the octanol solvent molecules in the most deviated conformation (solvent model 2) and in the most stable one (solvent model 1) is 7.76 Å^3, or about 37% of the average value over the library compounds.

We can conclude that using the susceptibility of bulk octanol obtained in the approximation of octanol molecule rigidity provides reasonable results for the solvation free energy for a large set of diverse compounds. The RMSD between the experimental data and the theoretical solvation free energies obtained for the octanol solvent represented with the most stable, minimum-energy conformer differs from that with the maximally distorted conformer by only 0.17% for the calculations using the KH functional with the UC. Interestingly, the difference increases to approximately 2.2% without the UC (still a good result). Thus, the universal correction not only improves the agreement between theory and experiment but also makes the theoretical prediction less sensitive to a choice of solvent molecule geometry and possibly force field parameters.

Octanol−Water Partition Coefficient. The logarithm of the octanol−water partition coefficient is calculated according to eq 1 as a free energy of transfer from water to octanol. The calculations were performed with the KH and GF functionals for the solvation free energy, both with and without the UC. As expected from the results of the free energy calculations of the previous sections, the best result (as estimated based on RMSEs) was obtained for the KH expression for the solvation free energy with the UC (Figure 3, Tables S1 and S2 of Supporting Information). The use of the GF functional only marginally affects the correlations (the correlation coefficients are 0.833 and 0.828 and the coefficients of determination are 0.695 and 0.686 for the KH and GF functionals, respectively) but makes RMSE worse in this case (1.28 for KH and 1.53 for GF). Slightly better (compared to the GF functional case) results can be obtained by using the GF functional for water and the KH functional for octanol (RMSE, the correlation coefficient, and the coefficient of determination are 1.32, 0.832, and 0.693, respectively). The correlations between the calculated partition coefficient and the experimental data can be improved by dropping the UC for octanol. Thus, in the case of the GF functional with the UC used for the hydration free energy only, the correlation coefficient and the coefficient of determination are 0.88 and 0.77. RMSE for these calculations increases to 3.97, which makes this level of theory less appealing compared to the combination of the KH functional and the UC used for both water and octanol.

We tested the performance of the new approach for prediction of the partition coefficient for different groups of compounds. The 3D-RISM-KH theory provides accurate and consistent results (see Table 2) for all large groups of compounds studied, including the molecules with nonpolar functional groups such as alkanes, alkenes, and alkynes (RMSE = 1.11), the compounds with halogens (RMSE = 1.0), and alcohols, ethers, aldehydes, ketones, acids, and esters (RMSE = 1.18). The agreement with experimental data is very good for the aromatic hydrocarbons (RMSE = 0.60); however, this group contains fewer compounds, making this conclusion less reliable. The results of calculations are less accurate for the compounds with nitrogen (amines, amides, nitriles, and compounds with nitrogen in heterorings) and phosphorus (with only one compound present in this group), mostly because of the less accurate prediction of the hydration free energy for these compounds (see Table S4 of the Supporting Information). This might be a consequence of a more polar character of these compounds and could be fixed by optimizing the force field parameters (partial charges) being input to 3D-RISM-KH calculations.

Table 2. Accuracy of Octanol−Water Partition Coefficients Obtained from the 3D-RISM-KH Theory and the GBSA Approach with Respect to Experimental Data[5,7] for the Library Compounds with Different Functional Groups[a]

		RMSE (log $P_{o/w}$)	
solute classes	no. of compds	3D-RISM-KH with UC	GBSA
alkanes, alkenes, alkynes	21	1.11	2.74
aromatic hydrocarbons	8	0.60	3.54
fluorides, chlorides, bromides, iodinates	38	1.00	2.94
alcohols, ethers, aldehydes, ketones, acids, esters	57	1.18	1.90
amines, amides, nitriles	22	1.72	1.38
compounds with nitrogen in heterorings	5	1.90	1.86
compounds with sulfur	6	1.08	2.41
compounds with phosphorus	1	3.68	0.49
total	158	1.28	2.32

[a]The 3D-RISM-KH solvation free energy is calculated from the KH functional with the UC using the correlation functions from 3D-RISM-KH. Included in the table are only the compounds with experimental data available for both water and octanol solvents.

Comparison between 3D-RISM-KH and GBSA Results. We also compared the predictions of the 3D-RIMS-KH theory with the UC for the solvation free energy in octanol and hydration free energy as well as for the partition coefficient with the results of calculations based on the implicit solvent GBSA approach. There are two groups of compounds, both with polar nitrogen, where GBSA performs slightly better than 3D-RISM-KH in prediction of the partition coefficient, as seen from Table 2. This can be traced down to better GBSA results for the hydration free energy for these compounds (Table S4 of the Supporting Information). The GBSA performance in prediction of the partition coefficient is surprisingly good for a single compound with phosphorus, but it is a result of cancellation of errors in the solvation and hydration free energies obtained with GBSA for that compound.

Overall, the 3D-RISM-KH theory performance is much better compared to that of the GBSA approach. Thus, RMSEs between the 3D-RISM-KH results and the experimental data for the partition coefficient can be as low as 1.28 (when the KH solvation free energy functional is used) or 1.53 (with the GF functional), compared to 2.32 obtained with GBSA (Figures 3 and 4, Tables S1−S3 of the Supporting Information). The correlation between 3D-RISM-KH and the experimental data is 0.83 and only 0.43 for GBSA. Also, the scaling coefficient and the intercept in the linear regression fit for the 3D-RISM-KH data are 1.37 and −0.58 (for the KH functional), while the scaling coefficient and the intercept obtained from GBSA are 0.1 and −0.54 (Tables S1 and S3 of the Supporting Information).

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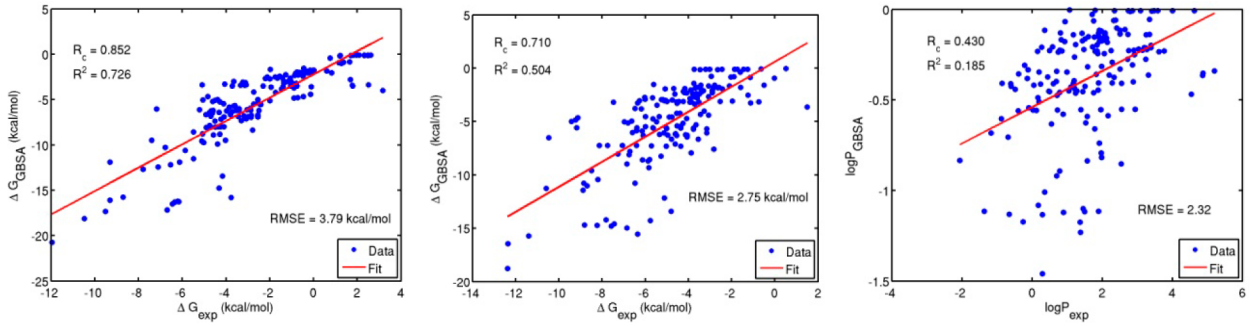

Figure 4. GBSA results for the hydration free energy (left panel), solvation free energy in octanol (middle panel), and logarithm of the octanol–water partition coefficient (right panel).

CONCLUSIONS

We have employed the statistical-mechanical, three-dimensional reference interaction site model with the Kovalenko–Hirata closure relation (3D-RISM-KH molecular theory of solvation) to predict the octanol–water partition coefficient for a large set of diverse compounds. The correlation functions of solvent sites around a compound molecule obtained from the 3D-RISM-KH integral equations are entered into the relevant solvation free energy functional and the Kirkwood–Buff/3D-RISM expression for the partial molar volume. In this context, we have tested the accuracy performance of the Kovalenko–Hirata (KH) functional[26,29] and the Gaussian fluctuation (GF) functional,[45,46,62,63] both with and without the phenomenological correction to the solvation free energy linear in the partial molar volume of the compound, or so-called "universal correction" (UC).[55] As shown previously, the UC provides substantial improvement of results for the hydration free energy.[55] We found that the UC also improves the agreement between the theory and experiment for the solvation free energy in octanol, especially for the GF solvation free energy functional. For octanol, the KH free energy functional provides much better results compared to the GF functional, both with and without the UC. The agreement of the solvation free energy in octanol calculated from the KH functional with the experimental data for the large set of compounds studied in the paper is reasonably good even without the UC (the RMSE is 1.37 kcal/mol and the correlation coefficient is 0.897). This is probably related to the better performance of the 3D-RISM-KH theory in reproducing the solvation free energy, particularly its entropic term, for octanol solvent molecules with long hydrophobic tales. In contrast, for spherically shaped water molecules an additional repulsive bridge correction is required to counter the 3D-RISM-HNC overestimation of water ordering around a hydrophobic solute. In any case, the use of the phenomenological UC optimized for the solvation free energy in octanol further improves the prediction accuracy and reduces the RMSE to as low as 1.03 kcal/mol. For the partition coefficient, the best agreement with the experimental data is obtained when using the KH functional with the UC for both water and octanol solvents (with the correlation functions obtained from the 3D-RISM-KH theory). We also note that the UC makes the theoretical prediction less sensitive to a choice of solvent molecule geometry and possibly of force field parameters.

ASSOCIATED CONTENT

Supporting Information

(i) Hydration free energies and solvation free energies in 1-octanol solvent for the library compounds obtained from the 3D-RISM-KH molecular theory of solvation with the Kovalenko–Hirata (KH) and Gaussian fluctuation (GF) solvation free energy functionals without the universal correction (UC) (Figures S1 and S4); (ii) hydration free energies and solvation free energies in 1-octanol solvent for the library compounds calculated from the KH and GF functionals, experimental data, and their difference plotted against the partial molar volume (PMV) calculated using the correlation functions obtained from the 3D-RISM-KH theory (Figures S2, S3, S5, and S6); (iii) linear regression between hydration free energies, solvation free energies in 1-octanol solvent, octanol–water partition coefficients calculated from the KH and GF functionals with the UC, and experimental data (Tables S1 and S2); (iv) linear regression between GBSA predictions for hydration free energy, solvation free energy in octanol solvent, octanol–water partition coefficients, and experimental data (Table S3); (v) comparison of the PMVs (Figure S7) and the solvation free energies from the KH functional without and with the UC term (Figures S8 and S9) using the correlation functions obtained from the 3D-RISM-KH theory for the library compounds in octanol solvent with all solvent molecules represented either with the most stable, minimum energy conformation (solvent model 1) or with a distinct conformation picked at a representative snapshot with the largest distance RMSD from the minimum energy structure in implicit solvent MD simulation of bulk octanol (solvent model 2); (vi) comparison between the experimental data for the solvation free energy in water and octanol and the predictions of the 3D-RISM-KH molecular theory of solvation and the GBSA continuum solvation approach for the library compounds with different functional groups (Table S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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