

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/51112712>

New Theoretical Method for Rapid Prediction of Solvation Free Energy in Water

ARTICLE in THE JOURNAL OF PHYSICAL CHEMISTRY B · JUNE 2011

Impact Factor: 3.3 · DOI: 10.1021/jp201949k · Source: PubMed

CITATIONS

31

READS

33

3 AUTHORS:



Shuangliang Zhao

East China University of Science and Techno...

35 PUBLICATIONS 174 CITATIONS

SEE PROFILE



Zhehui Jin

Reservoir Engineering Research Institute

18 PUBLICATIONS 331 CITATIONS

SEE PROFILE



Jianzhong Wu

University of California, Riverside

155 PUBLICATIONS 4,321 CITATIONS

SEE PROFILE

New Theoretical Method for Rapid Prediction of Solvation Free Energy in Water

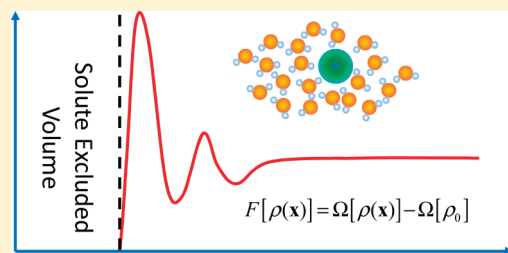
Shuangliang Zhao, Zhehui Jin, and Jianzhong Wu*

Department of Chemical and Environmental Engineering, University of California, Riverside, California 92521, United States

S Supporting Information

ABSTRACT: We present a new theoretical method for rapid calculation of the solvation free energy in water by combining molecular simulation and the classical density functional theory (DFT). The DFT calculation is based on an accurate free-energy functional for water that incorporates the simulation results for long-range correlations and the fundamental measure theory for the molecular excluded-volume effects. The numerical performance of the theoretical method has been validated with simulation results and experimental data for the solvation free energies of halide (F^- , Cl^- , Br^- , and I^-) and alkali (Li^+ , Na^+ , K^+ , Rb^+ , and Cs^+) ions in water at ambient conditions.

Because simulation is applied only to the particular thermodynamic condition of interest, the hybrid method is computationally much more efficient than conventional ways of solvation free energy calculations.



I. INTRODUCTION

Understanding dissolution of various chemical species in water has been an eternal pursuit of solution chemistry.^{1–4} While the literature is vast, recent interest has been mostly focused on the microscopic details of solute–water interactions and the effect of the local water structure on the chemical and biochemical affinities of dissolved species.^{5,6} Such information is indispensable for studying chemical/biochemical processes in aqueous systems including relaxation dynamics, stability of biomacromolecules, and “lock-key” interactions for rational drug design.^{7,8} Whereas traditional thermodynamic methods and the semiempirical theories of solvation (e.g., the Born model and the Langevin–Debye theory) treat water as an “inert” dielectric medium,^{9–12} recent theoretical and experimental investigations highlight the importance of the surrounding water molecules as an active component of the chemical and biochemical interactions.^{7,8} Despite significant progress in recent years toward a comprehensive understanding of solvation in water, quantification of the water structure at atomistic length scales and, more importantly, connection of the local water structure to the properties of dissolved species remain a daunting scientific challenge.

Current theoretical investigation of water structure at very small length scales is mostly based on molecular simulations.^{13,14} Given a semiempirical force field or an efficient first-principle algorithm for the solute–solvent interactions, computer simulation provides atomistic details of solvation in water including those pertinent to biological systems. While molecular simulation yields microscopic structure complementary to experimental measurements of the thermodynamic properties, lengthy calculation is often required to establish the structure–property relationships.¹⁵ Besides, approximation of the intermolecular interactions (or first-principle calculations) necessitates a certain discrepancy between simulation and experiment.¹⁶ Alternatively, solvation in water may be studied

with a number of analytical methods such as the integral-equation theories,^{17–20} the classical density functional theory,^{21–23} the scaled-particle theory,²⁴ and modified Born models.²⁵ These analytical methods are computationally efficient in comparison to molecular simulation and provide direct information on thermodynamic properties or/and explicit structure–property relationships. Regrettably, the numerical performance of conventional analytical methods is often limited not only by the semiempirical nature of the intermolecular potential but also by approximations for various multibody correlation effects.

In this work, we propose a new theoretical procedure to predict the solvation free energy in water by combining the merits of molecular dynamics (MD) simulation and the classical density functional theory (DFT). We use MD to calculate the microscopic structure up to atomic details and then the DFT to link the microscopic structure with thermodynamic properties. For efficient DFT calculations, the solute degrees of freedom are decoupled from those of the solvent molecules. The DFT free-energy functional incorporates the microscopic structure of water obtained from the simulation, the modified fundamental measure theory (FMT)^{26–28} for molecular excluded volume effects, and a bridge functional for long-range correlations. The new computational procedure has been validated with simulation and experimental data for the solvation free energies of halide (F^- , Cl^- , Br^- , and I^-) and alkali (Li^+ , Na^+ , K^+ , Rb^+ , and Cs^+) ions in water.²⁹

II. THEORY

We consider solvation of individual monovalent ions in water at ambient conditions. As being extensively studied before, water

Received: February 28, 2011

Revised: April 30, 2011

Published: May 10, 2011

molecules are represented by the SPC/E model,²⁹ and water–ion interactions are represented by the Lennard-Jones potential plus Coulomb forces.³⁰ While we use relatively simple models for calibration of the new theoretical method, a similar procedure can be extended to systems where both the solute and solvent molecules are more complicated.

The solvation free energy is defined as the reversible work to transfer a solute molecule from a hypothetical ideal-gas state into the pure solvent at a fixed temperature and the solvent chemical potential (or equivalently, the solvent temperature and pressure). To transfer a single solute molecule (or ion) from a vacuum to a solvent of constant temperature, volume, and chemical potential, the solvation free energy corresponds to the change in the grand potential, i.e.

$$F[\rho(\mathbf{x}); \mu, V, T] = \Omega[\rho(\mathbf{x}); \mu, V, T] - \Omega[\rho_0; \mu, V, T] \quad (1)$$

where $\rho(\mathbf{x})$ stands for the density profile of water molecules near the solute; composite vector $\mathbf{x} = (\mathbf{r}, \Theta)$ specifies the position and orientation of a water molecule; ρ_0 and μ are, respectively, the average density and the chemical potential of water molecules in the bulk; and T stands for the absolute temperature. For bulk water, $\rho(\mathbf{x}) = \rho_0 = n_0 / \int d\Theta$ where n_0 is the number density of water molecules in the bulk. Because the solvation free energy is an intensive thermodynamic quantity independent of the system size, numerical implementation of eq 1 requires that the system volume V must be sufficiently large such that the properties of water remote from the solute are the same as those corresponding to the bulk.

With a molecular model for water and water–solute interactions, it is straightforward to calculate the local density profile of water molecules by molecular simulation. Direct simulation of the solvation free energy, however, would entail an imaginary thermodynamic pathway to transfer a solute molecule from the ideal-gas state into bulk water. Because a large number of thermodynamic states must be used to represent the reversible process, the free-energy calculation is computationally demanding.^{31,32} Application of the DFT alleviates such numerical burden because it provides a direct connection between the microscopic structure and thermodynamic properties.

Water molecules around a single solute consist of an inhomogeneous system of *pure* water in the presence of an effective external field defined by the solute–solvent interactions. The grand potential is given by³³

$$\Omega[\rho(\mathbf{x}); \mu, V, T] = k_B T \int d\mathbf{x} \rho(\mathbf{x}) \{ \ln[\rho(\mathbf{x}) \Lambda^3] - 1 \} + \int d\mathbf{x} [V_{\text{ext}}(\mathbf{x}) - \mu] \rho(\mathbf{x}) + F^{\text{ex}}[\rho(\mathbf{x})] \quad (2)$$

where k_B stands for the Boltzmann constant; Λ is an effective thermal wavelength for water molecules; and $V_{\text{ext}}(\mathbf{x})$ represents the external potential (here the solute–solvent interaction). $F^{\text{ex}}[\rho(\mathbf{x})]$ denotes the excess *intrinsic* Helmholtz energy, i.e., deviation of the free energy from that of an ideal-gas state due to intermolecular interactions. Here, intrinsic means that the property depends only on the pair potential and the microscopic distribution of water molecules, not directly related to the water–solute interaction. In other words, the free energy functional is universally applicable to water at arbitrary inhomogeneous conditions. As described in the Supporting Information, eq 2 can also be used to calculate the self-solvation free energy (or

excess chemical potential) of pure water by tagging one water molecule in the bulk.

Formally, the excess intrinsic Helmholtz energy may be expressed relative to that of the bulk water at the same temperature and chemical potential^{34,35}

$$F^{\text{ex}}[\rho(\mathbf{x})] = F^{\text{ex}}[\rho_0] + \mu_0^{\text{ex}} \int d\mathbf{x} \Delta\rho(\mathbf{x}) - \frac{k_B T}{2} \int d\mathbf{x}_1 \int d\mathbf{x}_2 \Delta\rho(\mathbf{x}_1) \Delta\rho(\mathbf{x}_2) c(\mathbf{x}_1, \mathbf{x}_2; \rho_0) + F_B[\rho(\mathbf{x})] \quad (3)$$

where $\Delta\rho(\mathbf{x}) = \rho(\mathbf{x}) - \rho_0$; μ_0^{ex} and $c(\mathbf{x}_1, \mathbf{x}_2; \rho_0)$ stand for, respectively, the excess chemical potential and the two-body direct correlation function for the pure water; and $F_B[\rho(\mathbf{x})]$ is a bridge functional that accounts for thermodynamic nonideality beyond the two-body correlations. Without the bridge functional, eq 3 becomes equivalent to the hypernetted chain (HNC) approximation,³⁶ which has been used extensively for the solvation research (see for example, ref 37). As detailed in the Supporting Information, $\rho(\mathbf{x})$ and $c(\mathbf{x}, \mathbf{x}'; \rho_0)$ can be calculated from molecular simulation of bulk water.

We divide the bridge functional $F_B[\rho(\mathbf{x})]$ into a contribution due to the short-range (SR) molecular excluded-volume effects and that due to longer-range (LR) van der Waals and electrostatic interactions

$$F_B[\rho(\mathbf{x})] = F_B^{\text{SR}}[\rho(\mathbf{x})] + F_B^{\text{LR}}[\rho(\mathbf{x})] \quad (4)$$

The total bridge functional $F_B[\rho(\mathbf{x})]$ must satisfy the Euler–Lagrange equation

$$\delta F_B[\rho(\mathbf{x})] / \delta \rho(\mathbf{x}) = \ln y(\mathbf{x}) - \int d\mathbf{x}' c(\mathbf{x}, \mathbf{x}'; \rho_0) \Delta\rho(\mathbf{x}') \quad (5)$$

where $y(\mathbf{x}) \equiv \rho(\mathbf{x}) \exp[\beta V_{\text{ext}}(\mathbf{x})] / \rho_0$ denotes the solute–solvent cavity correlation function. Equation 5 is obtained by minimization of the grand potential (eq 2) with respect to $\rho(\mathbf{x})$. With the local density $\rho(\mathbf{x})$ obtained from molecular simulation, we can calculate $B(\mathbf{x}) \equiv \delta F_B[\rho(\mathbf{x})] / \delta \rho(\mathbf{x})$ from eq 5 over the region accessible to water molecules. Within the solute core, the density profile vanishes, but the solute–solvent cavity correlation function remains finite. In this region, the bridge functional is closely related to the molecular excluded-volume effects.

Whereas there is no a priori knowledge for the SR bridge functional, the excluded-volume contribution arises mainly from the physical size of water molecules. In this work, we assume that the short-range component of the bridge functional can be approximated by that of a hard-sphere system with the density profile identical to that of oxygen atoms in water, i.e.

$$F_B^{\text{SR}}[\rho(\mathbf{x})] \approx F_B^{\text{HS}}[n(\mathbf{r})] \quad (6)$$

where $n(\mathbf{r}) = \int d\Theta \rho(\mathbf{r}, \Theta)$. Because of the *universality* of intrinsic Helmholtz energy for water, the hard-sphere diameter d can be determined self-consistently by considering the excess chemical potential of pure water, i.e., by application of the same theoretical procedure to calculating the self-solvation free energy of a water molecule in bulk water (as detailed in the Supporting Information, we obtain $d = 2.85 \text{ \AA}$ for the SPC/E water considered in this work^{38,39}).

Table 1. Solvation Free Energies of Cations and Anions in SPC/E Water Obtained from Different Methods^a

	experiment		simulation		theory			
	Schmid et al ⁴⁷	Marcus ⁴⁴	Joung–Cheatham ³⁰	Jensen–Jorgensen ⁴⁵	this work		MSA ⁴⁶	Born ⁴⁶
					total	HNC		
Li ⁺	113.8	113.5	113.3	105.6	111.9	178.7	115.5	186.2
Na ⁺	88.7	87.2	88.4	76.4	88.4	153.2	96.4	141.3
K ⁺	71.2	70.5	71	59.5	69.5	127.3	79.6	107.8
Rb ⁺	66.0	65.7	65.6	54.5	64.2	118.7	75.6	100.6
Cs ⁺	60.5	59.8	60.5	48.6	60.3	110.3	68.9	89.2
F [−]	119.7	111.1	119.8	119.6	118	153.4	94.7	137.7
Cl [−]	89.1	81.3	89.3	91	86.5	107.7	74.1	90.6
Br [−]	82.7	75.3	82.7	85.8	81.5	97.6	69.6	90.1
I [−]	74.3	65.7	74.4	77.5	72.9	82.2	63.1	79.6

^a All values are negative and in the units of kcal/mol. The temperature is 300 K, and the mass density of SPC/E water is 0.996 g/cm³.

For the hard-sphere reference system, the bridge functional is given by

$$F_B^{\text{HS}}[n(\mathbf{r})] = F_{\text{HS}}^{\text{ex}}[n(\mathbf{r})] - F_{\text{HS}}^{\text{ex}}(n_0) - \mu_{0,\text{HS}}^{\text{ex}} \int d\mathbf{r} \Delta n(\mathbf{r}) + \frac{k_B T}{2} \int d\mathbf{r}_1 \int d\mathbf{r}_2 \Delta n(\mathbf{r}_1) \Delta n(\mathbf{r}_2) c_{\text{HS}}^{(2)}(|\mathbf{r}_1 - \mathbf{r}_2|) \quad (7)$$

where $\Delta n(\mathbf{r}) = n(\mathbf{r}) - n_0$, and $\mu_{0,\text{HS}}^{\text{ex}}$ and $c_{\text{HS}}^{(2)}(|\mathbf{r}_1 - \mathbf{r}_2|)$ are, respectively, the excess chemical potential and the direct correlation function of bulk hard spheres. Accurate equations are available for predicting the structural and thermodynamic properties of both uniform and inhomogeneous hard-sphere systems.⁴⁰ In this work, the properties of the reference hard spheres are calculated from the modified fundamental measure theory (MFMT).^{26,27} While water has a microscopic structure very different from that of bulk hard spheres, the hard-sphere reference system accounts for, approximately, the short-range component of the bridge functional, i.e., the intrinsic Helmholtz energy due to all higher-order correlations beyond HNC. In calculation of the bridge functional using eq 7, the structure of the hard-sphere reference system depends on the distribution of water molecules near the solute determined from MD simulation.

For a system with uniform density, the excess intrinsic Helmholtz energy reduces to that of the bulk system. As a result, both the SR and LR components of the bridge functional disappear as $\Delta\rho(\mathbf{x}) = 0$. Besides, it is known from previous work that the bridge functional is dominated by the short-range interactions.^{41–43} As a result, we expect that the LR component of the bridge functional is relatively small, and it may be approximated by a linear functional integration

$$F_B^{\text{LR}}[\rho(\mathbf{x})] \approx k_B T \int d\mathbf{x} \Delta\rho(\mathbf{x}) B^{\text{LR}}(\mathbf{x}) \quad (8)$$

where

$$B^{\text{LR}}(\mathbf{x}) = \begin{cases} \ln y(\mathbf{x}) - \int d\mathbf{x}' c(\mathbf{x}, \mathbf{x}'; \rho_0) \Delta\rho(\mathbf{x}') & \rho(\mathbf{x})/\rho_0 \geq \delta \\ 0 & \text{otherwise} \end{cases} \quad (9)$$

In eq 9, parameter δ defines the solvent accessibility: the space is solvent accessible if $\rho(\mathbf{x})/\rho_0 \geq \delta$ and inaccessible otherwise. Apparently, δ is intimately related to the hard-sphere diameter of the reference system. For calculations in this work, we use $\delta = 10^{-6}$. We find that the theoretical results are not sensitive to small variations of δ .

Once we have explicit expressions for the SR and LR components of the bridge functional (eqs 6 and 8), we can finally derive the solvation free energy from eq 1, which, after some algebra, becomes

$$F[\rho(\mathbf{x})] = k_B T \int d\mathbf{x} \{ \rho(\mathbf{x}) \ln y(\mathbf{x}) - \rho(\mathbf{x}) + \rho_0 \} - \frac{k_B T}{2} \int d\mathbf{x}_1 \int d\mathbf{x}_2 \Delta\rho(\mathbf{x}_1) \Delta\rho(\mathbf{x}_2) c(\mathbf{x}_1, \mathbf{x}_2; \rho_0) + F_B^{\text{SR}}[\rho(\mathbf{x})] - k_B T \int d\mathbf{x} \Delta\rho(\mathbf{x}) B^{\text{LR}}(\mathbf{x}) \quad (10)$$

As expected, the solvation free energy is immaterial to the effective thermal wavelength of water molecules. Without the terms related to the bridge functional, eq 10 would yield a solvation free energy identical to that from the HNC approximation.

III. RESULTS

We first use MD simulation to obtain the direct correlation function of bulk water and the local density profile of water molecules around individual ions (see Supporting Information for details). From the local density and bulk correlation functions, we then calculate the solvation free energies by numerical integrations of eq 10. In the region not accessible to solvent molecules ($\rho(\mathbf{x})/\rho_0 < \delta$), the cavity correlation function and the long-range component of the bridge functional make no contribution to the solvation free energy. In this region, the solvation free energy is determined by that of a hard-sphere reference system using MFMT.²⁷

Table 1 summarizes the theoretical results for the solvation free energies of alkali ions (Li⁺, Na⁺, K⁺, Rb⁺, Cs⁺) and halide ions (F[−], Cl[−], Br[−], I[−]) in water at 300 K and mass density 0.996 g/cm³. These monomeric ions are considered in this work because extensive experimental, simulation, and theoretical results are readily available from previous studies; thus, the published results

for these simple systems provide ideal benchmark data for calibration of the proposed computational procedure. For comparison, Table 1 also includes some representative results from previous theoretical investigations.

As well documented,^{48,49} the solvation free energies of individual ions are not accessible to direct experimental measurements. As a result, the conventional values are often tabulated relative to the solvation free energy of proton. These values cannot be directly used for comparison with the theoretical predictions. The two sets of experimental data shown in Table 1 correspond to the “absolute” values obtained from different estimations of the proton solvation free energy. The data from Schmidt et al. used the proton solvation free energy (-251.4 kcal/mol at 298 K) estimated from thermodynamic measurements for dissociation of water.⁴⁷ The much cited values tabulated by Marcus involve a so-called “extra thermodynamic assumption”; i.e., a large cation and a large anion of equal size and equally low electric charge have the same solvation free energy (as predicted by the Born model).⁴⁴ On the basis of the extra thermodynamic assumption and the Gibbs energy of solvation for tetraphenylarsonium tetraphenylborate (TABA), Marcus deduced a proton solvation free energy (-252.4 kcal/mol at 298 K) remarkably close to that given by Schmidt et al. (even though they differ much in both the enthalpy and entropy of the solvation). Besides the difference in the reference solvation free energy, additional discrepancies between the two sets of experimental data, in particular for the solvation free energies of anions, are probably due to different sources of experimental measurements. Table 1 also includes two sets of simulation data that differ slightly in terms of the Lennard-Jones parameters for the ion–water interactions.³⁰ The simulation results were obtained without evoking a hypothetical vacuum–water interface; i.e., the solvation free energies calculated do not include the phase or surface potential arising from anisotropic distribution of water molecules at the interface.⁵⁰

Table 1 shows that, with the same parameters for water–water and ion–water interactions, our theoretical predictions for the ion solvation free energy agree well with those from a recent simulation by Joung and Cheatham.³⁰ In comparison with the experiment data, the solvation free energies predicted from this work are comparable to the simulation results: while for alkali ion (Li^+ , Na^+ , K^+ , Rb^+ , Cs^+) the simulation results appear closer to experimental data, the opposite is true for the halide ion (F^- , Cl^- , Br^- , I^-). From a practical point of view, the difference between the theory and simulation is insignificant, in particular if we refer to another set of simulation data predicted with a slightly different set of parameters for the Lennard-Jones potential between ion and water reported by Jensen and Jorgensen.⁴⁵

We have also compared the solvation free energies predicted from this work with those from the Born solvation model and from the mean-spherical approximation (MSA).⁴⁶ The well-known Born model accounts for the self-electrostatic energy for ionization of a neutral particle in a continuous dielectric medium. According to this model, the solvation free energy depends only on the particle size and the bulk dielectric constant of the solvent. Because the local dielectric property of the solvent near an ion can be quite different from that in the bulk and because an appropriate selection of the ionic radius is often questionable, the Born model is not very reliable and has been much criticized. In comparison to the Born model, the MSA predictions are much closer to the experimental results. However, representation of water molecules in terms of hard spheres each with a point dipole

is an oversimplification from a microscopic point of view. Besides, the numerical performance of MSA is not reliable even within the highly idealized model.

Finally, we compare the solvation free energies predicted from eq 10 with those from the HNC approximation. These two methods differ only in terms of the bridge functional, i.e., contributions to the intrinsic Helmholtz energy beyond the quadratic terms. Table 1 shows that the agreement between the HNC predictions and the experimental results barely matches those from the Born model, indicating that a quadratic approximation is insufficient to capture the solvation free energy quantitatively.

IV. CONCLUSIONS

We present a new theoretical method for calculating the solvation free energies of ions in water using molecular dynamics (MD) simulation and the classical density functional theory (DFT). An accurate intrinsic Helmholtz energy functional for water has been developed by decomposing the intermolecular potential into a short-range (SR) repulsion and longer-ranged (LR) van der Waals and electrostatic interactions. The free energy due to the SR repulsion is accounted for by using an inhomogeneous hard-sphere reference system, and that due to the LR interactions is calculated from a linear approximation of the bridge functional. With the local density distribution of water molecules obtained from MD simulation, the DFT predicts the solvation free energies of halide and alkali ions in excellent agreement with simulation results. In comparison to conventional simulation methods, the new theoretical approach is computationally very efficient because it avoids simulation along a hypothetical thermodynamic pathway connecting the initial and final states of the solvation process.

We should point out that the new computational method is not limited to any particular force field for water or ion–water interactions. Indeed, the same procedure can be applied to any semiempirical models that assume a pairwise additive intermolecular potential for water. While the combination of the DFT with MD simulation greatly reduces the computational cost for free energy calculations, our method is intrinsically limited by the applicability of MD simulation concerning the system size (e.g., solvation of large proteins) and by the reliability of the semiempirical force field for water and for water–ion interactions.

■ ASSOCIATED CONTENT

S Supporting Information. Details of MD simulation and the computational procedure for calculation of the direct correlation function in bulk water as well as that for calculation of the solvation free energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jwu@engr.ucr.edu.

■ ACKNOWLEDGMENT

For financial support, the authors are grateful to the US Department of Energy (DE-FG02-06ER46296), the National Institute of Health (R21-AI077532), and the National Science Foundation (NSF-CBET-0852353). This work utilizes

supercomputers from the National Energy Research Scientific Computing Center (NERSC).

REFERENCES

- (1) Born, M. Z. *Phys.* **1920**, *1*, 45.
- (2) Mayer, J. E. J. *Chem. Phys.* **1950**, *18*, 1426.
- (3) Olivares, W.; McQuarrie, D. A. *Biophys. J.* **1975**, *15*, 143.
- (4) Huang, D. M.; Geissler, P. L.; Chandler, D. J. *Phys. Chem. B* **2001**, *105*, 6704.
- (5) Chandler, D. *Nature* **2005**, 437, 640.
- (6) Hirata, F. *Molecular theory of solvation*; Kluwer Academic Publishers: Boston, 2003.
- (7) Marcus, Y. *Chem. Rev.* **2009**, *109*, 1346.
- (8) Ball, P. *Chem. Rev.* **2008**, *108*, 74.
- (9) Marenich, A. V.; Olson, R. M.; Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Theory Comput.* **2007**, *3*, 2011.
- (10) Mennucci, B.; Cammi, R. *Continuum solvation models in chemical physics: from theory to applications*; John Wiley & Sons: Chichester, England; Hoboken NJ, 2007.
- (11) Ben-Naim, A. *Solvation thermodynamics*; Plenum Press: New York, 1987.
- (12) Ben-Amotz, D.; Underwood, R. *Acc. Chem. Res.* **2008**, *41*, 957.
- (13) Chandler, D. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 15111.
- (14) Senn, H. M.; Thiel, W. *QM/MM Methods for Biological Systems*; Springer-Verlag: Berlin Heidelberg, 2007; Vol. 268.
- (15) Khavrutskii, I. V.; Gorfe, A. A.; Lu, B. Z.; McCammon, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 1706.
- (16) Kirchner, B. *Phys. Rep.-Rev. Sect. Phys. Lett.* **2007**, *440*, 1.
- (17) Schmidt, K. F.; Kast, S. M. *J. Phys. Chem. B* **2002**, *106*, 6289.
- (18) Phongphanphanee, S.; Yoshida, N.; Hirata, F. *J. Am. Chem. Soc.* **2008**, *130*, 1540.
- (19) Chuev, G. N.; Fedorov, M. V.; Chiodo, S.; Russo, N.; Sicilia, E. *J. Comput. Chem.* **2008**, *29*, 2406.
- (20) Yoshida, N.; Kato, S. J. *Chem. Phys.* **2000**, *113*, 4974.
- (21) Ramirez, R.; Borgis, D. J. *Phys. Chem. B* **2005**, *109*, 6754.
- (22) Yoshimori, A. *J. Theor. Comput. Chem.* **2004**, *3*, 117.
- (23) Lum, K.; Chandler, D.; Weeks, J. D. *J. Phys. Chem. B* **1999**, *103*, 4570.
- (24) Ashbaugh, H. S.; Pratt, L. R. *Rev. Mod. Phys.* **2006**, *78*, 159.
- (25) Cramer, C. J.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 760.
- (26) Roth, R.; Evans, R.; Lang, A.; Kahl, G. J. *Phys.: Condens. Matter* **2002**, *14*, 12063.
- (27) Yu, Y. X.; Wu, J. Z. *J. Chem. Phys.* **2002**, *117*, 10156.
- (28) Rosenfeld, Y. *Phys. Rev. Lett.* **1989**, *63*, 980.
- (29) Berendsen, H. J. C.; Grigera, J. R.; Straatsma, T. P. *J. Phys. Chem.* **1987**, *91*, 6269.
- (30) Joung, I. S.; Cheatham, T. E. J. *Phys. Chem. B* **2008**, *112*, 9020.
- (31) Swanson, J. M. J.; Henschman, R. H.; McCammon, J. A. *Biophys. J.* **2004**, *86*, 67.
- (32) Leach, A. R. *Molecular modelling: principles and applications*, 2nd ed.; Prentice Hall: Harlow, England; New York, 2001.
- (33) Evans, R. *Adv. Phys.* **1979**, *28*, 143.
- (34) Evans, R. Density functionals in the theory of nonuniform fluids. In *Fundamentals of Inhomogeneous Fluids*; Henderson, D., Ed.; Marcel Dekker: New York, 1992; p 85.
- (35) Wu, J. Z. Density Functional Theory for Liquid Structure and Thermodynamics. In *Molecular Thermodynamics of Complex Systems*; Lu, X. H., Hu, Y., Eds.; Berlin, 2009; Vol. 131, p 1.
- (36) Hansen, J. P.; McDonald, I. R. *Theory of Simple Liquids*, 2nd ed.; Academic Press: London, 1986.
- (37) Hirata, F. *Molecular theory of solvation*; Kluwer Academic Publishers: Dordrecht; Boston, 2003.
- (38) Ji, J.; Cagin, T.; Pettitt, B. M. *J. Chem. Phys.* **1992**, *96*, 1333.
- (39) Hermans, J.; Pathiaseril, A.; Anderson, A. *J. Am. Chem. Soc.* **1988**, *110*, 5982.
- (40) Roth, R. J. *Phys.: Condens. Matter* **2010**, *22*, 063102.
- (41) Ratkova, E. L.; Chuev, G. N.; Sergiievskiy, V. P.; Fedorov, M. V. *J. Phys. Chem. B* **2010**, *114*, 12068.
- (42) Palmer, D. S.; Frolov, A. I.; Ratkova, E. L.; Fedorov, M. V. *J. Phys.: Condens. Matter* **2010**, *22*, 492101.
- (43) Freedman, H.; Le, L.; Tuszynski, J. A.; Truong, T. N. *J. Phys. Chem. B* **2008**, *112*, 2340.
- (44) Marcus, Y. *Biophys. Chem.* **1994**, *51*, 111.
- (45) Jensen, K. P.; Jorgensen, W. L. *J. Chem. Theory Comput.* **2006**, *2*, 1499.
- (46) Fawcett, W. R. *J. Phys. Chem. B* **1999**, *103*, 11181.
- (47) Schmid, R.; Miah, A. M.; Sapunov, V. N. *Phys. Chem. Chem. Phys.* **2000**, *2*, 97.
- (48) Pratt, L. R. *J. Phys. Chem.* **1992**, *96*, 25.
- (49) Lamoureux, G.; Roux, B. *J. Phys. Chem. B* **2006**, *110*, 3308.
- (50) Leung, K. J. *Phys. Chem. Lett.* **2009**, *1*, 496.