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Hydration Free Energies of Molecular Ions from Theory and Simulation

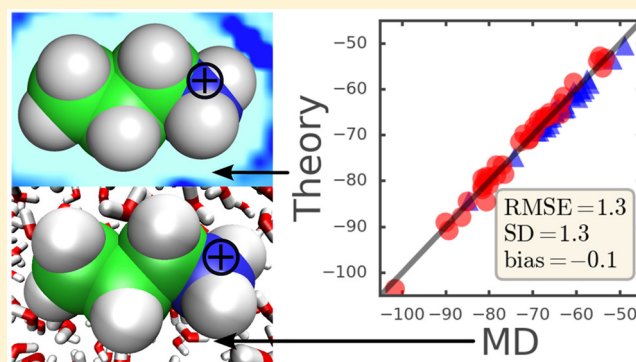
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S Supporting Information

ABSTRACT: We present a theoretical/computational framework for accurate calculation of hydration free energies of ionized molecular species. The method is based on a molecular theory, 3D-RISM, combined with a recently developed pressure correction (PC+). The 3D-RISM/PC+ model can provide ~ 3 kcal/mol hydration free energy accuracy for a large variety of ionic compounds, provided that the Galvani potential of water is taken into account. The results are compared with direct atomistic simulations. Several methodological aspects of hydration free energy calculations for charged species are discussed.



INTRODUCTION

Hydration free energy is the most important solvation parameter related to solubility, partitioning of compounds between different phases, and acidity and basicity constants.^{1–3} It is also widely used in the evaluation of ligand binding affinities and in various environmental models.^{4–6}

While there has been considerable progress in prediction of hydration free energy for neutral compounds, for which various methods can achieve below 1 kcal/mol accuracy,^{7–9} even the best computational models still show somewhat poor results for charged molecules.^{7,8} We note that research in this direction has been focused on implicit models, which approximate solvent as a dielectric continuum. However, these methods rely on heavy parametrization^{7,8} because they cannot provide information regarding solvent structure and neglect such important effects as solvent polarization, electrostriction, dielectric saturation, etc.^{10,11}

Explicit solvation models such as molecular dynamics (MD) provide a more realistic view of ionic solvation processes. Unfortunately calculation of solvation free energy is complicated by the need to perform simulations at many intermediate solvation stages. Also, ab initio and even polarizable charge MD is still very computationally expensive, meaning that one has to rely on approximate force fields, which have not been extensively tested nor optimized for ionic compounds. Moreover, for a long time, computation of ionic free energy has presented a substantial theoretical difficulty even with classical MD, mainly due to sensitivity of the obtained energies to the box size and the selected electrostatic method.^{10,12,13,78}

A group of semiexplicit models, such as three-dimensional reference interaction site model (3D-RISM) or classical density functional theory (CDFT), provide a nice combination of the

strengths of both explicit and implicit solvation models. They treat solvent via density correlation functions, capturing many solvation effects which are ignored by implicit models, without the need to simulate a huge number of explicit solvent molecules.^{1,14,15} Both of these models have been used to estimate solvation free energies of atomic ions, but no detailed benchmarks have been published on a series of molecular compounds that are of large interest to bioscience.^{16,17} Here we focus on 3D-RISM, partially because of a recently published pressure correction (PC+), which significantly improved the accuracy of the model,^{18,41} and partially because this method in recent years has become quite popular and has a readily available AMBER implementation.⁶⁷

This study is split into two parts. First, we compare the results obtained using the 3D-RISM/PC+ model to fixed charge molecular dynamic simulations. We note that charged solutes, unlike neutral ones, contain an additional contribution to solvation free energy that is related to the solvent Galvani potential.^{19–21} We propose a method to estimate it in the 3D-RISM framework and numerically demonstrate its validity. In the second part of the study, we compare classical force field results by the MD and 3D-RISM methods with experimental solvation free energies. In our benchmark we focus on *molecular* and not atomic ions. We show that even without taking into account effects such as water polarization or charge transfer, it is possible to obtain ionic hydration free energies with reasonable accuracy by employing commonly used force fields.⁷⁶

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77 ■ THEORY

78 **3D-RISM.** 3D-RISM allows one to predict the equilibrium
79 distribution of solvent around a solute without explicitly
80 sampling different system configurations. The structure of
81 solvent is described by solute–solvent site correlation
82 functions. The theory is based on the following equation

$$h_{\alpha}(\mathbf{r}) = \sum_{\beta=1}^{n_s} (\chi_{\alpha\beta} * c_{\beta})(\mathbf{r}) \quad (1)$$

84 where subscripts α and β denote indexes of sites in solvent
85 molecule, n_s is the total number of sites in solvent molecule, h_{α}
86 is the total correlation function, c_{α} is the direct correlation
87 function, and the asterisk (*) denotes convolution.^{1,14} $\chi_{\alpha\beta}$ is the
88 solvent susceptibility, typically obtained from 1D-RISM but in
89 principle also obtainable from an MD or an experimental
90 measurement.¹ In the hypernetted-chain approximation
91 (HNC), eq 1 is accompanied by the following closure

$$h_{\alpha}(\mathbf{r}) + 1 = \exp\left(-\frac{u_{\alpha}(\mathbf{r})}{kT} + h_{\alpha}(\mathbf{r}) - c_{\alpha}(\mathbf{r})\right) \quad (2)$$

93 where k is the Boltzmann constant, T is temperature, and u_{α} is
94 the potential energy between solute and solvent site α , provided
95 as an input. Both eqs 1 and 2 are written for each of the n_s
96 solvent sites. We note that these equations are approximate and
97 do not exactly reproduce solvent distributions obtained from
98 MD simulations, even when tested with the identical force
99 field.^{1,14}

100 While conceptually straightforward and thoroughly inves-
101 tigated, HNC suffers from poor computational convergence.²²
102 This problem can be reduced by the use of a partial series
103 expansion of the order n (PSE- n) of the HNC closure²³

$$h_{\alpha}(\mathbf{r}) = \begin{cases} \sum_{i=0}^n \Xi_{\alpha}^i(\mathbf{r})/i! - 1 & \text{if } \Xi_{\alpha}(\mathbf{r}) > 0 \\ \exp(\Xi_{\alpha}(\mathbf{r})) - 1 & \text{if } \Xi_{\alpha}(\mathbf{r}) \leq 0 \end{cases} \quad (3)$$

105 where $\Xi_{\alpha}(\mathbf{r}) = -u_{\alpha}(\mathbf{r})/kT + h_{\alpha}(\mathbf{r}) - c_{\alpha}(\mathbf{r})$. Typically larger n
106 values recover HNC results, while smaller n increase the
107 numerical stability of the solution. Choice of $n = 3$, denoted as
108 PSE-3, achieves a good balance between convergence and
109 accuracy and has been successfully applied in numerous
110 previous studies.^{24–26}

111 **Solvation Free Energy.** For a solute in solvent, its excess
112 chemical potential $\mu_{\text{sol}}^{\text{ex}}$ is given by Kirkwood's famous formula²⁷

$$\mu_{\text{sol}}^{\text{ex}} = \int_0^1 d\lambda \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_{\lambda} \quad (4)$$

114 where λ is a solute coupling parameter, $\langle \dots \rangle_{\lambda}$ indicates an
115 ensemble average at a particular λ , and $U(\lambda)$ is the potential
116 energy of the solute–solvent system. When a molecule's
117 internal degrees of freedom do not change upon phase transfer,
118 the excess chemical potential is equal to Ben-Naim's definition
119 of solvation free energy,²⁸ denoted here as simply ΔG . In this
120 work we assume that this is the case, as we are dealing with
121 primarily small molecules.

122 Equation 4 is in principle exact; direct implementation of this
123 formula in molecular simulations faces difficulties related with
124 numerical convergence and high computational costs for
125 modeling of a large number of intermediate states. Therefore,

more efficient ways to evaluate solvation free energy have been
developed in both MD- and 3D-RISM-based methods.^{1,31,78}

For MD, one can employ multistate Bennett acceptance ratio
(MBAR), a free energy estimation method which has been
shown to produce much lower error for the same number of
intermediate states between $\lambda = 0$ and $\lambda = 1$ for practically the
same computational cost.²⁹ The details of the derivation of the
method and its application have been described elsewhere.^{29,30}

When numerically evaluating ΔG_{MD} , one typically starts by
first decoupling electrostatic energy U_{Coulomb} and then
Lennard–Jones potential U_{vdW} .³¹ On the basis of this scheme
one obtains

$$\Delta G_{\text{MD}} = \Delta G_{\text{Coul}} + \Delta G_{\text{vdW}} \quad (5)$$

where ΔG_{vdW} corresponds to the process of insertion of a
molecule with partial charges set to 0 and ΔG_{Coul} corresponds
to the subsequent charging of the molecule. We note that this
equation only holds if intramolecular interactions inside solute
do not change during the whole process.

With RISM, one can skip evaluating energies at different
values of λ and obtain solvation free energy from a single-point
calculation.¹⁴ The exact form of the RISM free energy
functional depends on the closure. In the case of HNC^{14,32}

$$\Delta G_{\text{HNC}} = kT \sum_{\alpha=1}^{n_s} \rho_{\alpha} \int_V \left[\frac{1}{2} h_{\alpha}^2(\mathbf{r}) - c_{\alpha}(\mathbf{r}) - \frac{1}{2} c_{\alpha}(\mathbf{r}) h_{\alpha}(\mathbf{r}) \right] d\mathbf{r} \quad (6)$$

For PSE closure

$$\Delta G_{\text{PSE-}n} = \mu_{\text{HNC}}^{\text{ex}} - kT \sum_{\alpha=1}^{n_s} \rho_{\alpha} \int_V [\Theta(h_{\alpha}(\mathbf{r}))(\Xi_{\alpha}(\mathbf{r}))^{n+1} / (n+1)!] d\mathbf{r} \quad (7)$$

where Θ is a Heaviside step function.²³

Functionals presented above are derived from eq 4 and
contain no further approximations aside from those involved in
3D-RISM derivation.^{33,34} Unfortunately, these expressions are
known to yield severely overestimated values for hydration free
energies. A number of groups have proposed empirical
corrections to $\Delta G_{\text{3D-RISM}}$, but the scope of such corrections
remains undetermined.^{35–39}

One of the striking features of both HNC-RISM as well as
closely related CDFT in the HRF approximation is largely
overestimated solvent pressure, measured in hundreds of
atmospheres.^{25,40} Thus, a straightforward correction to over-
estimated solvation free energies predicted in both theories may
be written as^{41,42}

$$\Delta G_{\text{PC}} = \Delta G_{\text{theory}} - P_{\text{theory}} \Delta V + P_{\text{exp}} \Delta V \quad (8)$$

where PC stands for pressure correction and P_{exp} is
experimental pressure. In 3D-RISM/HNC⁴¹

$$P_{\text{HNC}} = \frac{n_s + 1}{2} \rho kT - \frac{kT}{2} \rho^2 \hat{c}(k=0) \quad (9)$$

where n_s is the number of solvent sites, ρ is the number density
of the solvent, and $\hat{c}(k=0)$ is the integral of solvent–solvent
direct correlation functions given in site–site formalism by

$$\hat{c}(k=0) = \sum_{\alpha=1}^{n_s} \sum_{\alpha'=1}^{n_s} 4\pi \int_0^{\infty} c_{\alpha\alpha'}(r) r^2 dr \quad (10)$$

173 Alternatively $\hat{c}(k=0)$ can be expressed using the pure solvent
 174 isothermal compressibility, χ_T , obtained during evaluation of
 175 χ_{af} from 1D-RISM: $\hat{c}(k=0) = 1/\rho - 1/(\rho kT\chi_T)$. We note that
 176 experimental expansion work $P_{\text{exp}}\Delta V$ in eq 8 is not strictly
 177 necessarily as at standard conditions this term is very close to 0.
 178 Recent results show that the pressure correction decreases the
 179 root-mean-square error of 3D-RISM/HNC predictions from
 180 around 16 to 4 kcal/mol for neutral organic molecules.⁴¹
 181 Interestingly, in both theories it is not the actual PC that is
 182 most successful in predicting experimental hydration free
 183 energies but a closely related PC+ correction^{18,41,43,44}

$$184 \quad \Delta G_{\text{PC}+} = \Delta G_{\text{theory}} - P_{\text{theory}}\Delta V + P_{\text{ideal}}\Delta V \quad (11)$$

185 where P_{ideal} is the ideal gas pressure given by $P_{\text{ideal}} = \rho kT$. Note
 186 that due to a misinterpretation, in earlier references^{18,43,44} PC+
 187 was originally called the initial state correction or ISC.
 188 Combination of PC+ correction and 3D-RISM/HNC (also
 189 PSE-3) approximations was shown to predict hydration free
 190 energies of neutral solutes with accuracies of around 1 kcal/
 191 mol, which is comparable to MD results with the similar force
 192 field.

193 As yet, there is no compelling explanation of why PC+ is
 194 more accurate than PC and why it provides significant accuracy
 195 improvement for both 3D-RISM and CDFT. In ref 18 we
 196 showed that the accuracy of PC+, unlike other approximate
 197 models, is independent of temperature. Li et al. also provided
 198 arguments in support of PC+ based on asymptotic analysis,⁴⁴
 199 but similar investigation done by Sergiievskiy et al. arrived at a
 200 different conclusion. The present work provides further support
 201 for PC+ by showing its success in application to charged
 202 molecules.

203 The 3D-RISM pressure, taken from ref 41, was derived for
 204 HNC closure. However, we believe it can be also used in
 205 combination with PSE-3. The difference in numerical
 206 predictions of these two closures is minimal, but the good
 207 convergence of PSE-3 makes it much more attractive for
 208 practical applications.²³ Therefore, in this paper all actual
 209 calculations are performed using PSE-3 closure.

210 Finally, we note that ΔG_{Coul} and ΔG_{vdW} can also be obtained
 211 using 3D-RISM.³⁸ Similarly to MD, $\Delta G_{\text{vdW}}^{\text{3D-RISM}}$ is the solvation
 212 free energy of solute with all partial charges set to 0. The
 213 Coulomb part is then

$$214 \quad \Delta G_{\text{3D-RISM}}^{\text{Coul}} = \Delta G_{\text{3D-RISM}} - \Delta G_{\text{3D-RISM}}^{\text{vdW}} \quad (12)$$

215 **Ionic Solvation Free Energy.** The suggested framework
 216 for calculation of ionic solvation free energy is largely based on
 217 reviews by Hunenberger et al.¹⁰ and Lin et al.¹⁹

218 Solvation free energy of a single ion can be defined using two
 219 hypothetical processes (Figure 1). In the first process, referred
 220 to as a physical process, the ion is reversibly transferred from
 221 vacuum to the bulk solvent. During the transfer the ion is
 222 moved from a sufficiently large distance from the solvent,
 223 through the surface, into the bulk solution. In the second
 224 process, referred to as an unphysical process, the ion is slowly
 225 "grown" into the solvent. At the initial stage the ion is present
 226 only as a ghost particle and does not interact with the solvent.
 227 Afterward, the van der Waals interactions between the ion and
 228 the system are reversibly switched on. At the final stage the ion
 229 is reversibly charged.

230 Two processes share essentially identical initial states (ion
 231 which does not interact with the solution is equivalent to ion in
 232 vacuum) and final states and thus should correspond to

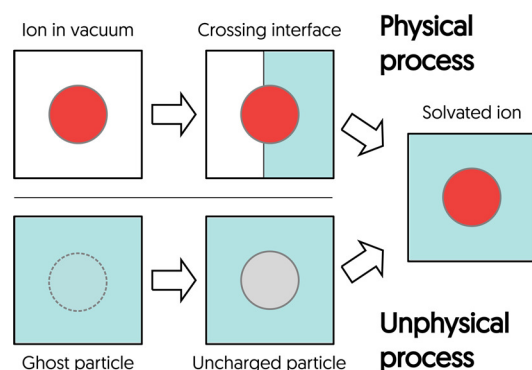


Figure 1. Two hypothetical processes describing solvation free energy of ion. The physical process (shown on top) has (1) ion in vacuum, (2) ion crossing liquid interface, and (3) ion in bulk solvent. The unphysical process (shown on bottom) has (1) ion completely noninteracting with liquid, (2) ion interacting with liquid via van der Waals forces, and (3) ion in bulk solvent. The figure is based on Figure 2.2 from ref 10

identical Gibbs free energy change, which we will refer to as the
 233 real solvation free energy ΔG_{real} . This free energy can be
 234 formally decomposed into the bulk and surface contribu-
 235 tions^{10,20,21,45–47}
 236

$$237 \quad \Delta G_{\text{real}} = \Delta G_{\text{intr}} + \Delta G_{\text{surf}} \quad (13)$$

The bulk contribution ΔG_{intr} is called the intrinsic solvation
 238 free energy and arises from the interaction between the ion and
 239 the local solution environment. The surface term ΔG_{surf} arises
 240 from the surface polarization, which in turns leads to an
 241 electrostatic potential jump of magnitude χ in air to liquid
 242 direction. The contribution of the surface term is purely
 243 electrostatic and given by the product of the total charge of the
 244 molecule Q and the electrostatic potential difference between
 245 the initial and the final positions of the molecule.¹⁰ When the
 246 outside potential (Volta potential) is 0¹⁹
 247

$$248 \quad \Delta G_{\text{real}} = \Delta G_{\text{intr}} + \chi Q = \Delta G_{\text{intr}} + \phi_G Q \quad (14)$$

where Q is the total charge of the ion and ϕ_G is the solvent
 249 Galvani potential.
 250

Note that physical and unphysical processes result in
 251 identical solvation free energies only if the solvent has an
 252 explicit surface. If the unphysical process is performed in a
 253 system where the whole space is occupied by the solvent,
 254 without any boundary between air and liquid, the resulting free
 255 energies are intrinsic. Thus, solvation free energies estimated
 256 using molecular dynamics with periodic boundary condition
 257 and Ewald summation as well as 3D-RISM are, in fact,
 258 intrinsic.^{10,19,48}
 259

While solvation free energies obtained from simulation are
 260 intrinsic, experimental solvation free energies are usually real.¹⁰
 261 In this article we are using experimental ionic free energies from
 262 a Minnesota solvation database.^{49,50} These values were
 263 obtained by determining solvation free energies of neutral
 264 pairs of ions, ΔG_{pair} , from a thermodynamic cycle. The
 265 individual hydration free energies were subsequently obtained
 266 by combining the single hydration free energy of proton,
 267 measured by Tissandier et al. (265.9 kcal/mol),⁵¹ with ΔG_{pair} .
 268 As follows from eq 14, ΔG_{pair} can be decomposed into either
 269 intrinsic or real solvation free energies
 270

$$\begin{aligned}\Delta G_{\text{pair}} &= \Delta G_{\text{real,C}} + \Delta G_{\text{real,A}} \\ &= \Delta G_{\text{intr,C}} + \Delta G_{\text{intr,A}} + 0 \times \phi_{\text{G}}\end{aligned}\quad (15)$$

where subscripts C and A stand for anion and cation. Ultimately, the question of whether the experimental hydration free energies of ions used in this study are real or intrinsic is related to the question of whether the free energy of hydration of a proton is real or intrinsic. A number of articles suggest that the value by Tissandier et al. is real and does contain a contribution from the surface potential.^{50,52,53}

Clearly, if we want to compare results obtained from simulations to experimentally measured solvation free energies, we need to make sure that both sets of energies are either real or intrinsic. Due to difficulties associated with measurement of the experimental Galvani potential,^{10,19} the only way we can make such comparison is by evaluating the Galvani potential from simulations and subsequently converting simulation intrinsic free energies to real ones.

Other authors have named additional arguments supporting the use of ΔG_{real} when discussing simulated results. First, intrinsic solvation free energies depend on the conventional quadrupole moment of the solvent molecule, which is problematic. Lin et al. point out that by embedding an isotropic quadrupole inside the oxygen core one can engineer two water models that will produce identical liquid structure and dynamics but yield arbitrary large differences in ΔG_{intr} (they would also have different ϕ_{G}).¹⁹ The difference will disappear if one considers ΔG_{real} instead.^{10,21,47,48,52,54} In addition, the use of real solvation free energies removes a hotly debated^{13,55–58} difference in the results obtained with P and M summation schemes.¹⁰ We note that these cancellations only occur if both intrinsic solvation free energies and Galvani potential were evaluated using the same theoretical model.

Calculations of Galvani Potential. In this section we discuss ways of evaluating the Galvani potential in both MD and 3D-RISM.

In molecular dynamics ϕ_{G} can be obtained by simulating a liquid droplet in an empty box and integrating the Poisson equation

$$\phi_{\text{G}} = \phi(z_{\text{w}}) - \phi(z_{\text{v}}) = \int_{z_{\text{v}}}^{z_{\text{w}}} dz' z' \langle \rho(z') \rangle \quad (16)$$

where ϕ is the potential relative to infinity, z_{w} and z_{v} are positions deep into liquid and vacuum, respectively, and $\langle \rho(z') \rangle$ is an average charge density at position z' . For SPC/E water it has been calculated to be -14.9 kcal/mol/e (-650 mV).⁵²

As simulating the explicit air–water boundary in a standard formulation of 3D-RISM is not possible, a different approach has to be adopted. For an orientationally disordered liquid, the Galvani potential is proportional to the trace of (conventional) quadrupole moment of the solvent molecule (here we are referring to the so-called internal potential).^{10,19,54} For a single-site solvent, the references cited above provide an analytical formula, but for the solvent with multiple sites, the Galvani potential has to be evaluated numerically by calculating the average electrostatic potential in the center of a small cavity (hard sphere).^{10,19} A small, hard cavity ensures that there is no significant perturbation of liquid near the surface of the cavity and that the only contribution to the potential inside the sphere is due to the quadrupole moment (extensive discussion regarding this can be found in section 4.3.8 of ref 10).

It was shown that this approximation is relatively correct for water at room temperature.¹³ In 3D-RISM the electrostatic potential at a given point can be calculated using⁵⁹

$$\phi(\mathbf{r}_0) = \frac{1}{4\pi\epsilon_0} \sum_{\alpha=1}^{n_s} \int_V \frac{g_{\alpha}(\mathbf{r}) \rho_{\alpha} q_{\alpha}}{r} d\mathbf{r} \quad (17)$$

where r is the distance from \mathbf{r}_0 to \mathbf{r} , ϵ_0 is the permittivity of vacuum, $g_{\alpha}(r) = h_{\alpha}(r) + 1$, ρ_{α} is the number density of the site α , and q_{α} is the partial charge of the site α . The Galvani potential of the solvent was estimated by calculating $\phi(\mathbf{r}_0)$ in the center of the cavity. Using the radius of the cavity equal to 0.5 Å (same as grid size), we estimated ϕ_{G} to be -13.43 kcal/mol/e for cSPC/e water and -12.55 kcal/mol/e for cTIP3P water.

Finite-Size Corrections. 3D-RISM is implemented on a nonperiodic grid and, therefore, corresponds to an infinitely diluted solute.⁶⁰ However, in PBC/Ewald MD simulations a solvated ion interacts with its periodic images; this introduces a number of periodicity related artifacts (finite-size effects).^{12,13,61–63} For single atomic ions there are analytical formulas which let one correct free energies resulting from MD simulation to reflect solvation in a nonperiodic system.^{10,13} For polyatomic ions there are no analytical formulas and one has to run two Poisson–Boltzmann simulations for periodic and nonperiodic systems to quantify the energetic effect of periodicity.^{63,64}

Fortunately, the magnitude of most of these errors scales as the ratio of the molecule size to the box length and becomes unimportant in the large box limit. A way to correct the finite-size errors without resorting to periodic Poisson–Boltzmann calculations has been suggested in the paper by Rocklin et al.⁶³

$$\Delta\Delta G_{\text{ANA}} = \Delta\Delta G_{\text{NET}} + \Delta\Delta G_{\text{USV}} + \Delta\Delta G_{\text{RIP}} + \Delta\Delta G_{\text{EMP}} \quad (18)$$

where $\Delta\Delta G_{\text{ANA}}$ stands for analytical corrections, $\Delta\Delta G_{\text{NET}}$ accounts for periodicity-induced net charge interaction, $\Delta\Delta G_{\text{USV}}$ is for periodicity-induced undersolvation, and $\Delta\Delta G_{\text{RIP}}$ is for residual integrated potential effects. $\Delta\Delta G_{\text{EMP}}$ is an empirical term. Out of all these corrections only two scale as an inverse length of the box L : $\Delta\Delta G_{\text{NET}}$ and $\Delta\Delta G_{\text{USV}}$. All other correction terms either decrease rapidly with increasing box size or become significant only for situations involving binding of charged species. Note that there is no need for us to correct the error associated with P summation since we are combining intrinsic free energies with ϕ_{G} , which leads to cancellation of this error.¹⁰

As we used a large box, only $\Delta\Delta G_{\text{NET}}$ and $\Delta\Delta G_{\text{USV}}$ were taken into account. All ionic hydration free energies obtained from molecular dynamics simulations were corrected as⁶³

$$\begin{aligned}\Delta G_{\text{MD,cor}} &= \Delta G_{\text{MD}} + \Delta\Delta G_{\text{USV}} + \Delta\Delta G_{\text{NET}} \\ &= \Delta G_{\text{MD}} - \frac{\xi}{8\pi\epsilon_0\epsilon_{\text{w}}} \frac{Q^2}{L}\end{aligned}\quad (19)$$

where ξ is the Wigner integration constant for cubic boxes (≈ -2.837297),⁶⁵ ϵ_{w} is the permittivity of model water (73.5 for SPC/E), and Q is the total charge of molecule. A similar shortened correction scheme has been used in other recent publications.^{19,66} We note that with the settings which were used in our study (3 nm sized box), the final finite-size correction is quite small, around 0.2 kcal/mol, and much smaller

382 smaller than the contribution due to water–vacuum potential
383 jump.

384 ■ METHODOLOGY

385 Experimental hydration free energies of ionic compounds and
386 their geometries were taken from the 2012 version of the
387 Minnesota solvation database.^{49,50} These values are based on
388 the hydration free energy of a proton = 265.9 kcal/mol.⁵¹
389 When selecting compounds from the database we avoided
390 water clusters as well as ions that were structurally similar to
391 other chosen molecules. We ended up selecting 70 compounds
392 in total: 36 anions and 34 cations.

393 For the ionic data set, we assigned GAFF force field
394 parameters and AM1-BCC charges using various programs
395 from the AmberTools 14 package.⁶⁷ We also tested the
396 performance of OPLS-2005⁶⁸ Lennard–Jones parameters
397 combined with Charge Model 5 partial charges (CM5).⁶⁹
398 Assignment of OPLS-2005 parameters was performed
399 automatically using Maestro.⁷⁰ For all calculations we used
400 Lorentz–Berthelot mixing rules.⁷¹ Evaluation of CM5 charges
401 required additional quantum mechanical calculations, which
402 were performed with Gaussian 09, Revision D.01,⁷² using the
403 M06-2X functional⁷³ and MG3S basis set.⁷⁴ Solvent was
404 represented using the SMD model.⁷ Charges were extracted
405 from output files using CMSPAC program.⁷⁵

406 Molecular dynamics simulations with ionic compounds were
407 performed using Gromacs 5.04.⁷⁶ We used a cubic box with
408 periodic boundary conditions. The water was represented using
409 a rigid SPC/E model.⁷⁷ In all simulations the system consisted
410 of a single ion and 1024 water molecules; no counterions were
411 used. All bonds with hydrogens were kept rigid using the
412 LINCS algorithm of 12th order. Dynamics was simulated using
413 the Langevin integrator, with a reference temperature of 298.15
414 K and a friction constant of 1.0 ps⁻¹.

415 For short-range interactions a pair list was generated using a
416 Verlet cutoff scheme. Lennard–Jones interactions were
417 smoothly switched off between 9 and 12 Å. The cutoff artifacts
418 were accounted for using long-range pressure and dispersion
419 corrections as implemented in Gromacs. Electrostatics
420 interactions were treated using the particle-mesh Ewald
421 (PME) method⁷⁹ with a 12 Å real space cutoff, 1.2 Å Fourier
422 spacing, 6th order spline interpolation, and tolerance set to
423 10⁻⁶.

424 To compute the hydration free energy using MD, we
425 performed 20 separate calculations at each λ , decoupling first
426 electrostatics and then Lennard–Jones interactions between
427 solute and solvent. Intramolecular interactions within solute
428 were kept the same at all lambda values. Calculations with
429 modified electrostatics interactions were performed at $\lambda = 0$,
430 0.25, 0.5, 0.75, and 1. Decoupling of the Lennard–Jones
431 interactions was done using calculations at $\lambda = 0, 0.05, 0.1, 0.2,$
432 0.3, 0.4, 0.5, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, and 1.0.

433 Prior to running MD simulation at each λ , we performed
434 5000 steps of steepest descent optimization. After that we
435 performed a 200 ps equilibration and 1300 ps production run.
436 The time step was set to 1 fs. In both equilibration and
437 production runs, pressure was kept constant at 1 bar using a
438 Berendsen barosta,⁸⁰ with time constant set to 1 ps and
439 compressibility to 4.5 $\times 10^{-5}$ bar⁻¹.

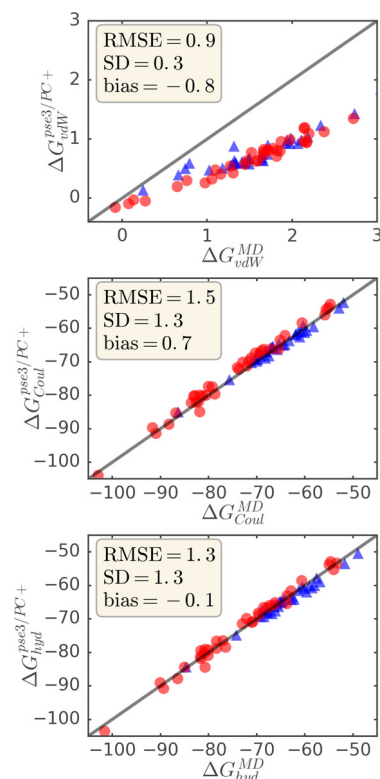
440 After completing the simulations, the intrinsic hydration free
441 energy was evaluated using the Multistate Bennett Acceptance
442 Ratio (MBAR).²⁹ The actual calculation was performed using a
443 python script `alchemical-analysis.py`.³¹

444 RISM calculations were performed with SPC/E and TIP3P
445 water models that have Lennard–Jones parameters on
446 hydrogen to improve convergence (cSPC/E and cTIP3P).⁸¹
447 Water susceptibility functions were generated using dielectri-
448 cally consistent 1D-RISM (DRISM)⁸² implemented in the
449 AmberTools 14 package. Water density was set to 997 kg/m³
450 and dielectric constant to 78.4 (experimental values at 298 K).
451 The DRISM equations were solved with tolerance set to 1 \times
452 10⁻¹² and grid spacing to 0.025 Å.

453 3D-RISM calculations were performed using the
454 `rism3d.snglpnt` program from the AmberTools 14 pack-
455 age.^{22,81,83} The grid spacing was set to 0.5 Å, buffer to 25 Å,
456 and tolerance to 1 $\times 10^{-5}$. While these parameters provide
457 slightly less accurate results compared to the ones used in our
458 previous work,¹⁸ the resulting errors in obtained hydration free
459 energies are only around 0.1 kcal/mol. On the other hand, they
460 led to a decrease in calculation time from minutes to seconds,
461 which in our opinion is a favorable trade-off. Both 1D-RISM
462 and 3D-RISM calculations were performed using the PSE-3
463 closure. Similarly to our previous work, calculation setup was
464 automated using a Python script available at https://github.com/MTS-Strathclyde/PC_plus.
465

466 ■ RESULTS AND DISCUSSION

467 **PC+ Model Verification.** Figure 2 compares insertion,
468 charging, and hydration free energies from 3D-RISM/PSE-3/
469



469 **Figure 2.** Comparison of predicted insertion free energies (top),
470 charging free energies (middle), and hydration free energies (bottom)
471 of ionic compounds from MD and PSE-3/PC+. In both models,
472 solutes were described using GAFF parameters and AM1-BCC
473 charges. Anions are shown as red circles and cations as blue triangles.
474 All energies are in kcal/mol. The box in the top left corner of each
475 figure shows root-mean-square error (RMSE), standard deviation
476 (SD), and bias of PSE-3/PC+ results compared to MD.

469 PC+ (from here on simply PC+) and MD/MBAR (or simply
 470 MD), both obtained using GAFF parameters, AM1-BCC
 471 charges, and SPC/E water models (cSPC/E for 3D-RISM).
 472 Both charging and hydration energies include the water–
 473 vacuum potential as well as finite-size corrections for MD
 474 results. The PC+ model underestimates insertion free energies
 475 with respect to MD, but the errors are systematic and
 476 proportional to the magnitude of the energy, unlike errors
 477 from the PSE-3 closure alone that are more or less random and
 478 are much larger in magnitude (uncorrected results are included
 479 in the Supporting Information). On the other hand, the
 480 agreement between charging free energies from both models is
 481 good, with errors of about 1.3 kcal/mol. Since the charging free
 482 energies are much larger in magnitude than insertion free
 483 energies, hydration free energies are in close agreement. Very
 484 similar results, but for neutral compounds, have also been
 485 obtained by Kleine et al.⁸⁴

486 Importantly, these results also justify our choice of
 487 approximating ϕ_G for 3D-RISM. Uncorrected results, which
 488 can be found in the Supporting Information, consistently
 489 overestimate the hydration free energy of anions and
 490 underestimate energies of cations compared to MD by about
 491 2 kcal/mol. Corrected results still contain charge-dependent
 492 bias, but it is much smaller: around 0.4 kcal/mol.

493 Both 3D-RISM and MD free energies have associated
 494 uncertainties, but with the parameters we used they are quite
 495 small: about 0.08 kcal/mol on average for MD and less than
 496 0.01 kcal/mol for 3D-RISM. These uncertainties are much
 497 smaller than errors associated with models and can be safely
 498 ignored for the purposes of this study.

499 The extent of agreement of PC+ results with MD is quite
 500 remarkable, considering that for ionic compounds energies are
 501 much larger in magnitude compared to neutral compounds.
 502 The observed differences can be attributed to the fact that 3D-
 503 RISM uses approximate closure, assumes additivity of direct
 504 correlation functions, omits third and higher order correlation
 505 functions, and does not sample solute conformations (this
 506 problem, however, can be solved by MD/3D-RISM⁸⁵). Overall,
 507 these results show that PSE-3/PC+ can serve as a good
 508 approximation to the much more expensive MD method:
 509 hydration free energies with 3D-RISM using parameters used in
 510 this study are evaluated in seconds on a single CPU, compared
 511 to approximately 6 h on 12 CPUs needed to obtain a single free
 512 energy from MD. This equates to about 4 orders of magnitude
 513 difference in computational power in favor of RISM.

514 **Comparison with Experiment.** Figure 3 shows a
 515 comparison between predicted and experimental solvation
 516 free energies. The two top graphs compare results from MD
 517 and PSE-3/PC+ obtained with GAFF/AM1-BCC parameters
 518 to experiment. The difference of errors from PSE-3/PC+ and
 519 MD is also much smaller than the difference between the
 520 models themselves. Thus, for a number of molecules PSE-3/PC
 521 + predicts hydration free energies more accurately than
 522 molecular dynamics. This might seem surprising at first,
 523 considering that 3D-RISM contains additional sources of errors
 524 due to a number of approximations. However, it has been
 525 shown that extra Lennard–Jones parameters on hydrogen in
 526 the cSPC/E model partially take into account polarization,⁸¹
 527 which might compensate for additional errors due to the model.

528 The accuracy of the results above is surprising and indicates
 529 that hydration free energies obtained with classical point charge
 530 models can be relatively reliable even without taking into
 531 account polarization, charge transfer, and an accurate

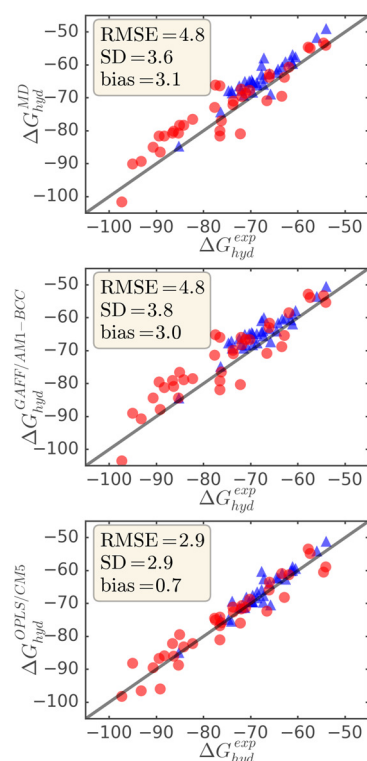


Figure 3. Comparison of hydration free energies of ionic compounds against experiment. (Top and middle) Results by MD and PSE-3/PC+, obtained using GAFF/AM1-BCC parameters. (Bottom) Results from PSE-3/PC+, obtained with OPLS/CMS parameters.

representation of dispersion interactions. Moreover, they
 further support the use of “real” hydration free energy as
 opposed to intrinsic (uncorrected results are provided in the
 Supporting Information and show clear biases for anions and
 cations).

To test whether we can improve our estimates using different
 Lennard–Jones parameters and partial charges, we repeated the
 3D-RISM calculations using combinations of the OPLS-2005
 force field Lennard–Jones parameters and CMS charges. We
 also reran all 3D-RISM calculations with cTIP3P water model,
 which was intended as a test for both PC+ and Galvani
 corrections. These results are shown in Table 1, where we
 additionally presented errors for cations and anions separately.

On the basis of the results in Table 1, we see that OPLS/
 CMS parameters outperform GAFF/AM1-BCC for both
 cSPC/E and cTIP3P water; individual data points obtained
 with these parameters and cSPC/E water are shown on the
 bottom graph of Figure 3. For both sets of nonbonded
 parameters cTIP3P results are slightly worse than cSPC/E. It is
 interesting that all models overestimate hydration free energy
 compared to experiment, similarly to the results obtained with
 the SMD model.⁷

Compared to GAFF/AM1-BCC, OPLS/CMS lowers both
 random error and bias, which is expected considering that this
 model was parametrized in order to accurately reproduce the
 electric field of a molecule and uses a more sophisticated
 electronic structure method to do it. This suggests that the use
 of QM/3D-RISM that has been proposed and implemented by
 a couple of other groups might lead to even better results.^{86,87}

To our knowledge the approach presented here is one of the
 most accurate ways of predicting ionic hydration free energies
 through computational models. The RMSE of about 3 kcal/mol

Table 1. Comparison of Predicted Hydration Free Energies with Experimental Data (kcal/mol)

method	force field	water model	combined			cations			anions		
			RMSE	SD	bias	RMSE	SD	bias	RMSE	SD	bias
MD	GAFF/AM1-BCC	SPC/E	4.76	3.61	3.13	4.43	2.28	3.82	5.05	4.46	2.47
PC+	GAFF/AM1-BCC	cSPC/E	4.84	3.79	3.04	3.93	2.24	3.25	5.56	4.84	2.85
PC+	OPLS/CM5	cSPC/E	2.94	2.87	0.73	2.41	2.07	1.27	3.37	3.41	0.22
PC+	GAFF/AM1-BCC	cTIP3P	5.40	3.85	3.82	3.50	2.19	2.76	6.72	4.75	4.82
PC+	OPLS/CM5	cTIP3P	3.20	2.87	1.45	2.28	2.07	1.02	3.87	3.44	1.86

564 obtained with OPLS/CM5 parameters and the cSPC/E water
 565 model is comparable to the 3.25 kcal/mol mean unsigned error
 566 reported for the SMVLE model, albeit on a larger data set.⁸ The
 567 approach also outperforms other popular models such as SMD⁷
 568 and SM8.⁸⁸ Importantly, the results presented here are
 569 obtained with force fields, which have not been parametrized
 570 for ionic solvation free energies. Therefore, they can be further
 571 improved by optimizing the force field parameters that is the
 572 subject of our ongoing research.

573 CONCLUSION

574 We proposed a new method for estimating the Galvani
 575 potential using 3D-RISM. The obtained estimate is then used
 576 to compute real hydration free energies of molecular ions with
 577 3D-RISM/PSE-3/PC+ models. Our values are in close
 578 agreement with both results of direct simulation by force
 579 field-based MD and with real experimental free energies. We
 580 found that the major source of errors in our calculations was
 581 related to the force field parameters and atomic partial charges
 582 and not to the approximations used in the 3D-RISM model.
 583 The use of OPLS-2005 Lennard–Jones parameters and CM5
 584 partial charges substantially decreased disagreement between
 585 the 3D-RISM hydration free energies and experiment, bringing
 586 the root-mean-square error on a set of 36 anions and 34 cations
 587 to about 3 kcal/mol. This level of accuracy makes the method
 588 proposed here competitive with the state of the art MD and
 589 continuum solvation approaches.^{8,88}

590 This study, together with our previous results for neutral
 591 compounds,¹⁸ shows that 3D-RISM, combined with PSE-3
 592 closure and PC+ correction, is a powerful method for
 593 predicting thermodynamic parameters of molecular solvation.
 594 The results suggest that at least for ionic compounds the
 595 accuracy of the 3D-RISM/PCE-3/PC+ model is more limited
 596 by the accuracy of the force fields than by the model
 597 approximations. A better parametrization of the force fields
 598 (potentially using fast 3D-RISM calculations for high-
 599 throughput optimization of parameters) should further reduce
 600 the observed errors. The study also revealed a problem related
 601 to the PC+ correction—systematic underestimation of the vdW
 602 component of the hydration free energy; we plan to address
 603 this problem in future articles.

604 ASSOCIATED CONTENT

605 Supporting Information

606 The Supporting Information is available free of charge on the
 607 ACS Publications website at DOI: 10.1021/acs.jpcc.5b10809.

608 Tables with experimental and computed hydration free
 609 energies for both data sets (csv); pdb structures of all
 610 molecules used in the calculations (zip); results obtained
 611 without taking into account Galvani potential or PC+
 612 correction are also presented (pdf).

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617 Notes

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