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Salting-out effects by pressure-corrected 3D-RISM

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In this paper, we demonstrate that using a pressure corrected three-dimensional reference interaction site model (3D-RISM/PC+) one can accurately predict salting-out (Setschenow's) constants for a wide range of organic compounds in aqueous solutions of NaCl . The approach, based on classical molecular force fields, offers an alternative to more heavily parametrized methods.

I. INTRODUCTION

Addition of ions to water affects solubilities, activities, and other thermodynamic parameters of solutes[1–4]. The environmental fate of compounds and their distribution between biological tissues are influenced by the salt content of solutions as well[5–8]. Techniques such as purification, polymorph control, and yield improvement, all utilize salt related effects[9–11]. Finally, interactions of ions with proteins are directly responsible for protein stability, with the strength of the effect conveniently described by Hofmeister series[12]. Despite that, there are only few theory-based approaches that can be applied to arbitrary molecules[13,14].

In this paper we demonstrate that a pressure corrected three-dimensional reference interaction site model (3D-RISM/PC+)[15–17] can be used to quantitatively describe NaCl effects on a solute, provided that suitable force field parameters are used. At the same time, the method requires only minimal computational resources. We finish by examining situations in which the proposed theory breaks down and discuss possible further improvements.

II. THEORY

Setschenow's constant. The effects of salt on partition coefficient can be quantified using Setschenow's equation[14]:

$$\log_{10}\left(\frac{K_{1/\text{water}}}{K_{1/\text{salt water}}}\right) = k_S C, \qquad (1)$$

where C is the molar concentration of salt in solution, k_S is the Setschenow's (or salting out) constant, and K is a partition coefficient of a compound between two phases, given by:

$$K_{1/water} = [\text{solute}]_{\text{water}} / [\text{solute}]_1 \qquad (2)$$

in which square brackets denote equilibrium concentrations. Setting phase 1 to a dilute gas, we can express the above equation in terms of corresponding solvation free energies[18] to get:

$$\Delta G_C = \Delta G_0 + k_S R T C \ln(10) \qquad (3)$$

where ΔG stands for solvation free energy, subscripts C and 0 denote salt concentrations in water, R is the universal gas constant, and T is temperature.

k_S is largely determined by molecular size. In sodium chloride solutions, the surface tension of water increases proportionally to the salt concentration[19], and thus, provides positive contribution to the solvation free energy of a molecule. However, this is not the only factor contributing to the Setschenow's constant[20]. Polar regions of molecules interact strongly with salts and this can provide negative contributions to ΔG[21]. Thus, to accurately predict k_S, one has to take into account the change of solvent surface tension, favourable interactions between solute and salts, and correlations between anions and cations.

3D-RISM. The theory behind 3D-RISM has been described in many previous publications[22–24]. Here we only briefly summarize it, focusing on the idea behind pressure corrections.

The solvation free energy predicted by 3D-RISM is strongly overestimated[23,25]. Sergiievskyi et al. have shown that this is mainly caused by a huge solvent pressure, which leads to an overestimated solute insertion work[15]. The pressure corrected (PC) 3D-RISM solvation free energy is given by:

$$\Delta G_{PC} = \Delta G_{3DRISM} - P\Delta V, \qquad (4)$$

where ΔV is the solute partial molar volume, and P is the 3D-RISM bulk solvent pressure, given by:

$$P = \frac{kT}{2}\sum_{i=1}^{N}\rho_i - \frac{1}{2\chi_T}, \qquad (5)$$

where N is the total number of sites (atoms) in solvent, k is the Boltzmann constant, ρ_i is the density of site i

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and χ_T is the isothermal compressibility of the solvent, computed with 1D-RISM.

While equation 4 greatly improves accuracy of 3D-RISM solvation free energy predictions, it still systematically underestimates experimental solvation free energies by a few kcal/mol[15]. In several recent articles, the benefits of a similar correction, called advanced pressure correction PC+ (previously ISc), have been demonstrated[16,17,26–28]:

$$\Delta G_{PC+} = \Delta G_{3DRISM} - P\Delta V + P_{id}\Delta V, \qquad (6)$$

where P_{id} is an ideal gas pressure of the solvent, given by $P_{id} = \rho kT$, in which ρ is the total density of all *species* in the solvent. Although, from a theoretical point of view the reason why PC+ performs well is not completely understood[15], it results in much better predictions of solvation free energy (at least for small molecules), comparable to those given by molecular dynamics[17,26]. For Setschenow's constants we do not expect the correction to be as significant since $P_{id}\Delta V$ term is relatively unaffected by the change in concentration, but the absolute values of solvation free energies in salt solution would be more accurate in PC+ and thus, we focus primarily on this approach.

For completeness, we note that recently a number of authors have proposed other ways of improving 3D-RISM results, which can provide alternative to PC/PC+ models[29–33]. Additionally, there are other studies investigating effects of salts on solutes using RISM approach, but they were mostly concerned with quantitative description of the problem[34–37]

III. METHODS

There are quite a few proposed NaCl force fields[38–41]. In this study we decided to limit our attention to those five sodium chloride models that were compatible with SPC/E water[42] and developed with Lorentz-Bertholet combination rules[43] in mind (table I). In all models, Na$^+$ and Cl$^-$ had +1 and −1 charges and differed only in Lennard-Jones parameters. The Dang's NaCl force-field parameters (da) were developed by fitting interaction energy, first peak of radial distribution function, and coordination number[44]. Joung and Cheatham's model (jc) is based on fitting the experimental hydration free energies of ions, as well as lattice constants and energies[45]. Deublein and co-workers (de) adjusted NaCl Lennard-Jones parameters to reproduce experimental density at a range of concentrations. Finally, Horinek et al. developed multiple force fields, by taking Dang's Cl$^-$ ion parameters and adjusting Na$^+$ parameters to match the solvation free energy of the ion pair. Since this approach does not lead to a unique pair of ϵ and σ, the authors proposed models based on small ϵ (we couldn't converge this model in 1D-RISM), large ϵ (ho$_a$), and medium ϵ values (ho$_b$).

Abbreviation	σ_{Na}	ϵ_{Na}	σ_{Cl}	ϵ_{Cl}	Ref.
da	2.584	0.100	4.401	0.100	44
jc	2.160	0.353	4.830	0.013	45
de	1.890	0.199	4.410	0.199	46
ho$_a$	2.130	1.540	4.400	0.100	47
ho$_b$	2.230	0.650	4.400	0.100	47

Table I. Lennard-Jones parameters of NaCl models used in this study. The values of σ are in Angstroms and ϵ in kcal/mol.

The experimental values for Setschenow's constants were taken from the article by Endo et al.[14]. This dataset consisted of 42 measurements made for environmentally relevant compounds, such as chlorinated alkanes/arenes, phtalates, and pharmaceuticals. Accurate measurement of Setschenow's constants ideally requires a vanishingly low concentration of solute in the water phase to prevent self-association from affecting the result. The authors used a headspace method and a microextraction technique to dissolve small amounts of solute in water and to ensure that the system reached equilibrium; their subsequent analyses found these techniques to be more reliable than a number of previous measurements. For this reason we used only data measured by Endo et al. to evaluate the accuracy of 3D-RISM based approach. Additionally, to directly compare predictions of 3D-RISM models with results from the article by Li et al.[13], we also used compounds utilized in their study.

The initial geometry guess for each molecule was created using the OpenBabel software package[48,49]. Afterwards, the geometry of each molecule was optimized using the M06-2X functional[50], and the MG3S basis set[51] as implemented in Gaussian 09, Revision D.01[52]. Solvent was represented using the SMD model[53]. Optimized solutes were assigned OPLS-2005[54] Lennard-Jones parameters and Charge Model 5 partial charges (CM5). Force-field parameters were determined automatically using Maestro[55]. Charges were extracted from Gaussian output files using the CM5PAC program[56,57].

Susceptibility functions for NaCl solutions were generated using dielectrically consistent 1D-RISM (DRISM)[58] implemented in the AmberTools 15 package. We used concentrations of 0.0, 0.1, 0.2, 0.3, 0.4, and 0.5 M. Dielectric constant was set to 78.4, density of water varied depending on NaCl concentration with data obtained using equation 1 from Ref 59. The DRISM equations were solved with tolerance set to 1×10^{-12} and grid spacing to 0.025 Å. To avoid numerical problems, we initially converged 1D-RISM solutions with KH closure, followed by PSE-3 and HNC[60]. In all calculations we used a modified SPC/E water model, taken from Ref. 61.

3D-RISM calculations were performed using the rism3d.snglpnt program from AmberTools 15 package[61–63]. The grid spacing was set to 0.5 Å, the buffer to 25 Å, tolerance to 1×10^{-5}. The equations were solved with PSE-3 closure. Using PC+ model,
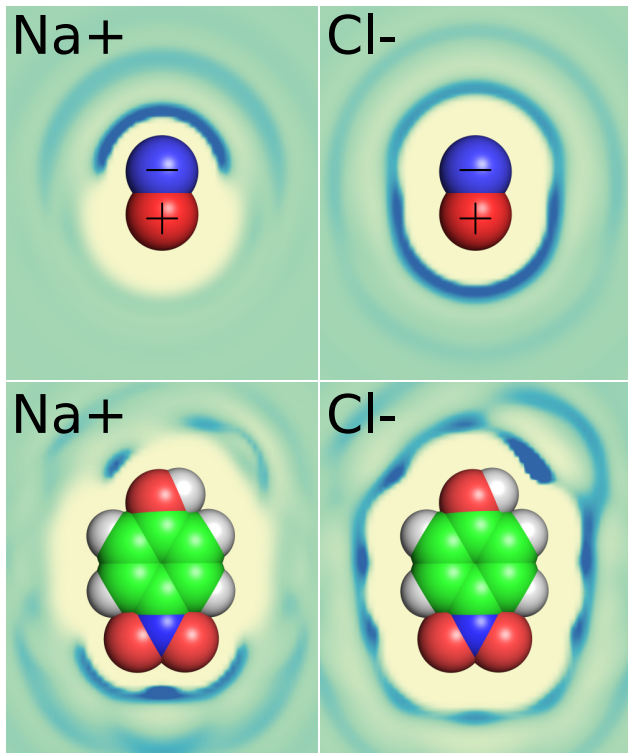
Figure 1. The 2D slices of spatial distribution of sodium ions (left) and chlorine ions (right) around a dipole (top) and p-nitrophenol (bottom). The yellowish colour corresponds to lower and blue to higher local density of ions. The concentration of NaCl was set to 0.5 M.

we evaluated solvation free energy of each solute at each salt concentration, and then used equation 3 to determine Setschenow's constant. The results of all calculations, script for generating susceptibility files, as well as optimized molecular geometries and topologies can be found in the Supplementary material.

IV. RESULTS AND DISCUSSION

We started by visualizing spatial distributions of ions around solutes, predicted by 3D-RISM. It is well known that chloride, due to its lower polarity compared to Na^+, approaches both interfaces and non-polar molecular surfaces; the sodium, on the other hand, is usually found only near negatively charged regions of molecules[64–67]. On figure 1 one can see slices of volumetric distributions from 3D-RISM around a hypothetical dipole and p-nitrophenol. As you can see, 3D-RISM predicts that compared to sodium, chloride is distributed more evenly around molecular surfaces: in line with previous studies. Additionally, near dipole one can also see considerable amount of overscreening[68–70].

Table II compares accuracies of Setschenow's constant predictions by different salt models. The results by poly-parameter linear free energy relationship (pp-LFER),

Table II. Accuracies of different models for predicting Setschenow's constant. The units are l/mol.

Model	RMSE	SDE	bias	r^2
da	0.029	0.028	0.009	0.853
ho_b	0.034	0.029	-0.018	0.839
jc	0.053	0.034	0.041	0.808
ho_a	0.056	0.029	-0.047	0.831
de	0.083	0.037	-0.075	0.731
pp-LFER	0.028	0.028	-0.002	0.844
SEA [a]	0.051	0.035	0.037	0.706
MD/TIP3P [a]	0.120	0.029	0.116	0.848
COSMO-RS	0.315	0.114	0.293	0.670

[a] The accuracy of model was evaluated on a different dataset.

semi-explicit assembly (SEA), molecular dynamics simulations with TIP3P water and Joung-Cheetham ions (MD/TIP3P), and COSMO-RS[71] are taken from previous studies[13,14]. In the literature, one can also find a few more chemoinformatics methods for Setschenow's constant prediction based on other descriptors or various machine learning methods[72–75], however the accuracy of these models did not significantly exceed the accuracy of pp-LFER approach. We found that predictions made with the Dang's salt force field (da) had the best agreement with experimental data among the studied 3D-RISM models, both in terms of its accuracy and the correlation. RISM calculations based on other salt models had similarly low random error, but larger biases.

The results from PC+ with the Dang's salt model are similar to the pp-LFER model that was fit on Endo's dataset using 6 adjustable descriptors. It outperforms both SEA and COSMO-RS models, which are both partially based on the idea that summing surface elements of a solute is a useful strategy for predicting solvation free energies. 3D-RISM, on the other hand, takes into account correlations between densities of solvent at the surface of solute, which most likely contributes to its better accuracy. Note that good estimates were obtained only with pressure corrected models, uncorrected 3D-RISM showed quite poor accuracy (the table with the results is included in the supporting information). It is also worth mentioning that accuracies of both SEA and MD/TIP3P models are evaluated on a different dataset for which 3D-RISM/PC+ with Dang's NaCl force field has RMSE = 0.038 l/mol, SDE = 0.029 l/mol, bias = −0.025 l/mol, and $r^2 = 0.798$; the results for other models can be found in the Supplementary material. The slight decrease of accuracy is likely explained by less reliable experimental data.

Molecular dynamics based predictions of Setschenow's constant, despite achieving impressive correlation with experimental data ($r^2 = 0.848$), have a large positive bias. We believe that the origin of this bias is likely related to the chosen salt model (jc) and force fields: GAFF with TIP3P water. It is likely that combination of Dang
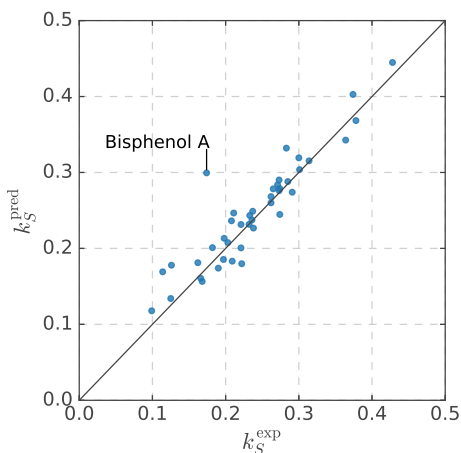
Figure 2. Setschenow's constants by 3D-RISM/PC+ with Dang salt model (y-axis) compared to experimental measurements by Endo et al. (x-axis). The units are in l/mol.
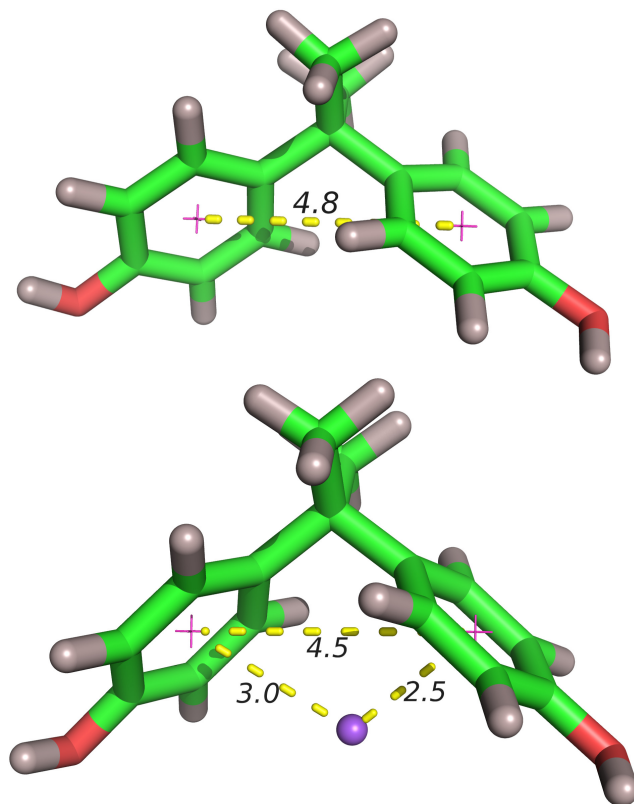

Figure 3. The optimized geometries of bisphenol A with and without Na^+ ion. The distances, shown in Angstroms, are measured between the centres of benzene rings and the ion.

salt model and SPC/E water would reduce the bias in the prediction and make molecular dynamics simulations one of the most accurate ways of predicting Setschenow's constant, although, quite time consuming.

On figure 2 you can see comparison between Setschenow's constants predicted by 3D-RISM with Dang's NaCl model and those from experimental measurements (similar figures for other models can be found in the Supplementary material. One major outlier is bisphenol A. 3D-RISM overestimates its k_S by 0.13 l/mol: more than four times greater than the average prediction error for Dang's model. This molecule was also an outlier in 3D-RISM calculations with other salt models. While potentially this might be the result of measurement error, we believe that the reason for this lies in the fact that Bisphenol A binds relatively strongly to sodium ion via π-cation interactions. We performed electronic density functional theory calculations to test this hypothesis. The optimization was done using the same level of theory and software as for initial molecule preparation (M06-2X/MG3S, with solvent approximated via SMD model). Optimized geometries for bisphenol A with and without sodium atoms, shown on figure 3, indicate significant structural rearrangement as well as considerable bonding between Na^+ and both phenol rings. These type of interactions are difficult to characterize using conventional force fields[76], and would require a quantum mechanics approach to dispersion interactions. Additionally, conventional 3D-RISM operates with rigid solutes and does not capture salt-induced changes in solute conformation.

To conclude, we have found that the 3D-RISM/PC+ model, combined with the Dang's NaCl parameters can be used to accurately predict Setschenow's constants for a wide range of molecules, without prior parametrization. The model has RMSE=0.03 l/mol and $r^2 = 0.85$ on an accurate set of measurements produced by Endo et al. The approach in principle can be extended to other so-lutions, although such developments will require further research and will be a subject of our future work.

SUPPLEMENTARY MATERIAL

See supplementary material for more detailed information on performance of 3D-RISM models as well as calculation input files.

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REFERENCES

[1] K. J. Tielrooij, N. Garcia-Araez, M. Bonn, and H. J. Bakker, "Cooperativity in ion hydration," Science **328**, 1006–1009 (2010).

[2] Y. Marcus, "Effect of ions on the structure of water: Structure making and breaking," Chem. Rev. **109**, 1346–1370 (2009).

[3] D. R. Robinson and W. P. Jencks, "The effect of concentrated salt solutions on the activity coefficient of acetyltetraglycine ethyl ester," J. Am. Chem. Soc. **87**, 2470–2479 (1965).

[4] W. F. McDevit and F. A. Long, "The activity coefficient of benzene in aqueous salt solutions," J. Am. Chem. Soc. **74**, 1773–1777 (1952).

[5] M. G. Cacace, E. M. Landau, and J. J. Ramsden, "The hofmeister series: salt and solvent effects on interfacial phenomena," Q. Rev. Biophys. **30**, 241–277 (1997).

[6] J. W. Readman, R. F. C. Mantoura, and M. M. Rhead, "The physico-chemical speciation of polycyclic aromatic hydrocarbons (PAH) in aquatic systems," Z. Anal. Chem. **319**, 126 (1984).

[7] W. Mabey and T. Mill, "Critical review of hydrolysis of organic compounds in water under environmental conditions," J. Phys. Chem. Ref. Data **7**, 383–415 (1978).

[8] R. A. Park, J. S. Clough, and M. C. Wellman, "AQUATOX: modeling environmental fate and ecological effects in aquatic ecosystems," Ecological Modelling **213**, 1–15 (2008).

[9] B. A. Holmberg, H. Wang, J. M. Norbeck, and Y. Yan, "Controlling size and yield of zeolite y nanocrystals using tetramethylammonium bromide," Microporous and Mesoporous Materials **59**, 13–28 (2003).

[10] S. Sasaki, S. Koga, R. Imabayashi, and H. Maeda, "Salt effects on the volume phase transition of ionic gel induced by the hydrophobic counterion biding," J. Phys. Chem. B **105**, 5852–5855 (2001).

[11] W. Melander and C. Horváth, "Salt effects on hydrophobic interactions in precipitation and chromatography of proteins: An interpretation of the lyotropic series," Archives of Biochemistry and Biophysics **183**, 200–215 (1977).

[12] Y. J. Zhang and P. S. Cremer, "Chemistry of hofmeister anions and osmolytes," Annu. Rev. Phys. Chem. **61**, 63–83 (2010).

[13] L. Li, C. J. Fennell, and K. A. Dill, "Small molecule solvation changes due to the presence of salt are governed by the cost of solvent cavity formation and dispersion," J. Chem. Phys. **141**, 22D518 (2014).

[14] S. Endo, A. Pfennigsdorff, and K.-U. Goss, "Salting-out effect in aqueous NaCl solutions: Trends with size and polarity of solute molecules," Environ. Sci. Technol. **46**, 1496–1503 (2012).

[15] V. Sergiievskyi, G. Jeanmairet, M. Levesque, and D. Borgis, "Solvation free-energy pressure corrections in the three dimensional reference interaction site model," J. Chem. Phys. **143**, 184116 (2015).

[16] M. Misin, D. S. Palmer, and M. V. Fedorov, "Predicting solvation free energies using parameter-free solvent models," J. Phys. Chem. B (2016).

[17] M. Misin, M. V. Fedorov, and D. S. Palmer, "Hydration free energies of molecular ions from theory and simulation," J. Phys. Chem. B **120**, 975–983 (2016).

[18] A. Ben-Naim, *Molecular Theory of Solutions* (OUP, Oxford, 2006).

[19] Y. Marcus, "Individual ionic surface tension increments in aqueous solutions," Langmuir **29**, 2881–2888 (2013).

[20] M. A. Schlautman, S. Yim, E. R. Carraway, J. H. Lee, and B. E. Herbert, "Testing a surface tension-based model to predict the salting out of polycyclic aromatic hydrocarbons in model environmental solutions," Water Research **38**, 3331–3339 (2004).

[21] W. Li and Y. Mu, "Hydration patterns and salting effects in sodium chloride solution," J. Chem. Phys. **135**, 134502 (2011).

[22] D. Beglov and B. Roux, "An integral equation to describe the solvation of polar molecules in liquid water," J. Phys. Chem. **101**, 7821–7826 (1997).

[23] E. L. Ratkova, D. S. Palmer, and M. V. Fedorov, "Solvation thermodynamics of organic molecules by the molecular integral equation theory: Approaching chemical accuracy," Chem. Rev. **115**, 6312–6356 (2015).

[24] F. Hirata, *Molecular Theory of Solvation* (Kluwer Academic Publishers, New York, 2003).

[25] G. N. Chuev, S. Chiodo, S. E. Erofeeva, M. V. Fedorov, N. Russo, and E. Sicilia, "A quasilinear RISM approach for the computation of solvation free energy of ionic species," Chem. Phys. Lett. **418**, 485–489 (2006).

[26] M. Misin, M. V. Fedorov, and D. S. Palmer, "Communication: Accurate hydration free energies at a wide range of temperatures from 3D-RISM," J. Chem. Phys. **142**, 091105 (2015).

[27] B. Li, A. V. Matveev, and N. Rösch, "Three-dimensional reference interaction site model solvent combined with a quantum mechanical treatment of the solute," Comput. Theor. Chem. **1070**, 143–151 (2015).

[28] J. Johnson, D. A. Case, T. Yamazaki, S. Gusarov, A. Kovalenko, and T. Luchko, "Small molecule hydration energy and entropy from 3D-RISM," J. Phys.: Condens. Matter **28**, 344002 (2016).

[29] T. Sumi, A. Mitsutake, and Y. Maruyama, "A solvation-free-energy functional: A reference-modified density functional formulation," J. Comput. Chem. **36**, 1359–1369 (2015).

[30] G. Jeanmairet, M. Levesque, V. Sergiievskyi, and D. Borgis, "Molecular density functional theory for water with liquid-gas coexistence and correct pressure," J. Chem. Phys. **142**, 154112 (2015).

[31] Y. Ebato and T. Miyata, "A pressure consistent bridge correction of kovalenko-hirata closure in ornstein-zernike theory for lennard-jones fluids by apparently adjusting sigma parameter," **6**, 055111 (2016).

[32] F. Mrugalla and S. M. Kast, "Designing molecular complexes using free-energy derivatives from liquid-state integral equation theory," J. Phys.: Condens. Matter **28**, 344004 (2016).

[33] T. Hayashi, H. Oshima, Y. Harano, and M. Kinoshita, "Water based on a molecular model behaves like a hard-sphere solvent for a nonpolar solute when the reference interaction site model and related theories are employed," J. Phys.: Condens. Matter **28**, 344003 (2016).

[34] M. Kinoshita and F. Hirata, "Analysis of salt effects on solubility of noble gases in water using the reference interaction site model theory," **106**, 5202–5215 (1997).

[35] T. Imai, M. Kinoshita, and F. Hirata, "Salt effect on stability and solvation structure of peptide: An integral equation study," **73**, 1113–1122 (2000).

[36] R. Ishizuka, G. A. Huber, and J. A. McCammon, "Solvation effect on the conformations of alanine dipeptide: Integral equation approach," J. Phys. Chem. Lett. **1**, 2279–2283 (2010).

[37] Y. Maruyama, N. Yoshida, and F. Hirata, "Electrolytes in biomolecular systems studied with the 3D-RISM/RISM theory," Interdiscip Sci Comput Life Sci **3**, 290–307 (2011).

[38] F. Moučka, I. Nezbeda, and W. R. Smith, "Molecular force fields for aqueous electrolytes: SPC/E-compatible charged LJ sphere models and their limitations," J. Chem. Phys. **138**, 154102 (2013).

[39] B. Hess, C. Holm, and N. v. d. Vegt, "Osmotic coefficients of atomistic NaCl (aq) force fields," J. Chem. Phys. **124**, 164509 (2006).

[40] M. Patra and M. Karttunen, "Systematic comparison of force fields for microscopic simulations of NaCl in aqueous solutions: Diffusion, free energy of hydration, and structural properties," J. Comput. Chem. **25**, 678–689 (2004).

[41] A. Asmadi, T. Kirchner, W. Abdallah, M. V. Fedorov, and M. R. Stukan, "Influence of the drude charge value on the performance of polarisable water model: A test for microscopic and macroscopic parameters," J. Mol. Liq. **188**, 245–251 (2013).

[42] H. J. C. Berendsen, J. R. Grigera, and T. P. Straatsma, "The missing term in effective pair potentials," J. Phys. Chem. **91**, 6269–6271 (1987).

[43] M. P. Allen and D. J. Tildesley, eds., *Computer Simulation of Liquids* (Clarendon Press, Oxford, UK, 1987).

[44] L. X. Dang, "Mechanism and thermodynamics of ion selectivity in aqueous solutions of 18-crown-6 ether: A molecular dynamics study," J. Am. Chem. Soc. **117**, 6954–6960 (1995).

[45] I. S. Joung and T. E. Cheatham, "Determination of alkali and halide monovalent ion parameters for use in explicitly solvated biomolecular simulations," J. Phys. Chem. B **112**, 9020–9041 (2008).

[46] S. Deublein, J. Vrabec, and H. Hasse, "A set of molecular models for alkali and halide ions in aqueous solution," J. Chem. Phys. **136**, 084501 (2012).

[47] D. Horinek, S. I. Mamatkulov, and R. R. Netz, "Rational design of ion force fields based on thermodynamic solvation properties," J. Chem. Phys. **130**, 124507 (2009).

[48] N. M. O'Boyle, M. Banck, C. A. James, C. Morley, T. Vandermeersch, and G. R. Hutchison, "Open babel: An open chemical toolbox," J Cheminform **3**, 33 (2011).

[49] N. M. O'Boyle, C. Morley, and G. R. Hutchison, "Pybel: a python wrapper for the OpenBabel cheminformatics toolkit," Chemistry Central Journal **2**, 1–5 (2008).

[50] Y. Zhao and D. G. Truhlar, "The m06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four m06-class functionals and 12 other functionals," Theor Chem Account **120**, 215–241 (2007).

[51] B. J. Lynch, Y. Zhao, and D. G. Truhlar, "Effectiveness of diffuse basis functions for calculating relative energies by density functional theory," J. Phys. Chem. A **107**, 1384–1388 (2003).

[52] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, *Gaussian˜09 Revision D.01*, Gaussian Inc., Wallingford CT (2009).

[53] A. V. Marenich, C. J. Cramer, and D. G. Truhlar, "Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions," J. Phys. Chem. B **113**, 6378–6396 (2009).

[54] J. L. Banks, H. S. Beard, Y. Cao, A. E. Cho, W. Damm, R. Farid, A. K. Felts, T. A. Halgren, D. T. Mainz, J. R. Maple, R. Murphy, D. M. Philipp, M. P. Repasky, L. Y. Zhang, B. J. Berne, R. A. Friesner, E. Gallicchio, and R. M. Levy, "Integrated modeling program, applied chemical theory (IMPACT)," J. Comput. Chem. **26**, 1752–1780 (2005).

[55] *Maestro*, Schrödinger, LLC, New York, NY (2014).

[56] A. V. Marenich, S. V. Jerome, C. J. Cramer, and D. G. Truhlar, "Charge model 5: An extension of hirshfeld population analysis for the accurate description of molecular interactions in gaseous

and condensed phases," J. Chem. Theory Comput. **8**, 527–541 (2012).

[57] A. Marenich, C. Cramer, and D. Truhlar, *CM5PAC*, University of Minnesota, Minneapolis, MN (2013).

[58] J. Perkyns and B. M. Pettitt, "A site–site theory for finite concentration saline solutions," J. Chem. Phys. **97**, 7656–7666 (1992).

[59] P. Novotny and O. Sohnel, "Densities of binary aqueous solutions of 306 inorganic substances," J. Chem. Eng. Data **33**, 49–55 (1988).

[60] S. M. Kast and T. Kloss, "Closed-form expressions of the chemical potential for integral equation closures with certain bridge functions," J. Chem. Phys. **129**, 236101 (2008).

[61] T. Luchko, S. Gusarov, D. R. Roe, C. Simmerling, D. A. Case, J. Tuszynski, and A. Kovalenko, "Three-dmensional molecular theory of solvation coupled with molecular dynamics in amber," J. Chem. Theory Comput. **6**, 607–624 (2010).

[62] A. Kovalenko and F. Hirata, "Potentials of mean force of simple ions in ambient aqueous solution. i. three-dimensional reference interaction site model approach," J. Chem. Phys **112**, 10391–10402 (2000).

[63] A. Kovalenko and F. Hirata, "Self-consistent description of a metal-water interface by the kohn-sham density functional theory and the three-dimensional reference interaction site model," J. Chem. Phys. **110**, 10095–10112 (1999).

[64] M. Lund, L. Vrbka, and P. Jungwirth, "Specific ion binding to nonpolar surface patches of proteins," J. Am. Chem. Soc. **130**, 11582–11583 (2008).

[65] P. E. Smith, "Computer simulation of cosolvent effects on hydrophobic hydration," J. Phys. Chem. B **103**, 525–534 (1999).

[66] P. Jungwirth and D. J. Tobias, "Surface effects on aqueous ionic solvation: A molecular dynamics simulation study of NaCl at the Air/Water interface from infinite dilution to saturation," J. Phys. Chem. B **104**, 7702–7706 (2000).

[67] P. B. Petersen and R. J. Saykally, "On the nature of ions at the liquid water surface," Annu. Rev. Phys. Chem. **57**, 333–364 (2006).

[68] M. V. Fedorov and A. A. Kornyshev, "Unravelling the solvent response to neutral and charged solutes," Mol. Phys. **105**, 1–16 (2007).

[69] Y. Levin, "Electrostatic correlations: from plasma to biology," Rep. Prog. Phys. **65**, 1577 (2002).

[70] M. V. Fedorov and A. A. Kornyshev, "Ionic liquids at electrified interfaces," Chem. Rev. **114**, 2978–3036 (2014).

[71] A. Klamt, *COSMO-RS: From Quantum Chemistry to Fluid Phase Thermodynamics and Drug Design* (Elsevier Science, Amsterdam, 2005).

[72] N. Ni and S. H. Yalkowsky, "Prediction of setschenow constants," International Journal of Pharmaceutics **254**, 167–172 (2003).

[73] Y. Li, Q. Hu, and C. Zhong, "Topological modeling of the setschenow constant," Ind. Eng. Chem. Res. **43**, 4465–4468 (2004).

[74] J. Xu, L. Wang, L. Wang, X. Shen, and W. Xu, "QSPR study of setschenow constants of organic compounds using MLR, ANN, and SVM analyses," J. Comput. Chem. **32**, 3241–3252 (2011).

[75] X. Yu and R. Yu, "Setschenow constant prediction based on the IEF-PCM calculations," Ind. Eng. Chem. Res. **52**, 11182–11188 (2013).

[76] F. Archambault, C. Chipot, I. Soteras, F. J. Luque, K. Schulten, and F. Dehez, "Polarizable intermolecular potentials for water and benzene interacting with halide and metal ions," J. Chem. Theory Comput. **5**, 3022–3031 (2009).