

Optimized ion force fields from free energy simulations

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August 31, 2007

Abstract

The prediction of hydration free energies of single ions by atomistic simulations strongly depends on the simulation protocol. Most of the current parameter sets are based on simulations in a finite water droplet. We develop a set of (unpolarizable) parameters for halide anions and alkali cations to be used with simulations of periodic systems with Ewald summation for the long-range Coulomb interactions with SPC/E water. We optimize the parameters to reproduce the solvation free energy and entropy.

The developed parameters give a good reproduction of the first maximum of the ion-oxygen radial distribution functions, which serves as a measure of structural properties of the solution.

1 Introduction

Ion solvation is important in many areas of practical interest, including interface physics, environmental chemistry, and the study of biological molecules, colloids, surfactants and polyelectrolytes. [1] In biology, ions are critical to the structure and function of nucleic acids, proteins, and lipid membranes, and biological activity varies strongly between different ion types.[2] This ion specificity arises from ion-solvent interactions, and the complexity of the system poses a serious obstacle for a rigorous and predictive statistical mechanical explanation [3]. Classical atomistic simulations are a powerful approach for the modeling of such complex systems, because no assumptions on solvent mediated forces have to be made. They only require the definition of the forces between the individual atoms of the system as input. Consequently, reliable results can only be obtained from such simulations, if the underlying force field gives a correct description of the system's energetics. The development of accurate force fields for condensed-phase simulations, specially in aqueous environment, is a complex problem. The

different simulation setups are considered, we find these variations astonishing. For the goal of performing simulations of ion specific effects in bulk solution and in interfacial systems, we have to rely on a robust set of parameters that can be used in systems with periodic boundary conditions. The parameter set of Åqvist [15], selected because it is incorporated in force field databases, leads to big errors in thermodynamic quantities when used with our simulation method, as can be seen in Fig 2. Taking all this into account, we have little confidence that we find a reliable and complete set of parameters that is suited for the applied simulation protocol. Therefore, we develop two sets of force field parameters for halide anions and alkali cations. The parameter optimization is performed constructing the surfaces of solvation free energy and solvation entropy as a function of σ and ϵ , and determining the optimal parameters for every ionic species which reproduce the experimental solvation free energy and entropy. The parameters are optimized for SPC/E water[16], but are applicable also with other three-site water models like SPC and TIP3P. Their performance is then judged based on predictions of R_1 , the position of the first maximum of the radial distribution function.

2 Computational methods

Molecular dynamics simulations are performed using the AMBER8 package.[17] A single ion is placed in a cubic box of size $25\text{\AA} \times 25\text{\AA} \times 25\text{\AA}$ containing 506 SPC/E water molecules. The SPC/E water model assigns partial charges of -0.8476 and 0.4238 to oxygen and hydrogen. The geometry is fixed at a bond length of 1.0 Å and a bond angle of 109.47°. Lorentz-Berthelot combination rules for the Lennard-Jones parameters are assumed:

$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}, \quad \sigma_{ij} = \frac{\sigma_i + \sigma_j}{2}.$$

A cut-off distance of 9 Å is chosen for the Lennard-Jones interactions. Periodic boundary conditions are applied in all three directions, and long-ranged electrostatic forces are calculated using particle-mesh Ewald summation (PME)[18] with tin-foil boundary conditions. The geometry of the water molecules is constrained using shake.[19] Molecular dynamics simulations are performed with 1 fs time step. The simulations are carried out in the NpT ensemble using the Berendsen weak coupling method to keep a temperature of 300 K and a reference pressure of 1 bar.

The solvation free energy of an ion is calculated using thermodynamic integration (TI).[20] In TI, one exploits the fact that the free energy is a function of state, and that the solvation free energy is thus independent of the specific path of solvation. For a given path of solvation, the free energy is given as

$$\Delta G = \int_0^1 \left\langle \frac{\partial H}{\partial \lambda} \right\rangle d\lambda, \quad (2)$$

where the transition coordinate λ is 1 in the solvated case and 0 in the unsolvated state. The integration can be discretized in n intervals, given that the step size $\Delta\lambda$ is sufficiently

energy of solvation in our simulation calculated on the base of potential energy term and does not contain any translational motion terms. Therefore we consider the process of solvation as consisting of two steps, one inserting the solute at the fixed point in a solvent without thermal motion, and second where the solute allowed to move. In the first step volume of the system changes by the excluded volume of the solute, V_{ex} . In the second step volume changes due to ion motion (liberation).

The entropy of solvation includes three correction terms in addition the entropy change from simulation:

$$\Delta S_{total} = \Delta S_{sim} + k_B(T\alpha_s - 1) - k_B\rho_w V_{ex} \quad (5)$$

where, $\alpha = 257.21 \cdot 10^{-6} K^{-1}$ is the thermal expansion of the water ($T\alpha = 0.077$, so it can be omitted). The first term, $-k_B$, comes from the expression of derivative of the chemical potential difference of the ions in the ideal gas and in liquid phase $\Delta\mu(g \rightarrow l)$ [27]. The second term $k_B\rho_w V_{ex}$ appears as the result of volume exclusion due to ion solvation [26]. The excluded volume is calculated by Kirkwood-Buff expression for the partial volume [24] which becomes

$$V_{ex} = \int (g_{iw} - 1) dr, \quad (6)$$

where g_{iw} is the radial distribution function of ion-oxygen atom of water molecule.

The quality of the internal energy ΔU and free energy ΔG is assessed by the estimation of the implied numerical errors, since the systematic errors are corrected. The errors of $dH/d\lambda$ at every step of the thermodynamic integration and the error of U are estimated by block averaging [28], and the uncertainties of ΔU , ΔG and ΔS are calculated by statistical error propagation.

First, we determine the free energy and entropy of solvation for the parameters developed by Åqvist[15]. We then sample σ and ε on a 7×3 grid for each ion charge. For monovalent ions the range 2.5 to 5.5 is studied. For an efficient optimization of σ and ε , a numerical evaluation of ΔG and ΔS for a given (σ, ε) is mandatory. This is achieved approximating the surfaces of the solvation free energy and entropy by third order polynomials in ε and σ

$$\Delta G = \sum_{i=0}^3 \sum_{j=0}^3 g_{ij} \sigma^i \varepsilon^j \quad (7)$$

$$\Delta S = \sum_{i=0}^3 \sum_{j=0}^3 s_{ij} \sigma^i \varepsilon^j. \quad (8)$$

The coefficients g_{ij} and s_{ij} are determined minimizing the mean squared error. From the fitted free energy and entropy surfaces, we determine the optimal parameters for every ion as the point in the (σ, ε) plane that reproduces the solvation free energy exactly and yields the minimum error for the solvation entropy.

For the thus determined parameter sets, we determine the solvation free energy and entropy again by MD simulations, and calculate the ion-oxygen radial distribution function.

For Na^+ and Cl^- , we also determine the solvation free energy with the water models SPC and TIP3P.

The free energies obtained from our simulations strongly depend on the sign of the ion's charge: anion solvation is much more preferred than cation solvation. This disagrees with the Born solvation model, which predicts solvation free energies independent of the sign of the charge. It is related to a positive potential that is induced by the solvent at the position of a neutral cavity in water.[22]

Experimentally, single ion solvation free energies are not determined by thermodynamics, where only the solvation of a neutral set of ions is measurable. We compare our simulation results with data compiled by Marcus, [23] which are based on the absolute hydration free energy of the proton. These solvation free energies are different for anions and cations of similar size. Thus, it is obvious that the anisotropy of the solvation free energy is not simply a simulation artefact. A detailed structural study of the ion's solvation shell [30] lead to the conclusion that water molecules in the solvation sphere of an anion are able to maintain more favourable water-water interactions compared to water in a cation's solvation sphere.

Solvation entropy. For the accurate calculation of solvation entropies using the thermodynamic relation $\Delta S = 1/T(\Delta U - \Delta G)$, it is necessary to get ΔU with similar accuracy as ΔG . The direct evaluation $\Delta U = \langle U \rangle_{\lambda=1} - \langle U \rangle_{\lambda=0}$ thus requires long simulation times, in our case 3 ns are required to get ΔU converged to ± 0.2 kJ/mol. The resulting statistical error of ΔS is less than ± 5 J/molK for all studied simulations. Fig. 7 shows the simulation results for ΔS as a function of σ for the studied values of ϵ for $q = -1$ and $+1$.

Contrary to the solvation free energy, which shows similar trends for ions of each charge, the solvation entropy behaves qualitatively differently for ions of different charge. For monovalent anions, ΔS is monotonically increasing with increasing σ , and the ϵ dependence is comparably weak, similarly to the behavior of ΔG . For the anions, ΔS varies from -275 J/molK for $\sigma = 2.6$ Å to 0 for $\sigma = 5.3$ Å. Still, ϵ has a stronger effect on ΔS than on ΔG . For monovalent cations, the results are qualitatively different. We find the smallest solvation entropies, ranging from -100 to 0 J/molK. ΔS has a pronounced maximum for σ in the range of 4 - 5 Å. Taking the small numbers for ΔS into account, it follows that the relative effect of ϵ is strongest for the monovalent cations.

Even for the largest anions studied, we do not find a similar maximum of the solvation entropy.

From the preceding, it is clear that the solvation entropy is much more sensitive towards variation in ϵ than the solvation free energy. This is a case of enthalpy-entropy compensation,[cite] where the entropically unfavorable stronger ion binding is compensated by a favorable increase in binding energy.

Free energy and entropy surfaces. The polynomial fit gives a smooth representation of the free energy surface in (σ, ϵ) space. We obtain a mean square error χ of 0.9 kJ/mol for the anion surface and 0.3 kJ/mol for the cations. A polynomial expansion up to second order gives less satisfactory results. In principle, higher order terms in the expansion would give an even better reproduction of the simulation data, but oscillations in the areas between the fit points would make interpolations between the points less reliable. The fit parameters g_{ij} are shown in Table 1. The resulting surface for anions as a function of σ and ϵ is shown in Fig.

and Cl^- parameters for solvation in SPC and TIP3P water. In all cases, we get good results for the solvation free energy. We did not test the transferability of the other parameters, but we expect that the other ions are also described accurately with the other three-site water models.

4 Conclusions

Thermodynamic integration calculations in the context of MD simulations have been used for optimizing a set of Lennard-Jones parameters for the halide ions, F^- , Cl^- , Br^- , and I^- , and for the alkali metal ions, Li^+ , Na^+ , K^+ , and Cs^+ . Contrary to previous approaches to ion parameters we consider the solvation free energy and the solvation entropy. The optimization based on these two properties gives well-determined set of Lennard-Jones parameters that differs from known parameter sets. The new ion parameters reproduce free energies of hydration with an average error below 1 kJ/mol and entropy of solvation with error of 5 J mol⁻¹K⁻¹. Structural characteristics (radial distribution function) are well reproduced for cations and slightly overestimated for anions.

5 Acknowledgements

Sh.I.M. acknowledges support from the IDB Post-Doctoral Scholarship Program.

References

- [1] Conway, B. *Solid State Ionics* **1997**, *94*, 165–170.
- [2] Kunz, W.; Lo Nostro, P.; Ninham, B. W. *Curr. Op. Coll. Int. Sci.* **2004**, *9*, 1–18.
- [3] Horinek, D.; Netz, R. *submitted* **2007**.
- [4] Grossfield, A.; Ren, P.; Ponder, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 15671.
- [5] Guillot, B. *Journal of Molecular Liquids* **2002**, *101*, 219.
- [6] Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; Hermans, J. In *Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; Hermans, J.; Pullman, B., Ed.; Dordrecht*, 1981; p 331.
- [7] Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys* **1983**, *79*, 926–935.
- [8] Patra, M.; Karttunen, M. *J. Comp. Chem.* **2004**, *25*, 678.
- [9] Kastenzholz, M. A.; Hünenberger, P. H. *J. Chem. Phys* **2006**, *124*, 124106.

Table 1: Parameters for the polynomial fits $\Delta G = \sum \sum g_{ij} \sigma^i \epsilon^j$ and $\Delta S = \sum \sum s_{ij} \sigma^i \epsilon^j$. The units of the parameters are $\text{\AA}^{-i}(\text{kJ/mol})^{-j} \text{kJ/mol}$ for g_{ij} and $\text{\AA}^{-i}(\text{kJ/mol})^{-j} \text{J/molK}$ for s_{ij} .

q/e	g_{00}	g_{10}	g_{20}	g_{30}	g_{01}	g_{11}	g_{21}	g_{31}
-1	-8515.0	10554.1	-4550.5	654.59	26353.3	-36267.8	16296.2	-2396.3
+1	-847.51	509.54	-129.75	12.896	15.290	120.32	-84.661	12.859
	g_{02}	g_{12}	g_{22}	g_{32}	g_{03}	g_{13}	g_{23}	g_{33}
-1	28521.2	39476.4	-17794.2	2621.3	9204.4	-12775.9	5767.5	-850.27
+1	-3.365	-39.036	13.347	2.2582	18.624	-29.510	21.724	-5.6135
	s_{00}	s_{10}	s_{20}	s_{30}	s_{01}	s_{11}	s_{21}	s_{31}
-1	-685.58	246.20	61.726	-21.620	-442.40	762.21	-370.88	54.713
+1	-1130	1790	-799.97	120.18	3772	-5404	20496	-385.96
	s_{02}	s_{12}	s_{22}	s_{32}	s_{03}	s_{13}	s_{23}	s_{33}
-1	64.601	-22.936	-2.555	0.714	241.542	-403.05	196.18	-29.489
+1	2257.4	3187.7	-1383.08	191.44	621.12	-907.92	407.95	-58.847

Table 3: Solvation free energy in different three-site water models for Na^+ and Cl^- in kJ/mol. The parameters perform well in all studied three site water models, indicating good transferability between these water models.

Ion	σ (Å)	ε (kJ/mol)	SPC	SPC/E	TIP3P	Exp.
Cl^-	4.44	1.73	-343.4	-346.6	-344.5	-347
Na^+	2.22	2.11	-375.8	-375.3	-375.9	-375

Figure 2: Correlation between experimental and calculated solvation free energies and entropies using the parameters of Åqvist,[15] and our newly optimized parameters. The failure of the literature parameters in combination with our simulation method is obvious. Our newly defined parameters are optimized based on the presented data, therefore they reproduce the experimental results accurately.

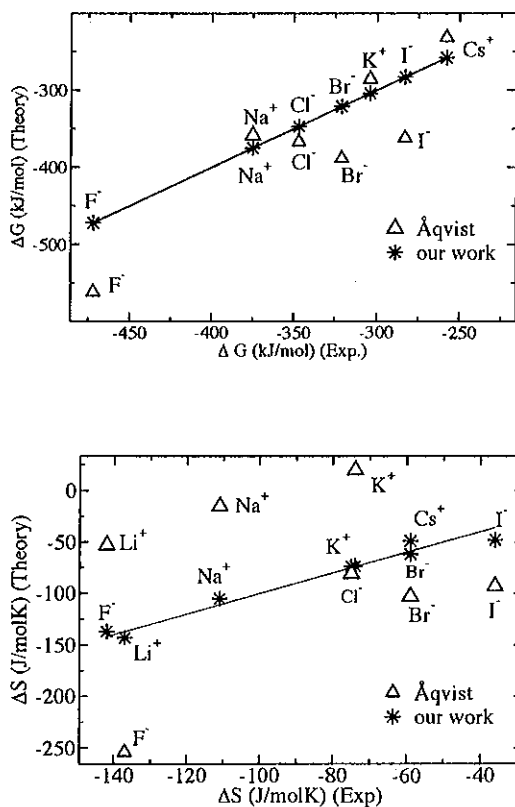


Figure 4: Radial distribution function for Na^+ and Cl^- with the new parameters at 300 K. The first maximum in the Na-OW radial distribution function is at $r=2.4 \text{ \AA}$, the one is for the Cl-OW radial distribution function is at $r= 3.4 \text{ \AA}$.

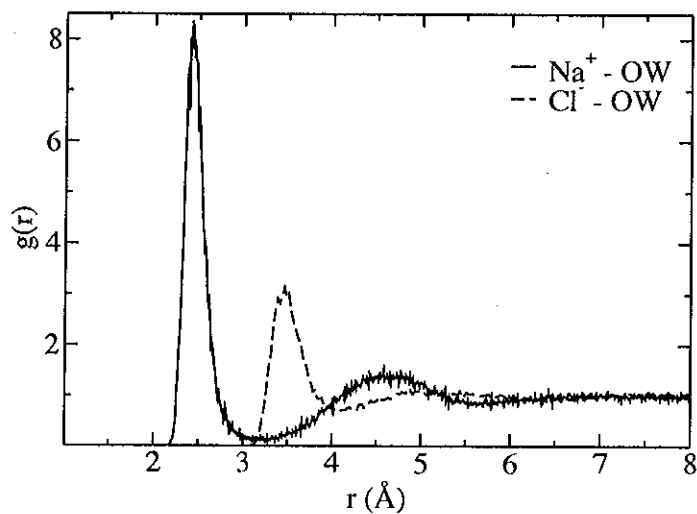


Figure 8: Solvation free energy surface for anions as a function of σ and ϵ . Shown is the polynomial approximation with the parameters shown in Table 1.

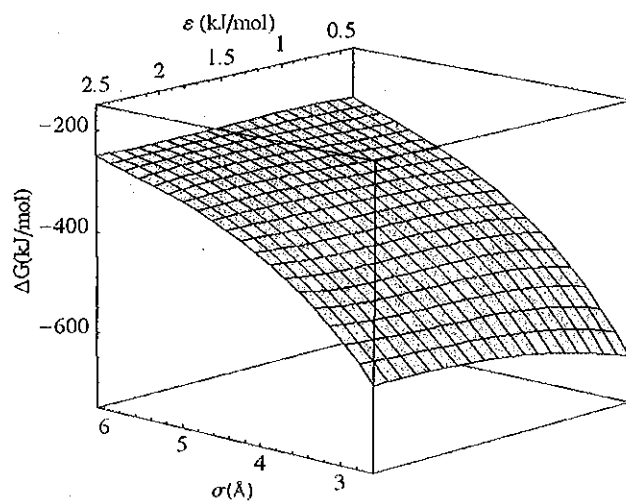


Figure 10: Solvation entropy surface for cations as a function of σ and ϵ . Contrary to all surfaces, there is maximum of ΔS for $\epsilon \approx 2.2$ kJ/mol and $\sigma \approx 4 \text{ \AA}$.

Figure 11: Solvation entropy surface for anions as a function of σ and ϵ .

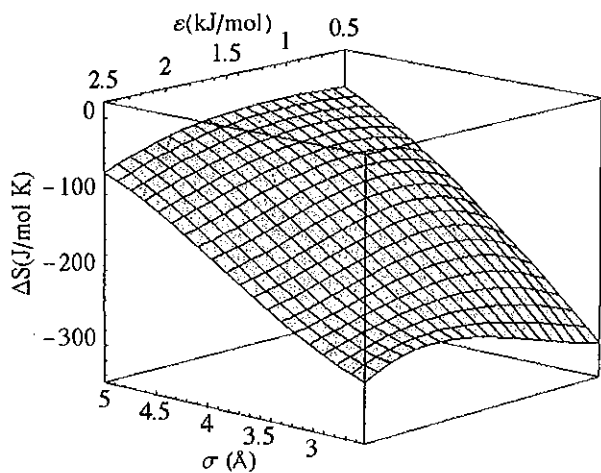
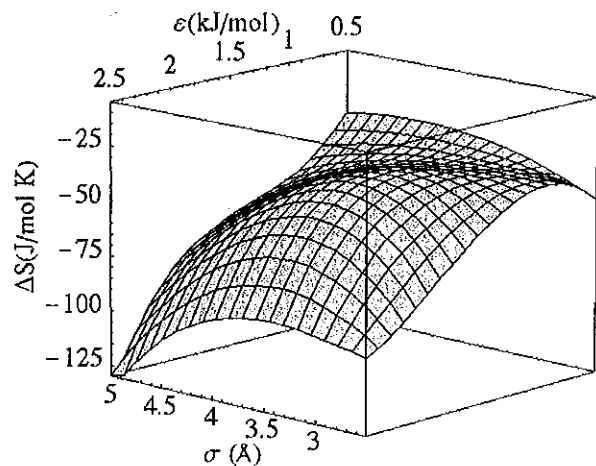


Figure 13: Force field construction for cations: the full lines represent the experimental solvation free energy of every ion, the dashed lines represent the respective solvation entropy. The crossing point of the two lines defines the new σ and ϵ parameters. The found parameters have substantially larger ϵ -values than previously reported. The parameters define a curve with a maximum of $\epsilon = 2.2$ kJ/mol for K^+ (see also Fig.1).

