

Accounting for Electronic Polarization Effects in Aqueous Sodium Chloride via Molecular Dynamics Aided by Neutron Scattering

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KEYWORDS: electronic continuum correction, ion pairing, scaled charges, aqueous solution

Abstract

Modelled ions, described by non-polarizable force fields, can suffer from unphysical ion pairing and clustering in aqueous solutions well below their solubility limit. The electronic continuum correction takes electronic polarization effects of the solvent into account in an effective way by scaling the charges on the ions, resulting in a much better description of the ionic behavior. Here, we present parameters for the sodium ion consistent with this effective polarizability approach and in agreement with experimental data from neutron scattering, which could be used for simulations of complex aqueous systems where polarization effects are important.

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Introduction

It is a well known problem of non-polarizable force fields for ions that many parameter sets lead to unphysical ion pairing and clustering in aqueous solutions well below the solubility limit.¹⁻⁴ This is mainly due to two artifacts. The first problem is the overestimation of interionic interactions by applying full charges on the ions as if they were in the gas phase, omitting the electronic polarization effects of the solvent. The second issue is connected with the Lennard–Jones parameters, in particular with combinations of very small well depth ϵ with large radii σ .⁵ The first problem can be cured, without explicitly including electronic polarization terms into the force field, by the so-called electronic continuum correction (ECC).^{4,6-11} ECC takes electronic polarization of the solvent effectively into account by scaling the ionic charge by the inverse square root of the electronic part of the dielectric constant of the surrounding medium.^{9,10,12} For water the ionic scaling factor is roughly 0.75.¹⁰ This approach has been applied successfully to aqueous solutions containing lithium,⁴ carbonate,¹³ and guanidinium ions,⁶ and lately also to calcium.^{7,14} Since the original ionic radii are determined together with the full charges, they have to be refined after charge scaling accordingly.⁷ Results from this further refinement are denoted as electronic continuum correction with rescaling (ECCR).⁷ Concerning the second problem, considerable work was done on the parametrization of sodium, which resulted in several parameter sets, see Refs. 15–18 and reference herein. Also, a slight improvement for solutions with concentrations around 1 m and below can be reached using Lorentz–Berthlot mixing rules instead of the geometric averages for both Lennard–Jones parameters.² In general, the overestimation of interactions of fully-charged sodium ions with biological molecules could be a problem, e. g., when describing sodium-potassium-pumps which transport the ions through cell membranes.

In our earlier studies, neutron diffraction with isotopic substitutions (NDIS) was shown to be a reliable tool for the validation of the size, i. e. the σ parameter of the Lennard–Jones potential, of the ions.^{4,7,19} Sodium has no naturally occurring isotopes, which could be used in NDIS experiments, therefore, another approach was adopted here. Assuming that

the water structure and the solvation structure around the chloride ion is approximately the same for equally molar lithium chloride and sodium chloride solutions, their neutron scattering data can be subtracted. Additional application of a 'null' water mixture (i. e., a mixture of light and deuterated water which gives zero for it) should lead to cancellation of additional contributions from water and chloride to the neutron scattering signal.

The two aims of this publication are i) to establish force field parameters for the sodium cation using the ECCR ansatz and ii) to provide a more detailed insight into the comparison of neutron scattering experiments to the simulated data for aqueous sodium chloride. The neutron scattering data, which were acquired within the framework of this project, serve the purpose of benchmarking the simulations, especially when establishing the radius of the sodium ion. Also, the influence of different combinations of Lennard-Jones parameters on the ion pairing properties are explored within this framework.

Computational Details

The simulated bulk systems consist of 502 ion pairs of NaCl or LiCl in 6002 water molecules resulting in a molar ratio of 4 mol of ions to 55.55 mol of water, for convenience hereafter referred to as 4 m. Two different water models were employed, namely SPC/E²⁰ and TIP4P/2005.²¹ The Lennard–Jones parameters initially used for sodium, were taken from Ref. 22 and 23, thereafter referred to by the indexes 'Dang' and 'gmx'. The parameter for lithium are from Refs. 5 and 4 and the parameters for chloride from Refs. 24 and 19 and 7, thereafter referred to by the indexes 'PFMJ' and 'KMJ'. Parametrization with full charges on the ions are denoted as 'full'. The results from charge and size rescaling⁷ of the ions are denoted as electronic continuum correction with rescaling ('ECCR') throughout the paper: Since the van der Waals radii were determined together with full charges an adjustment of the ionic sizes after rescaling the charges is needed. All the parameters are summarized in Table 1. The mixed Lennard–Jones parameters were derived applying Lorentz–Berthelot

mixing rules.

All classical molecular dynamics (MD) simulations were performed with the Gromacs 4.6.3 program package²³ using a time step of 2 fs. Periodic boundary conditions were applied in all three dimensions. Long-range electrostatic interactions were handled using the particle-mesh Ewald algorithm²⁵ with a real space cut off of 12 Å. The van der Waals interactions were truncated at 12 Å and no long-range Lennard-Jones correction for pressure was applied since its effect was found to be within the statistical uncertainty of the results. The temperature was maintained at 298 K by the velocity rescaling thermostat²⁶ with a coupling time of 0.5 ps. The pressure was controlled by the Parrinello–Rahmann barostat²⁷ at 1 bar with a coupling time of 0.5 ps. For the water molecules bonds and angles were constrained by the Lincs algorithm.²⁸ After minimization, simulations of a length of 30 ns were performed for all systems, from which the last 20 ns were taken for analysis.

Table 1: Force field parameters of the ions employed in this study.

Na			
	σ (Å)	ϵ (kJ/mol)	charge
full _{Dang} ²²	2.350	0.544284	+1.0
full _{gmx} ²³	2.575	0.061774	+1.0
ECCR _{Dang}	2.115	0.544284	+0.75
ECCR _{gmx}	2.318	0.061774	+0.75
Li			
	σ (Å)	ϵ (kJ/mol)	charge
full _{Åqvist} ⁵	2.126	0.07647	+1.0
ECCR _{Åqvist} ⁴	1.800	0.07647	+0.75
Cl			
	σ (Å)	ϵ (kJ/mol)	charge
full ²⁴	4.4499	0.4184	-1.0
ECCR _{PFMJ} ¹⁹	4.100	0.4928	-0.75
ECCR _{KMJ} ⁷	3.7824	0.4184	-0.75

Experimental Methods

Heavy water (99.9 atom % D) and light water (H, 18 M Ω) were mixed together (78.688 g H₂O and 48.975 g D₂O). The hydrogen in this mixed water had an average coherent neutron scattering length of 0 fm (i.e., for this mixture the scattering from hydrogen and deuterium cancel each other). LiCl and NaCl were dried in a vacuum oven at 150° C overnight. Solutions of LiCl and NaCl were then prepared by direct dissolution of salt in water. In each case 5 mL samples were prepared. From each solution, 0.75 mL was transferred to a null scattering Ti/Zr cell, and neutron scattering data of each sample was recorded on the D20 diffractometer for around 2 h. The scattering data was then corrected for multiple scattering and absorption prior to being normalized versus a standard vanadium sample to yield the total scattering pattern for each solution. The corresponding equations and weighting coefficients are provided as Supporting Information (SI).

Results and Discussion

Figure 1 shows representative snapshots of 4 m lithium chloride and sodium chloride solutions for scaled charges with rescaled van der Waals radii (ECCR). These snapshots illustrate visually how structurally similar these two solutions are to each other. This is also displayed in the very similar number densities in experiment (0.0975 atoms/Å³ vs. 0.0976 atoms/Å³), as well as in the simulations, see Table S3 in the SI. The two systems differ in the amount of ion pairing which is in the sodium chloride solution about twice as pronounced as in the lithium chloride solution. This is also displayed in the Na/Li-Cl coordination numbers (CN_{Na/Cl} = 0.63, while CN_{Li/Cl} = 0.27). Various additional coordination numbers for sodium chloride solutions are presented in Table S4 in the SI.

The results of the first-order difference functions both in the Q-space ($\Delta S(Q) = S_{\text{NaCl}}(Q) - S_{\text{LiCl}}(Q)$) and the r-space ($\Delta G(r) = G_{\text{NaCl}}(r) - G_{\text{LiCl}}(r)$) from neutron scattering experiments and from MD simulations are shown in Figure 2 for sodium with full (from Ref. 22) vs.

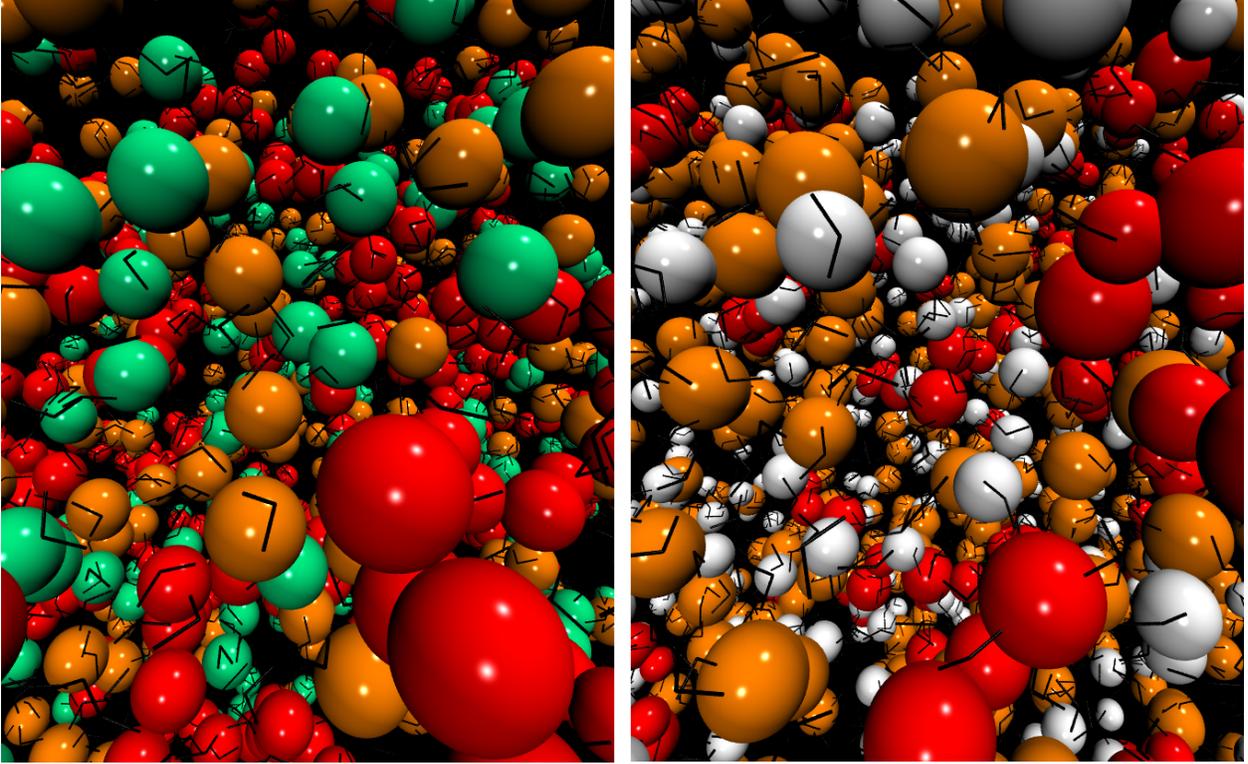


Figure 1: Representative snapshots of the sodium chloride solution (left-hand side) and the lithium chloride solution (right-hand side). Sodium is colored in green, lithium in white, and chloride in orange, except for contact ion pairs which are colored in red. Water molecules are presented as black wire frame.

scaled charges. Here, the difference between the data from the sodium chloride solution and the lithium chloride solution is presented. Q denotes the radial scalar part of the scattering vector. The r -space representation is the Fourier transform of the Q -space representation and, therefore, the information contained in them is in principle the same. Nevertheless, both are shown here, since they emphasize different aspects of the structure of the solutions. The peak positions, which translate into the phasing in Q -space, can be more easily compared in Q -space. In contrast, the peak heights can be more easily determined from r -space data.

To illustrate which features in the r -space representation come from which correlation a dissection into its components $\Delta g_{M/O}(r)$, $\Delta g_{M/Cl}(r)$, $\Delta g_{O/O}(r)$, and $\Delta g_{Cl/O}(r)$ (with $M = \text{Li}$ or Na) is shown in Figure 3. The components $\Delta g_{M/M}(r)$ and $\Delta g_{Cl/Cl}(r)$ have been omitted in this figure, since they are very small. The first feature around 2.2 Å is due to the oxygen

atoms in the first solvation shell of lithium and sodium. Two distinct peaks for $\Delta g_{M/O}(r)$ can be observed in Figure 3, the first one corresponding to lithium-oxygen correlation and the second to the sodium-oxygen correlation. Both peaks are positive because lithium has a negative scattering length. These peaks are fused together in the r-space representation of Figure 2, because here the experimental resolution (mostly determined by the Q range of the diffractometer) was applied also for the simulation data to make the comparison more direct. Convoluting the experimental resolution makes the simulated peaks broader and shorter. Also, a minor contribution to this first peak comes from the difference in ion pairing between the two solutions (green curve in Figure 3), resulting in a shoulder for the $ECCR_{Dang/PFMJ}$ (red curve in Figure 2).

The second peak differs much more than the first peak between the full charged system (blue curve in Figure 2) and that with scaled charges. This peak is due to differences in the water network (blue line in Figure 3) with a small contribution from the solvation of the chloride ion (violet line in Figure 3). The shape of this second peak is much better reproduced by the scaled charges, though its position is somewhat shifted to larger value of r. Note that also the second solvation shell around sodium and lithium contributes to that peak. Further scaling of the van der Waals radius of sodium does not lead to any improvement for the position of this peak (data not shown). Using a slightly smaller chloride ion does not shift the peak either, see Figures S1 and S2 in the SI. The third peak in the experimental data, positioned around 6 Å (Figure 2), cannot be fully reproduced by the simulations. This third peak results from the different solvation of the chloride anion and ion pairing in the two solutions. In conclusion, the comparison with experiment for ECCR concerning the first and the second peak is better than for full charges but the improvement is not as impressive as, e. g., for calcium.⁷ This strengthens the thesis expressed in our previous studies that the scaling of charges is important primarily for ions with a high charge density.^{4,7}

In Figures 4 and 5 the results for another sodium model, taken from the gmx-ff parametrization, which is a commonly used biomolecular force field,²³ are displayed. It can be easily

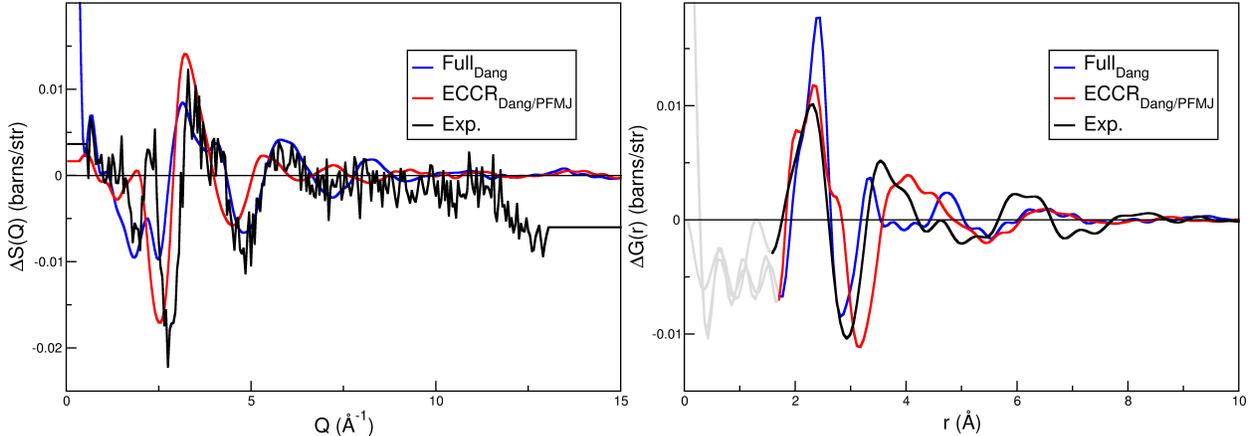


Figure 2: First-order difference function in Q -space (left-hand side) and in r -space (right-hand side) for the simulations with full charges (blue) and scaled charges with rescaled van der Waals radius (ECCR) in red and the experimentally measured curve in black.

seen that the comparison for $\text{ECCR}_{\text{gmX}/\text{PFMJ}}$ is not as good as for $\text{ECCR}_{\text{Dang}/\text{PFMJ}}$. The problem is that ion pairing is scaled up to a point where $\text{CN}_{\text{Na}/\text{Cl}}$ is increased almost to one, see Table S4 in the SI. Small clusters consisting of several ions can also be detected. Ion pairing decreases slightly upon rescaling of the van der Waals radius, but the first peak is then too high and also shifted to smaller distances; it is also too high and too narrow. This is due to the fact that the signal for the oxygen-lithium correlations and that for the oxygen-sodium correlations come at nearly identical distances. This is also illustrated in the splits of the total functions in Figure 5. Nevertheless, some improvement for the scaled charges over the full charges can still be detected, e. g., the shape of the second peak agrees well with experiment, although the position is shifted. This can be explained by a better description of the first solvation shell of chloride (compare also $\text{CN}_{\text{Cl}/\text{H}_2\text{O}}$ in Table S4 in the SI) and the water structure.

The main problem of the sodium parameters from the gmX force field, due to which we cannot get a good comparison with experiment within the ECCR approach, is the suspiciously small Lennard–Jones parameter ϵ , see Table 1.²³ Problems with this kind of parameters are already known in literature^{2,15,29} where a too small ϵ leads to an underestimated steric repulsion between the ions and thus excessive ion pairing.

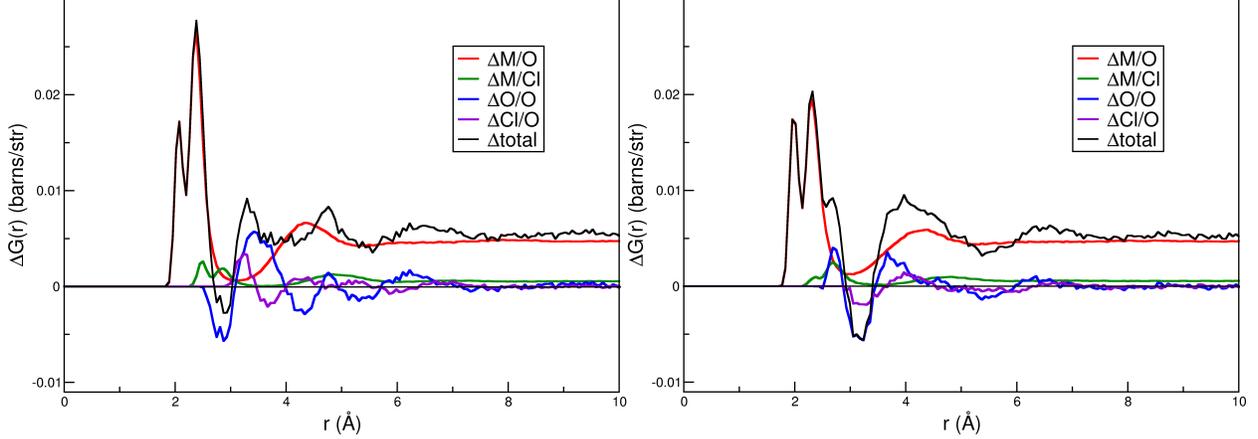


Figure 3: Difference function $\Delta G(r)$ as calculated from the simulations in this study in black for full charges on the left-hand side and for ECCR on the right-hand side together with dissections of the r-space data in the different contributions (colored lines). $M = \text{Li}$ or Na

A more detailed insight into this problem can be gained from Figure 6. The upper panel on the left-hand side and the two lower panels show the Lennard-Jones potentials for lithium, sodium, and potassium with Lennard-Jones parameters from Åqvist,⁵ Dang,^{22,30,31} or gmxff,²³ and the oxygen atom of SPC/E water. For lithium, the potential from Åqvist's and Dang's parameters look very similar to each other, just the potential well is slightly deeper for the latter. This similarity explains why a good fit to neutron scattering measurement for lithium based on Åqvist parameters was found in our earlier work.⁴ As an additional test, we applied Dang's Lennard-Jones parameters for both lithium and sodium in analogous simulations and subtracted the r-space data from each other. The result is displayed in the upper right panel of Figure 6. In the case of ECCR the same σ as before in combination with Dang's ϵ was taken. The main conclusions are the same as for the analogous comparison in Figure 4 due to the similarity of the two potentials for lithium. For sodium, the difference between the potentials is much more pronounced (see lower left panel in Figure 6), which is not only due to the small ϵ but also because of the large σ , which is responsible for the much earlier steep rise of the repulsive part of the potential. The parameters from the gmxff force field result in a curve which fits in the repulsive region from Dang's parameters reasonably, but the potential well is more shallow, resulting in increased ion pairing. The artificial step

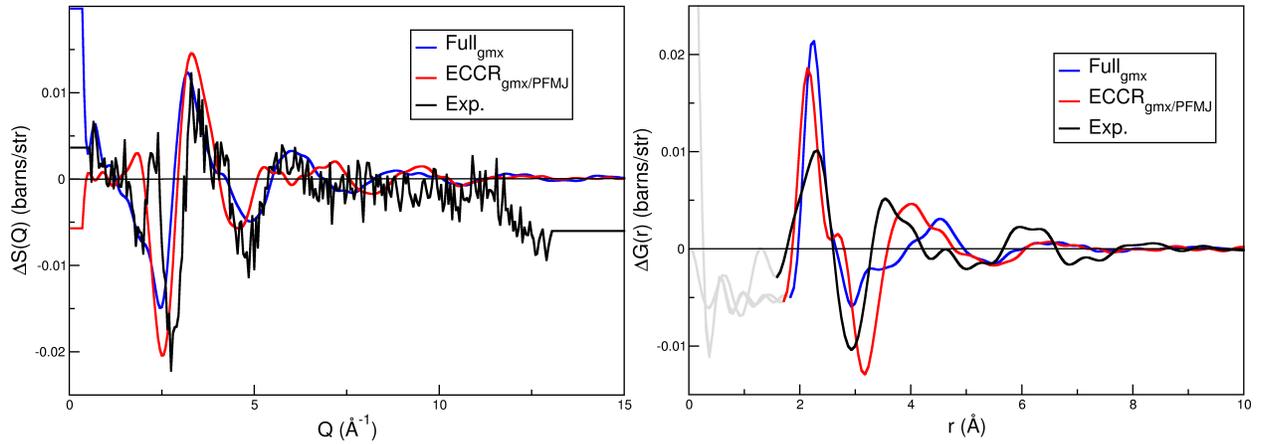


Figure 4: First-order difference function in Q-space (left-hand side) and in r-space (right-hand side) for the simulations with full charges (blue) and scaled charges with rescaled van der Waals radius (ECCR) in red and the experimentally measured curve in black.

early rise is even more pronounced for potassium where almost no potential well is visible for the Åqvist-parameters (bottom right panel in Figure 6. These trends go along with an increase in ion pairing.²

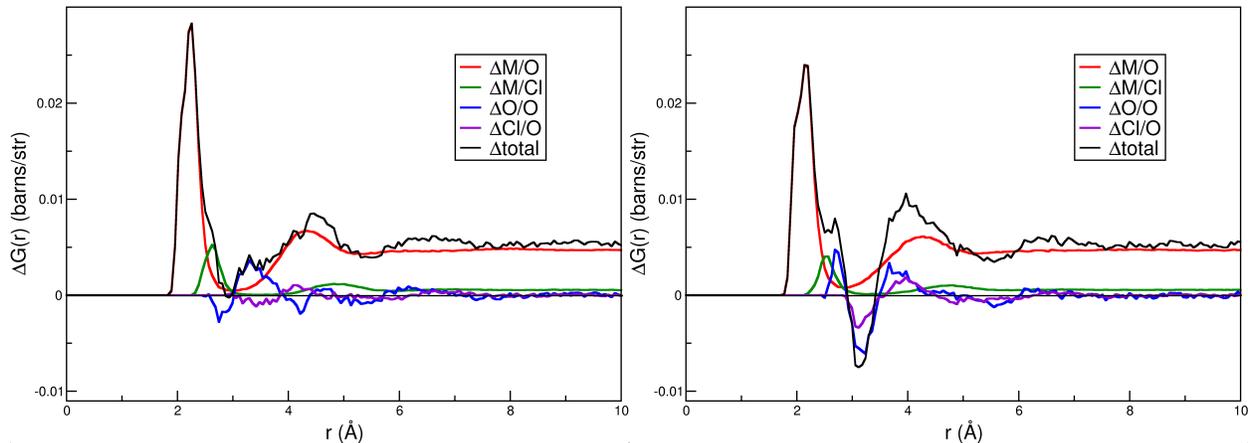


Figure 5: Difference function $\Delta G(r)$ as calculated from the simulations in this study in black for full charges on the left-hand side and for ECCR on the right-hand side together with dissections of the r-space data in the different contributions (colored lines). $M = \text{Li}$ or Na

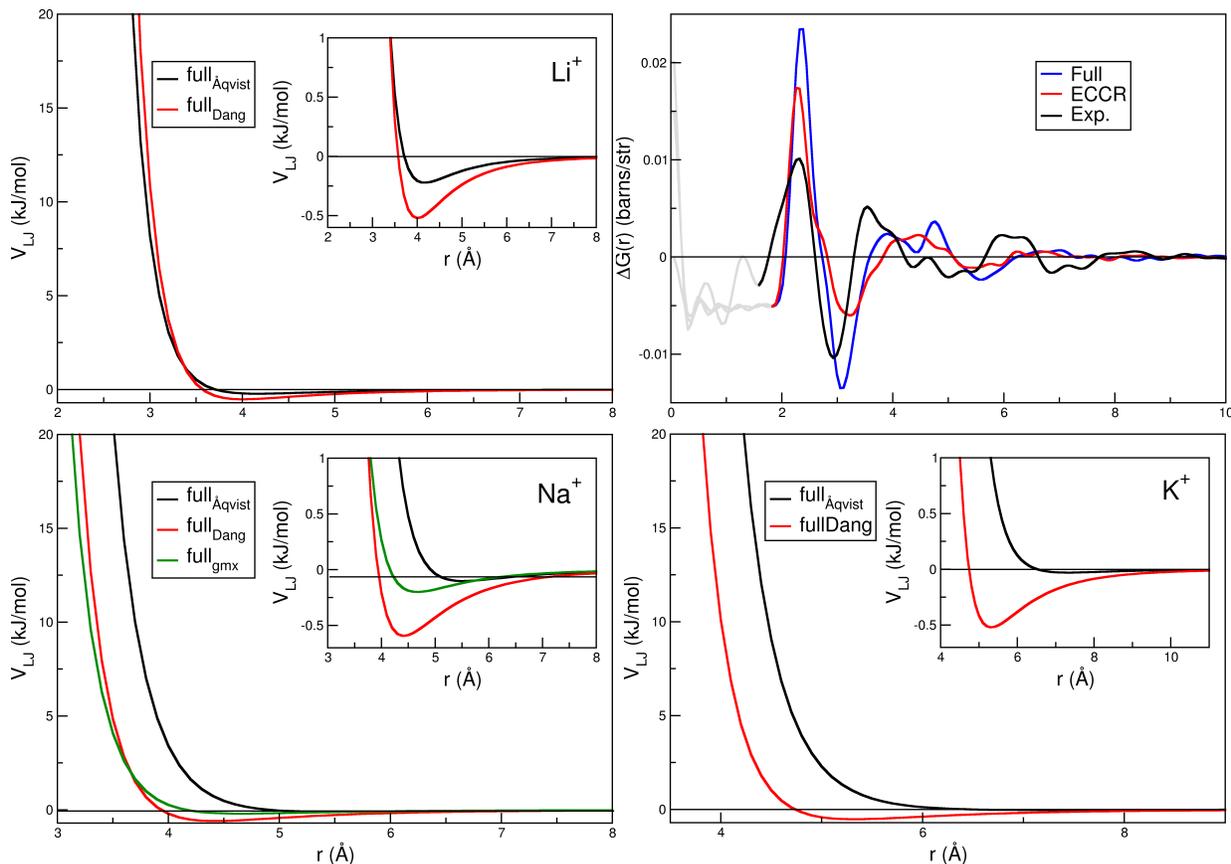


Figure 6: Lennard–Jones potentials for the interaction of Li, Na, and, K with the oxygen atom of SPC/E water. Parameters for the ions were taken from Åqvist,⁵ gmxf, ²³ or Dang.^{22,30,31} The insets show close-up views of the potential well regions. The upper right panel shows the r-space difference for simulations (full charges in blue and scaled charges in red) using Dang’s parameters for lithium and sodium and experiment (black curve).

Finally, the results for different water models are compared. Up to this point all simulations were done in SPC/E water, while here we use for comparison the more recent TIP4P/2005 model. This is done to demonstrate that the improvements due to charge scaling are transferable between water models. Figure 7 shows the corresponding Q - and r -space data. The curves for the two water models agree well with each other and with the experiment. Also, only a very small difference in ion-pairing, which is slightly increased in TIP4P/2005 water, can be observed (compare also the corresponding coordination numbers in Tables S4 and S5 in the SI).

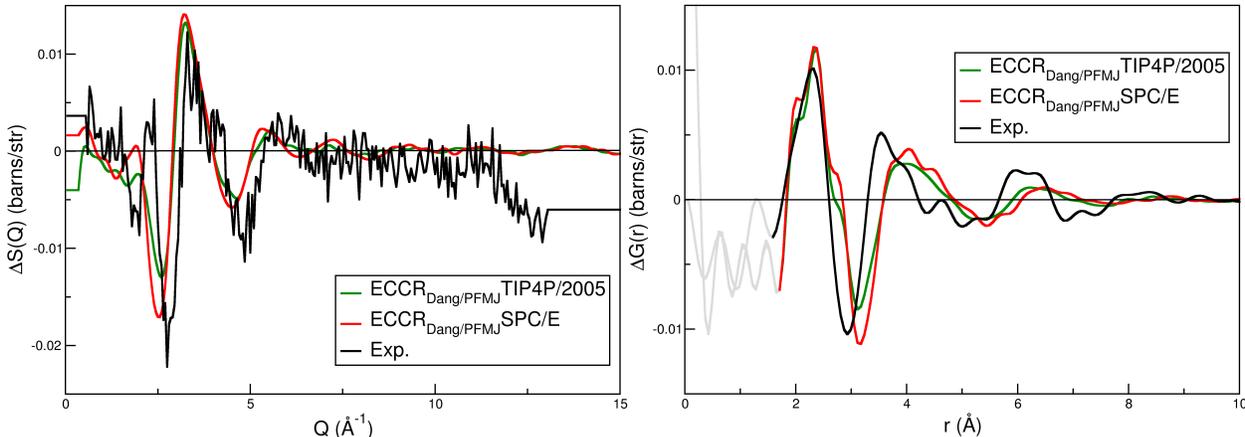


Figure 7: First-order difference function in Q -space (left-hand side) and in r -space (right-hand side) for the simulations with SPC/E (red) and TIP4P/2005 (green) water models and the experimentally measured curve in black.

Conclusions

In this study, we present and critically analyze a simple way to account for electronic polarization effects in aqueous sodium chloride. The approach applied here is based on the physically well-justified assumption that the effect of the electronic polarizability of the aqueous solvent on ions can be accounted for in a mean-field way by scaling the charges by the inverse square root of the electronic part of the dielectric constant of water.^{8–10,12} The force field development is done here in a systematic fashion starting from two different sodium ion

models, testing different chloride ion and water models, and comparing directly with neutron scattering data. In contrast to our previous studies demonstrating significant merits of this approach for calcium⁷ and lithium,⁴ charge scaling leads only to a slight improvement for aqueous sodium ions. This supports the thesis, that charge scaling is important mainly for ions with a high charge density which can strongly polarize surrounding water molecules. Nevertheless, sodium is very often present in simulations of biological systems as a counterion or as an ion maintaining the physiological ionic strength. To have a consistent setup for effective polarizable simulations, all ionic charges should be treated by the ECCR approach, therefore, there is need for appropriate sodium parameters which can be then combined with charge scaling models of higher charge density ions. Our study shows that it is possible to develop such a consistent set of ionic models by simultaneously scaling the charges and systematically adjusting the Lennard–Jones parameters.

Acknowledgement

This work was supported by the Czech Science Foundation (grant number P208/12/G016). PJ thanks the Academy of Sciences for the Praemium Academiae award. We thank the ILL Grenoble for allocated beamtime and the staff of beamline D20, particularly Dr. Henry Fischer, for fantastic help with the experiments.

Supporting Information Available

Supporting Information Available: In the SI further results from simulations using a additional parameter set are presented together with tables containing number densities and coordination numbers for all setups mentioned in the paper. Also, all equations concerning the neutron scattering experiments can be found in the SI. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

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