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# Cluster formation of NaCl in bulk solutions: Arithmetic vs. geometric combination rules<sup>☆</sup>

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## ABSTRACT

We have investigated the usability of three common ionic force fields, the AMBER-99, the OPLS-AA and the CHARMM-27 parameter sets for simulation of intermediate concentration NaCl solutions. We have found that the Amber and Opls force fields produce NaCl crystallites at concentrations between 1 and 2 m, when used with arithmetic combination rules to derive the Lennard-Jones  $\sigma_{ij}, i \neq j$  parameters. When switching to a geometric rule to derive these parameters, the NaCl solubility improves somewhat, but crystallisation still occurs at higher electrolyte concentrations. On the other hand, when using the Charmm force field, we observe no signs of crystallisation up to 2.0 m already for the arithmetic combination rules. In addition to the simulations with these ‘well-tempered’ parameter sets we have also performed simulations, in which the combination rules were applied individually for cation–anion, cation–(water) oxygen and anion–oxygen pairs. The altogether eight different parameter sets that can be obtained from combining three interactions with two combination rules have revealed that the  $\text{Cl}^-$ -oxygen interactions are the most sensitive quantity. When switching from arithmetic to geometric combination rules, the value of the size parameter  $\sigma_{ij}, i \neq j$  is always smaller than the corresponding one for arithmetic averaging, which gives rise to larger Coulomb and thus larger total interaction energies. As a consequence, applying geometric combination rules to the  $\text{Cl}^-$ -oxygen interactions improves solubility, applying it to the  $\text{Cl}^-$ - $\text{Na}^+$  interactions reduces solubility and increases crystallisation; because the sodium cations are usually quite strongly solvated, the effect of combination rules is small for the cation–oxygen interactions.

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## 1. Introduction

Structure, dynamics, stability and conformation of polymers and biomolecules in aqueous solution are strongly influenced by ion size, charge and concentration (ionic strength) [1–8]. Classical molecular dynamics (MD) simulation methods are widely used to understand how ions influence the different properties of macromolecules at the microscopic level. The empirical force field parameters used in such MD simulations are usually derived using experimental and quantum mechanical data. However, even for monovalent alkaline and halogenide ions the development of accurate and reliable parameters of monovalent ions is a persistent challenge [9].

Several sets of parameters exist as part of widely used ‘standard’ force fields such as Amber, Opls, Charmm, or Gromos, often even in several parametrisations with slightly different numerical values of

the parameters that reflect to some extent the historical development of insight into the limitations of the parametrisation. These ‘standard’ force fields are, as a consequence of demands of efficiency of evaluation, based on a combination of (nonpolarisable) electrostatics and the (12-6) Lennard-Jones (LJ) functional form

$$V_{ij}^{LJ} = 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r} \right)^{12} - \left( \frac{\sigma_{ij}}{r} \right)^6 \right], \quad (1)$$

where  $r$  is the distance between two sites, and  $\epsilon_{ij}$  and  $\sigma_{ij}$  are, respectively, the well depth and the distance at which the energy is zero. Many attempts to fine-tune these LJ parameters have been made for various purposes (e.g., [9–12]) by systematic comparison of experimental and calculated properties [11,12], with the goal to improve their reliability. One important aspect in such studies is always the application of the proper *combination rules*, i.e., the specification how to derive the cross terms  $\epsilon_{ij}$  and  $\sigma_{ij}$  ( $i \neq j$ ) from the corresponding terms for  $i = j$ . In a recent study of eight different alkali halide solutions in SPC/E water at physiologically relevant concentration (around

<sup>☆</sup> This work has been dedicated to Prof. Vojko Vlachy on the occasion of his 70th birthday.

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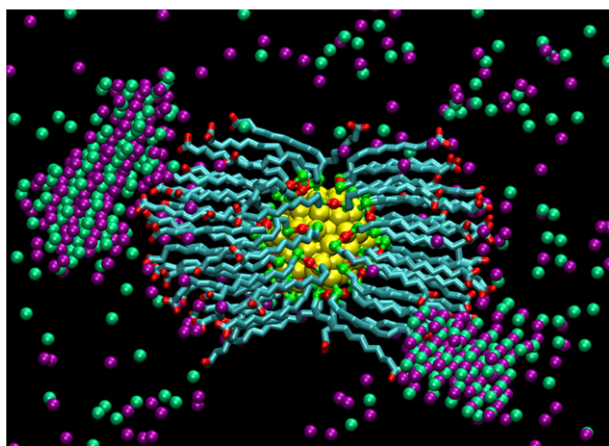
E-mail address: [eckhard.spohr@uni-due.de](mailto:eckhard.spohr@uni-due.de) (E. Spohr).

0.3 m), Fyta and Netz [13] concluded that the standard Lorentz-Berthelot mixing rules work well for similar size cation/anion pairs.

Often, the LJ parameters are not well balanced and exhibit unphysical behaviour at higher concentrations [14,15]. This can then result in aggregation of ions in the vicinity of biomolecules [16–19]. In another recent publication, Marchand et al. [20] observed a high sensitivity of the equilibrium structure of poly-L-glutamic acid specifically towards the  $\text{Na}^+$  ion parameters in standard pair-potentials, even if the ion models lead to reasonable  $\text{Na}^+$  solvation structures.

Recently, we observed a similar phenomenon of aggregation leading eventually to crystal formation of  $\text{Na}^+$  and  $\text{Cl}^-$  ions in the vicinity of gold nanoparticles functionalised with hydrocarbon chains and terminated with charged ammonium and carboxylate groups [21]. The GNP was dissolved in an aqueous solution with a NaCl background electrolyte at approximately 1.0 molal concentration. Fig. 1 shows a snapshot obtained after 20 ns from a simulation with the Amber force field parameters, using arithmetic combination rules. The obvious crystal formation caused us to change the force field to the CHARMM-27 force field parametrisation with arithmetic combination rules (see below) for the GNP simulations in Ref. [22].

Here, we investigate this issue in more detail. Although a number of related studies have been performed in the past, we want to only mention a few. A decade ago, Auffinger et al. [14] performed all-atom MD simulations of aqueous solutions of KCl at three different concentrations. They used the Amber parameter set [23] and the parameter set by Dang and Kollmann [24] together with the popular (SPC/E [25] and TIP3P [26]) water models. They reported that the observed formation of excessive ion pairing at 1 molal concentration, well below the solubility limit, was due to an imbalance of force-field parameters in the Amber force field, and that the Dang/Kollmann parameter set alleviated this. Interestingly, the alternative parameters are very similar to the original ones. Therefore, they suggested to replace Åqvist's ion parameters [27], which have been adopted in Amber, with the Dang/Kollmann parameters and use them together with the remaining Amber parameters. Pappu et al. [15] performed MD simulations of NaCl, KCl and CsCl aqueous solutions using the AMBER-99 and the OPLS-AA [28] force fields, together with geometric and arithmetic (Lorentz-Berthelot) mixing rules. They also observed unphysical cluster formation at concentrations well below the solubility limit and advocated to use the Åqvist Opls cation and anion parameters, which are anyway similar to the Amber parameters, together with the other Amber parameters for nucleic acids.



**Fig. 1.** Functionalised gold nanoparticle [21] with 60  $(\text{CH}_2)_{11} - \text{COO}^-$  chains including  $\text{Na}^+$  (green) and  $\text{Cl}^-$  (purple) around the gold nanoparticle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the present manuscript, we report MD simulations of aqueous NaCl solutions at three different concentrations (1.1, 1.5 and 2.0 m) using the TIP3P water model [26] together with three force field parameter sets (AMBER-99 [23], CHARMM-27 [29,30] and OPLS-AA [28]) for the ion parameters together with two combination rules (arithmetic and geometric), in order to identify which parameter sets do and do not give rise to crystal formation at ambient conditions in the intermediate 1–2 molal concentration range. In the next section we describe the simulation methodology. This is followed by results concerning radial distribution functions (RDFs) and coordination numbers (CNs) and a discussion.

## 2. Computational methods and simulation details

We have produced initial configurations of aqueous NaCl solutions in TIP3P water at concentrations of molality 1.1, 1.5 and 2.0 in a periodic box of size  $80 \times 80 \times 80 \text{ \AA}^3$ , which corresponds to 330, 460, and 613  $\text{Na}^+$  and  $\text{Cl}^-$  ions dissolved in 15,726, 15,466, and 15,160 water molecules, respectively. Ions were added to a water box using the TopoTools plugin of VMD, Release 1.9.1 [31]. The initial ion-ion distance was at least 5 Å.

We chose the parameter sets AMBER-99, CHARMM-27 and OPLS-AA as the basis for our investigation and combined them with two combination rules, the so-called arithmetic and geometric rules. In the arithmetic combination rules,  $\sigma_{ij}$  is obtained as the arithmetic mean of  $\sigma_{ii}$  and  $\sigma_{jj}$ , according to  $\sigma_{ij} = \frac{1}{2}(\sigma_{ii} + \sigma_{jj})$ . In the geometric combination rules the corresponding geometric mean  $\sigma_{ij} = (\sigma_{ii} \cdot \sigma_{jj})^{0.5}$  is taken.  $\epsilon_{ij}$  is always obtained from the geometric mean as  $\epsilon_{ij} = (\epsilon_{ii} \cdot \epsilon_{jj})^{0.5}$ . As the TIP3P water model has been used with all three force fields, we expect some consistency among the parameters. The force field parameters as taken from the literature are summarised in Table 1.

The LAMMPS [32] (version 31, March 2011) molecular dynamics package is employed to simulate all systems. Temperature, volume and number of particles are held constant during the NVT ensemble simulations, to keep the macroscopic density constant and the temperature at a meaningful average value during the occasionally large changes of potential energy during crystallisation. A Nosé-Hoover thermostat [33] with a time constant of 1 ps was used to keep the system temperature constant at the desired value. The Lennard-Jones interactions were cut off at a distance of 10 Å and the SHAKE [34] algorithm was used to constrain O–H bonds and H–O–H angles. The particle–particle–particle–mesh (PPPM) method has been used with an accuracy parameter (relative error in per-atom forces calculation) of  $10^{-4}$  to compute long range Coulomb interactions. Several short runs of 100 ps have been performed with time steps of less than 1 fs to come close to equilibrium quickly. Production runs were performed with a time step of 1 fs and a skin distance for the neighbour tables of 0.1 nm, which was updated every 5 steps. Systems were equilibrated for  $\approx 1$  ns and analysis has been performed over subsequent production runs which all lasted 20 ns.

**Table 1**  
Force field parameters.<sup>a</sup>

Force field	$\text{Na}^+$		$\text{Cl}^-$	
	$\sigma$ [Å]	$\epsilon$ [kcal/mol]	$\sigma$ [Å]	$\epsilon$ [kcal/mol]
AMBER-99	3.3284	0.00277	4.40104	0.1000
OPLS-AA	3.3304	0.00280	4.41720	0.1178
CHARMM-27	2.4299	0.04690	4.04470	0.1500
	O		H	
TIP3P	3.1506	0.1521	0.4000	0.0460

<sup>a</sup> All parameters taken from the lines 'Na', 'Cl' and 'O(3)' of the 'Amber-1999', 'OPLS-AA' and 'Charmm-27' subtables of Table 1 in Ref. [29].

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