<http://www.diva-portal.org>

Postprint

This is the accepted version of a paper published in *Journal of Chemical Physics*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the original published paper (version of record):

Ahlstrand, E., Zukerman Schpector, J., Friedman, R. (2017)

Computer simulations of alkali-acetate solutions: Accuracy of the forcefields in difference concentrations.

Journal of Chemical Physics, 147: 1-10

<https://doi.org/10.1063/1.4985919>

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

Permanent link to this version:

<http://urn.kb.se/resolve?urn=urn:nbn:se:lnu:diva-68822>

Computer simulations of alkali-acetate solutions: accuracy of the forcefields in different concentrations

Emma Ahlstrand,¹ Julio Zukerman Schpector,² and Ran Friedman^{1, a)}¹⁾ Linnæus University, Department of Chemistry and Biomedical Sciences, Linnæus University, 391 82 Kalmar, Sweden²⁾ Universidade Federal de São Carlos, Departamento de Química, CP 676, 13565-905 São Carlos, SP, Brazil

(Dated: 24 October 2017)

When proteins are solvated in electrolyte solutions that contain alkali ions, the ions interact mostly with carboxylates on the protein surface. Correctly accounting for alkali-carboxylate interactions is thus important for realistic simulations of proteins. Acetates are the simplest carboxylates that are amphipathic, and experimental data for alkali acetate solutions is available and can be compared with observables obtained from simulations. We carried out molecular dynamics simulations of alkali acetate solutions using polarizable and non-polarizable forcefields, and examined the ion-acetate interactions. In particular, activity coefficients and association constants were studied in a range of concentrations (0.03, 0.1, and 1 M). In addition, quantum-mechanics (QM) based energy decomposition analysis was performed in order to estimate the contribution of polarization, electrostatics, dispersion and QM (non-classical) effects on the cation-acetate and cation-water interactions. Simulations of Li-acetate solutions in general overestimated the binding of Li^+ and acetates. In lower concentrations, the activity coefficients of alkali-acetate solutions were too high, which is suggested to be due to the simulation protocol and not the forcefields. Energy decomposition analysis suggested that improvement of the forcefield parameters to enable accurate simulations of Li-acetate solutions can be achieved, but may require the use of a polarizable forcefield. Importantly, simulations with some ion parameters could not reproduce the correct ion-oxygen distances, which calls for caution in the choice of ion parameters when protein simulations are performed in electrolyte solutions.

I. INTRODUCTION

The ionic strength of biological cells is ~ 0.10 - 0.15 M, whereas *in vitro* experiments involving proteins are typically carried out in concentrations that range from 10^{-2} to 10^0 M. These are remarkably different conditions, since the electrostatic potential (Coulomb cage) around proteins and similar molecules is much larger in volume when the concentration of salt is low, whereas it diminishes at high ionic strengths^{1,2}. Ideally, we should be able to simulate proteins in electrolyte solutions of any ionic strength, from almost zero to the solubility limit. At the very least, simulations of macromolecule-ion interactions should be realistic in physiological concentrations. Fortunately, ion concentrations do not seem to affect simulated protein structure and dynamics too much^{3,4}, although they do affect local interactions.

The most common cations in biological systems are K^+ and Na^+ , which are abundant in the intra- and extra-cellular environments, respectively. Li^+ , Rb^+ and Cs^+ appear only in low concentrations (in the micromolar range⁵). These ions, however, are important due to their chemical similarity to K^+ and Na^+ , and their significance in medicine and health (Li , ^{87}Rb , and ^{137}Cs). In physical chemistry, alkali cations are often used in simulations and experiments to study specific ion interactions⁶⁻⁹, i.e., interactions that depend on the specific composition of

electrolytes (the ions in solution) rather than just on their concentrations (unlike colligative properties).

Cl^- is the only mono-atomic anion which is common in biological systems. For this reason, many studies concentrated on specific cation effects when the aim was to study effects of physiological relevance. Specific cation effects include the selectivity of ion channels¹⁰, and may be the basis for protein folding, signaling, aggregation and catalysis¹¹. Such effects were measured experimentally by potentiometric and spectroscopic methods^{12,13}. In order to perform realistic simulations of proteins or peptides in solutions, it is important that the forcefield parameters account for the energetics of ions in electrolyte solutions and at the same time in solutions that contain proteins¹⁴⁻¹⁶. Alkali ions bind mostly to the carboxylates^{3,4,15}. Hence, the ability to correctly account for interactions between the cations and carboxylates is important for coherence between experiments and simulations¹⁷.

Modern forcefields have been developed since the early 1990s for simulations with alkali cations^{18,19}. These and newer classical, non-polarizable forcefields involve electrostatics (Coulomb) and Lennard-Jones (LJ) interactions and are still in common use today. Polarizable forcefields are potentially more accurate, as the charges are not fixed on the centers of atoms (or at any other point). Their main drawback is that they make the simulations slower to run (compared to nonpolarizable forcefields). Also, more complex inter-atomic potentials make such forcefields less transferable between software packages. Different polarizable forcefields are available for

^{a)} Electronic mail: ran.friedman@lnu.se

ions, including Drude or 'particle on a spring' type forcefields²⁰, forcefields that rely on induced dipoles²¹, forcefields that use a multipole approach²², and forcefields that allow charge-transfer²³⁻²⁶.

Non-polarizable forcefields have been used routinely and successfully to study proteins and other macromolecules, typically in NaCl or KCl solutions²⁷⁻³⁵. Interestingly, using energy decomposition analysis (EDA) we have recently found out that polarization contributes 29% of the interaction free energy between Li^+ and first-shell water molecules and as much as 23-25% of the same interaction for Na^+ .⁴ Polarization was apparently much less important for K^+ . Owing to these results, we wanted to compare the performance of a polarizable forcefield with that of some of the non-polarizable ones for simulations of alkali-acetates in water. The polarizable forcefield of choice here was the **Drude-2013** forcefield.

This article is organized as follows. In the next section (Approach), we describe our approach in detail. This is followed by the Methods section, where we explain how simulations were carried out. We then report on and discuss the results of the simulations and analysis. The article is then summarized in the Conclusions section.

II. APPROACH

A range of non-polarizable forcefields parameters was used to simulate acetate-alkali cation solutions, see Table I. We opted to employ parameters that were used together with proteins or that were, in principle at least, possible to use for protein simulations. The choice was somewhat arbitrary and by no means conclusive. There are tens if not hundreds of different parameters available, and simulating all of them was not possible.

Polarizable forcefield parameters for ions are much less numerous. The **Drude-2013** polarizable forcefield was used in this study, for two main reasons. First, the forcefield can be used in many different MD simulation software, including the widely used CHARMM³⁶⁻³⁸, GROMACS³⁹⁻⁴², and NAMD^{43,44} (a different set of polarizable forcefield parameters was developed and used with AMBER⁴⁵). Second, parameters for acetate were included in the forcefield. Ion parameters in the **Drude-2013** forcefield were developed by matching single-ion properties such as geometries and energies of monohydrates, and the solvation free energy at the infinite dilution limit²⁰. The parameters were thereafter optimized to reproduce osmotic pressure data, in order to enable simulations of concentrated solutions⁴⁶. The forcefield parameters were further optimized to represent the interactions between ions (K^+ , Na^+ , Ca^{2+} and Cl^-) and coordinating amino-acid residues⁴⁷.

Ab initio molecular dynamics of ions in solutions can be performed, and many such studies have been reported (e.g.,⁴⁸⁻⁵²). Unfortunately, such simulations are limited to small systems and short periods. Static QM representations can be studied with larger basis sets and

post Hartree Fock methods, and are therefore useful for parametrization of ion interactions⁵³. Energy decomposition analysis (EDA) methods can yield important insights in this respect, because they can report on interactions that non-polarizable and polarizable forcefield miss. In this study, we used the EDA-PCM⁵⁴ formulation to study complexes between alkali-ions and acetate in a continuum solvent model (polarizable continuum model, PCM). In this formulation, the interaction free energies are divided into contributions from electrostatics, exchange, repulsion, polarization, dispersion and desolvation.

Ideally, forcefield parameters should be applicable when the same system is studied under different salt concentrations. For this reason, we carried out simulations at concentrations of 0.1 and 1 M, and with the non-polarizable forcefields also at 0.03 M. The forcefields were compared with respect to observables extracted directly from the simulations, without any bias. For this reason, free energy perturbation or thermodynamic integration were not executed.

III. METHODS

A. Preparation of the simulated systems

Simulations of alkali ion-acetate in aqueous solution at concentrations of 0.03 M (only with non-polarizable forcefields), 0.1 M and 1 M were performed in a periodic cubic box with approximately 1700 water molecules. Box volumes were between 50-54 nm³. A concentration of 0.03 M corresponds to a single ion pair, 0.1 M to three ion pairs and 1 M to 30 ion pairs.

1. Simulations with pairwise fixed charge forcefields

The simulations were performed with the GROMACS software, version 5.1.2⁴². Acetate molecules were modeled by use of CGenFF atom types⁵⁵ that are compatible with the CHARMM pairwise forcefield^{56,57} implemented in Gromacs⁵⁸. Acetate parameters are given in the supplementary material Table S1. Non-bonded LJ-parameters σ and ϵ for the ions are presented in Table I. The Lorentz-Berthelot mixing rule was applied for σ , while the geometric mixing rule was used for ϵ , as is the standard procedure in the CHARMM forcefield. Water were modeled as SPC/E⁵⁹ or TIP3P⁵⁶, except for simulations with the ion parameters developed by Knecht et. al.⁵ that were developed for and also simulated only with the original SPC model⁶⁰. The parameters Li^+ and K^+ from Hess¹⁷ were originally developed for the OPLS-AA force field and with the SPC/E water model, but were here simulated with the CHARMM force field for compatibility, and since previous calculations have shown no significant differences when small solutes were modeled with ions using OPLS/AA or CHARMM⁶¹. The Li^+

and Na⁺ Lennard-Jones interactions between the water oxygen and the ions were scaled down by a factor λ , (Tables I and II, refs^{5,62}). Prior to the MD simulations, internal constraints were relaxed by energy minimization. After the minimization, an equilibration run was performed for 5 ns. Five replicates of 100 ns NPT MD-simulations were run thereafter. The LINCS algorithm⁶³ was used to constrain the lengths of all the bonds in acetate, whereas in the simulations with TIP3P water only bonds to H were constrained, according to CHARMM conventions. The water molecules were kept rigid in all simulations by use of the SETTLE algorithm⁶⁴. The temperature was kept constant at 298 K by use of the velocity-rescaling algorithm⁶⁵ and the pressure was coupled to an external bath with the Parrinello-Rahman algorithm⁶⁶ with 1 ps time constant. Long-range electrostatic forces were dealt with by use of the particle mesh Ewald (PME) method⁶⁷ and van der Waals forces were truncated at 1.0 nm with a plain cutoff in the simulations with SPC/E water, while in the simulations with TIP3P water a van der Waals force switch were applied from 1.0-1.2 nm. Dispersion corrections were applied for the energy and pressure in the simulations with SPC/E water molecules. The timestep between subsequent MD steps was 2 fs. The simulation speed was 0.58 h/ns on a 64-bit Intel machine (CPU frequency 2.4 MHz, 8 cores with hyperthreading, 16 threads) or 0.10 h/ns on a different 64-bit Intel machine (CPU frequency 2.3 GHz, 20 cores).

2. Simulations with a polarizable forcefield

Input files for simulations with polarizable force field were prepared with Drude Prepper in CHARMM-GUI⁶⁸. Boxes with 0.1 and 1 M alkali ion-acetate solutions were prepared with parameters for the cations according to the references in Table I and for acetate from the Drude-2013e polarizable forcefield⁶⁹, see Table S2. A mass of 0.4 amu was assigned to each Drude particle and subtracted from the associated atom mass and the Drude bonding constant was set to 40000 kcal mol⁻¹ Å⁻². In the Drude Prepper program a maximal bond length for the Drude oscillator is set to 0.25 Å and a non-bonded Thole cutoff to 5.0 Å and those setting were kept in the simulations. A hard well was applied for the Drude particle. The simulations were performed with the NAMD software⁴³ version 2.11. The temperature was kept constant at 298 K with dual Langevin dynamics, with damping coefficients of 20.0 ps⁻¹ and 5.0 ps⁻¹ for the relative and center-of-mass motions of the Drude-particle and the associated atom, respectively. The systems were energy minimized and equilibrated for 100 ps before collection of data over 10 ns. The polarizable model SWM4-NDP⁷⁰ was used for water molecules. The internal bonds in the water molecules were kept rigid by use of the SETTLE algorithm⁶⁴ while in the acetates only the bonds to hydrogens were constrained. Electrostatic interactions were

treated using the PME method⁶⁷ with a cutoff at 1.2 nm and a force switch from 1.0 nm. For the nonbonded LJ interactions a cutoff was set to 1.2 nm. The simulations with the Drude-2013 FF took 0.3-0.5 days/ns on a 64-bit Intel machine (CPU frequency 2.4 MHz, 8 cores with hyperthreading, 16 threads) or 0.11 days/ns on a different 64-bit Intel machine (CPU frequency 2.3 GHz, 20 cores).

TABLE I. Lennard Jones parameters for alkali ions and the corresponding water models.

Ion	σ_{ii} (nm)	ϵ_{ii} (kJ/mol)	Water model	λ^a
Li ⁺ KB ⁵	0.15000	1.547E+2	SPC	0.05
Li ⁺ HV ¹⁷	0.20000	5.000E-1	SPC/E	1
Li ⁺ HV ¹⁷	0.20000	5.000E-1	TIP3/P	1
Li ⁺ HV ¹⁷	0.20000	5.000E-1	TIP3/P	0.4
Li ⁺ Å ¹⁸	0.21645	7.648E-2	SPC/E	1
Li ⁺ Å ¹⁸	0.21645	7.648E-2	TIP3/P	1
Li ⁺ Drude ^{20,46}	0.19599	1.255E-1	SWM4-NDP	1
Na ⁺ WS ⁶²	0.24500	3.200E-1	SPC/E	0.75
Na ⁺ WS ⁶²	0.24500	3.200E-1	TIP3/P	0.75
Na ⁺ Dang ⁶	0.25830	4.186E-1	SPC/E	1
Na ⁺ Dang ⁶	0.25830	4.186E-1	TIP3/P	1
Na ⁺ Drude ^{20,46,47}	0.26044	1.318E-1	SWM4-NDP	1
K ⁺ KB ⁵	0.30300	2.185	SPC	1
K ⁺ HV ¹⁷	0.38000	2.000E-1	SPC/E	1
K ⁺ HV ¹⁷	0.38000	2.000E-1	TIP3/P	1
K ⁺ Drude ^{20,46,47}	0.30052	5.938E-1	SWM4-NDP	1
Rb ⁺ KB ⁵	0.45000	1.227E-6	SPC	1
Rb ⁺ Drude ^{20,46}	0.31814	1.143	SWM4-NDP	1
Cs ⁺ KB ⁵	0.40800	4.446E-7	SPC	1
Cs ⁺ CHM ⁵⁸	0.37417	7.950E-1	SPC/E	1
Cs ⁺ CHM ⁵⁸	0.37417	7.950E-1	TIP3/P	1
Cs ⁺ Drude ^{20,46}	0.36060	1.157	SWM4-NDP	1

^aScaling of the ion-water LJ interactions.

$\lambda=1$ if the interactions were not scaled.

TABLE II. Interatomic Lennard Jones parameters between the alkali ions (i) and water oxygens (j) after scaling.

Ion	Water model	λ	σ_{ij} (nm)	ϵ_{ij} (kJ/mol)
Li ⁺ KB ⁵	SPC	0.05	0.2332785	0.501460
Li ⁺ HV ¹⁷	SPC/E	1	0.2582785	0.570172781
Li ⁺ HV ¹⁷	TIP3/P	1	0.22913925	0.564087759
Li ⁺ HV ¹⁷	TIP3/P	0.4	0.22913925	0.225635104
Na ⁺ WS ⁶²	SPC/E	0.75	0.2807785	0.342104
Na ⁺ WS ⁶²	TIP3/P	0.75	0.2800287	0.338452655

B. Analysis of the molecular dynamics simulations

Radial distribution functions, (rdf, $g(r)$), were calculated with the alkali ion as reference to the position of either of the oxygens in acetate (or water). The rdf were

normalized by the number of alkali ions, the volume of the bin width (0.002 nm), and the average particle density of the acetate, so that the $g(r) = 1$ at infinity. The number of water molecules in first solvation shell was estimated from the average number of cation–water interactions within the ion–oxygen distances that are not larger than the first minimum of $g(r)$.

Ion–acetate association constants (K_a [M^{-1}]) were defined as:

$$K_a = [CH_3COOM]/([M^+][CH_3COO^-]) \quad (1)$$

where $M = Li, Na, K, Rb$ or Cs . The association constants were calculated according to the equation¹⁵:

$$K_a = \alpha/[(1 - \alpha)C] \quad (2)$$

where α is the fraction of simulation time during which a contact ion pair (CIP) was present (i.e., when the metal to oxygen distance was smaller than the first rdf minimum, for numbers from respective simulation see Table S3), and C is the salt concentration. Free energies of complexation between ions and ligands were estimated as:

$$\Delta G_a = -RT \ln K_a. \quad (3)$$

The activity coefficient (γ) was also calculated based on the time fraction spent in complex, α , and was hence simply defined as:

$$\gamma = 1 - \alpha \quad (4)$$

The interaction energies, ΔE_{int} , between alkali ion and acetate were calculated from the simulations as a sum of the short-range LJ and Coulomb interaction energies between the components (ions and acetate molecules). The interaction energies were calculated for all simulation frames during which a contact ion pair (CIP) was present between an acetate and a cation. Similarly, ΔE_{int} values between alkali ion and water were calculated for Li^+ and Na^+ , with a criterion of four water ligands for Li^+ and six water ligands for Na^+ . Since the larger ions (K^+ , Rb^+ and Cs^+) are softer and the first water shell was less distinct, the interaction energies could not be calculated in the same way for these ions.

C. Quantum chemistry

Interaction free energies (ΔG^{tot}) were calculated as⁷¹:

$$\Delta G^{tot} = G_{complex}^{PCM} - (G_{M^+}^{PCM} + G_{acetate}^{PCM}) \quad (5)$$

where ΔG^{tot} is the free energy in solvent estimated by calculating the free energy of the solvated compound. The dielectric constant of the water was adjusted to the temperature, whereas vibrational effects are not considered. ΔG^{tot} was decomposed into contributions from

electrostatics, exchange, repulsion, polarization, dispersion and desolvation by Localized Molecular Orbital Energy Decomposition Analysis (LMOEDA)⁷² as developed for use with PCM (EDA-PCM)^{54,72}. QM calculations were carried out in GAMESS⁷³. Water beyond the first solvation shell (for hydrated complexes) or all water (for alkali ion–acetate complexes) were represented by PCM⁷⁴. Energies were calculated with the MP2 method⁷⁵. The def2-TZVPD⁷⁶ basis set, used in energy calculations for all atoms, was downloaded from the EMSL basis set exchange database^{77,78}. Effective core potentials (ECP) were applied for Rb (ECP-28) and Cs (ECP-46)⁷⁹. Valence calculations for these ions were performed with the def2-TZVPD basis set. The MP2 method and def2-TZVPD⁷⁶ basis set were used for structure optimization unless stated otherwise. Default sphere radii (as implemented in GAMESS⁸⁰) were used for all atoms except Li^+ for which no parameter was available in the program. The sphere radius for Li^+ was set to 0.59 nm following previous work⁴.

IV. RESULTS AND DISCUSSION

A. Structural properties

The radial distributions of acetate oxygens around alkali ions simulated at different concentrations (0.03, 0.1, and 1 M) are summarized in Table III, and the rdf for one of the non-polarizable parameters (with the best matching log K_a -value) and the polarizable forcefields are shown in Figure 1. The first peak, r_1 , can be interpreted as direct ion complexation or (closed sphere complex, or CIP). The second peak, r_2 , corresponds to a solvent separated ion pair interaction (solvent-separated ion pair, SIP). Experimental values for distances between alkali ions and acetate were extracted from crystal structures of carboxylate-ion complexes deposited to the Cambridge Structural Database, CSD version 5.38 (Figure S1). A good agreement between the distances observed in the simulations and the crystallographic values (with differences smaller than <0.01 nm) was observed with most of the FF combinations for ions and water. However, the use of the parameters developed by Hess and van-der-Vegt for the Li^+ ion, with the scaling factor of 0.4 for the ionwater interaction resulted in SIP but not CIP for Li^+ –acetate interactions (in disagreement with the crystal structures). Other dissimilarities involved the **Drude-2013** and KB-based parameters. The Drude polarizable parameters resulted in bond length between Na^+ and acetate that were too short. CIP distances were also smaller for Rb^+ and Cs^+ calculated with the parameters derived based on Kirkwood-Buff theory for alkali-chlorides⁵, because the cations were too soft, i.e., the LJ ϵ was rather small (which might have been necessary to obtain the right activities in alkali-chloride solutions). Further analysis was therefore not performed with those KB-based parameters. The rdf for Li–acetate simulated

with Drude polarizable forcefield showed a second peak at $d_{CIP} < d < d_{SIP}$. Examination of the simulations revealed a preference for a monodentate binding conformation for the Li-acetate complex studied with this forcefield. This led to uneven distances between the small Li^+ ion and the carboxylate oxygens, with the first peak (to the proximal oxygen) at 0.208 nm and the second peak (to the distal oxygen) at 0.325 nm.

The QM-optimized distances between alkali ion and the two acetate oxygen are given in Table III. QM distances were 0.04 nm shorter than the reported crystallographic measurements for Li^+ and 0.01-0.02 nm shorter for the other cations. This ambiguity may stem from different reasons, one of which is the choice of the atomic radii used in the PCM calculations. To examine the effect of the choice of radius for Li^+ , the ion-acetate complex was re-optimized after setting the ionic radius of Li^+ to 0.70 nm. This resulted in ion-oxygen distances of 0.40 nm and 0.43 nm, which were 0.2 nm longer than the experimental value. For this reason, further calculations with $r_{\text{Li}^+} = 0.7$ nm were not carried out, and the previously used radius (0.59 nm) was preferred. Other aspects that can contribute to the disagreement between the QM and experimental results are interactions with other atoms in the crystal, experimental inaccuracies, and the choice of solvent model, calculation method and basis set in QM calculations. Since the ions are not expected to maintain the minimal contact distance throughout the simulations, further efforts to examine this difference were not made.

The number of water molecules in the first solvation shell and the peaks of ion-water rdf from the simulations are also reported in Table III. The use of the TIP3P water model generally resulted generally in a slightly larger number of water molecules in the first solvation shell than for simulations with the SPC/E water model. For Li^+ , there were approximately 5 water molecules in the first solvation shell with TIP3P rather than the expected number of four. Na^+ ions were surrounded by 5-6 water molecules in the MD-simulations, and differences between the non-polarizable simulations set ups were small. However, the use of the polarizable force field parameters for the Na^+ resulted in strong association between Na^+ and acetate during the simulations. Clusters of Na^+ and acetate molecules were observed in the simulations, which indicated that the Na^+ were only partly exposed to the water molecules. Owing to the softer character and larger sizes of the Rb^+ and Cs^+ ions, the first solvation shell of these ions was hard to define. The numbers of water molecules within the first solvation shells of Rb^+ and Cs^+ were estimated as 7.2 and 8-10, respectively.

B. QM interaction free energies and energy decomposition analysis

The calculated ion-acetate interaction free energies (ΔG^{tot}) were -100 to -110 kJ/mol for the K^+ , Rb^+ and Cs^+ -acetate complexes, whereas the interactions were

more favorable for Na^+ -acetate (-130 kJ/mol) and Li^+ -acetate (-150 kJ/mol). The contributions from polarization to the alkali ion-acetate were evaluated to account for 23-56% of the total free energies of interaction based on PCM-EDA (Table IV). Although this contribution was very significant, it is much smaller in magnitude than ΔG^{elec} (which is large and negative) and ΔG^{desolv} (which is large and positive). Polarization contributed more to the cation-acetate interactions than dispersion, and for Li^+ and Na^+ also more than QM exchange. Interestingly, when examining $\Delta G^{\text{pol}}/\Delta G^{\text{tot}}$ the relative contribution of polarization is in the order $\text{Li}^+ > \text{Cs}^+ > \text{Rb}^+ > \text{K}^+ > \text{Na}^+$. This is not in par of the same calculation for the water complexes, where the order is $\text{Li}^+ > \text{Na}^+ > \text{K}^+ \sim \text{Rb}^+ \sim \text{Cs}^+$. Overall, in the case of Li^+ , polarization is more significant for cation-water than for cation-acetate interactions, whereas for the other ions polarization is less significant (with respect to the overall interaction) when they are solvated.

C. Association constants

Reproducing the ion-carboxylate association constants is important for obtaining quantitative results from the simulations⁸¹. Overestimation of K_a results in overbinding, and in activity coefficients that are too low. Underestimation of K_a leads to ions that are too stable in water. In principle, reproducing the activity derivatives¹⁷ can yield parameters that reproduce the experimental values for the association constants irrespective of the salt concentration. Bjerrum estimated a critical distance for contact formation that depends on the ionic charge, solvent dielectric and temperature⁸², but not on the specific ion. Here, the association constants were estimated from the simulations as K_{CIP} , i.e., critical distances corresponded to the first minimum of the ion-oxygen rdf. The CIP-distances used for each calculation are presented in Table S3. Values of $\log K_{CIP}$ are given in Table V and were compared to experimental $\log K_a$ for 0.1 M solutions. The association constants depend on the concentration, and should in principle be smaller for more concentrated solutions due to charge screening.

Examination of the K_{CIP} values revealed that ion pairing between Li^+ and acetate was too strong in almost all simulations, except for the scaled Li^+ parameters (from Hess and van der Vegt) and the polarizable forcefield were almost no CIP occurred. Overbinding was also observed in the simulations with the polarizable parameters for Na^+ and K^+ , which resulted in the formation of Na-acetate salt clusters in the solutions. For Rb^+ and Cs^+ , K_{CIP} values calculated with the polarizable forcefield were in good agreement with the experiment for 0.1 M solutions. The non-polarizable alkali ion parameters resulted in too negative $\log K$ values, i.e. complexes were disfavored. Some fixed atomic charge forcefields were off by as much as 0.7 $\log K$ units, whereas others were within 0.07-0.13 $\log K$ units, i.e., much closer to

the experimental values.

It is also possible to consider whether K_{SIP} , i.e., setting a cutoff that matches the second minimum in the cation-acetate rdf could be more appropriate as a theoretical match for the association constant. However, regardless of the ion and forcefield, calculated $\log K_{SIP}$ values clearly overestimate $\log K_a$ (Table S3). Indeed, the generic cutoff suggested by Bjerrum for ions in water at $T=298$ K is 0.36 nm is within the range of distances for CIP (0.275-0.380 nm). The solvent-separated ion pair definition appears to be too loose for the purpose of calculating K_a from the simulations.

D. Energetics of the cation-acetate and cation-water interactions

The association constants can be used to calculate the free energies of complexation, which are given in Table V. These values can reveal whether and to which extent the differences between experimental and calculated association constants are meaningful compared to the thermal energy (2.48 kJ/mol). Indeed, most of forcefields parameters used here resulted in reasonably accurate calculations of the free energies of ion-acetate complexation at 0.1 M, and differences between the complexes simulated at the different concentrations were rather small (even for Li^+ , where $\Delta G_{exp} = 0.25$ kJ/mol, calculated from K_a). A single exception was the value obtained with the scaled non-polarizable Li^+ parameters (HV), $\Delta G = 14$ kJ/mol. For Na^+ , the WS parameter set underestimates the binding free energies by some 4 kJ/mol. A common test for the accuracy of ion forcefields is the ability to reproduce the hydration free energies, which is in itself not a trivial experimental value to compare with²⁰. It is possible to get the cation hydration free energies right but still over- or underestimate the complexation energies, which depends on the cation-acetate and acetate-water interactions as well. The interaction energies, ΔE_{int} for the cation-acetate and cation-water-shell can be calculated directly from the simulations if a non-polarizable forcefield is used and the solvation shell is defined. Those values were given (when possible) in Table V. This analysis revealed that the main difference between the WS and Dang parameter sets for Na^+ was due to the interactions between the ions and water molecules.

E. Activity coefficients

The activity coefficients, γ , were estimated experimentally to be ~ 0.8 for all alkali-acetate salts in 0.1 M solutions⁸³. In 1 M solutions, the difference between Li^+ , Na^+ and the larger alkali ions was more eminent (Table V). The decrease of the value of γ was most apparent for Li-acetate solutions ($\Delta\gamma = -0.11$ when a solution is concentrated from 0.1 to 1 M), smaller for Na-acetate ($\Delta\gamma = -0.04$), and not apparent in solutions containing

the larger alkali cations. The activity coefficients were calculated from the simulations in order to examine how well the different forcefields reproduced the experimental values (Table V). For Li^+ , the non-polarizable parameter set from Åqvist simulated with SPC/E water resulted in activity coefficients that were in par with the experimental values at 0.1 M, whereas the HV parameter set and the polarizable force field parameters overestimated γ at the same concentration. The situation was different with 1 M solutions, where the activity coefficient was underestimated by all forcefields, with the polarizable parameter set leading to the best agreement with the experiment. For Na^+ , calculations of γ from simulations with the parameter set from Dang, but not WS, resulted in a value very similar to the experiment for 1 M sodium acetate. One explanation for the higher γ obtained from simulations of Na-acetate with the parameters from Weerasinghe and Smith can be that the Na^+ -water interaction energy was too favorable, so that the Na^+ ion had a tendency to stay solvated.

The calculated activity coefficients for 0.1 M solutions of Na, K, Rb and Cs-acetate were lower than the values estimated from experiments, regardless of the parameter set, whereas better agreement between simulation and experiment was observed in 1 M solutions. In 0.1 M electrolyte solutions, the average distance between two oppositely charged ions is much larger than the cutoff (the density of each ion is 0.06 ions/nm³, and their average distance would thus be 2.59 nm if they are randomly dispersed). In 1 M solutions, chance encounters within 1.0 nm are much more common (the average distance between the ions would be 1.22 nm if they are randomly dispersed). Of note, the diffusion coefficients of the ions are in par with the experiment (Table S4), which indicates that the dynamics are realistic.

TABLE III. Radial distribution functions (rdf) calculated from MD simulations for cation-acetate (+-) and metal cation-water oxygen (+w) (values are calculated from 1 M concentration simulations). r_1 and r_2 is the separation distances in nm for the first and second peak maximum. #w is the average number of water molecules in the first solvation shell calculated from simulations carried out with the lowest concentration of ions, i.e. 0.03 M or 0.1 M.

Ion	Water model	+-		#w	+w	
		r_1	r_2		r_1	r_2
Li ⁺ experiment		0.210 ^a			0.190-0.228 ^c	
Li ⁺ QM		0.164/0.167 ^b		4	0.197 ^b	
Li ⁺ KB ⁵	SPC	0.23	0.42	n/a	0.19/0.26	0.47
Li ⁺ HV ¹⁷	SPC/E	0.22	0.43	4.4	0.22/0.29	0.48
Li ⁺ HV ¹⁷	TIP3P	0.21	0.40	5.5	0.22/0.29	0.50
Li ⁺ HV ¹⁷ scaled 0.4	TIP3P	0.40	0.59	4.0	0.18/0.25	0.44
Li ⁺ Åqvist ¹⁸	SPC/E	0.20	0.40	3.3	0.21/0.28	0.46
Li ⁺ Åqvist ¹⁸	TIP3P	0.20	0.41	4.9	0.21/0.28	0.48
Li ⁺ Drude ^{20,46}	SWM4-NDP	0.21	0.32/0.47	3.6	0.20	0.42
Na ⁺ experiment		0.24-0.25 ^a			0.24-0.25 ^c	
Na ⁺ QM		0.233/0.235 ^b		6	0.246-0.251 ^b	
Na ⁺ WS ⁶²	SPC/E	0.23	0.44	5.6	0.23/0.30	0.48
Na ⁺ WS ⁶²	TIP3P	0.23	0.45	5.8	0.24/0.30	0.50
Na ⁺ Dang ⁶	SPC/E	0.23	0.44	5.6	0.25/0.31	0.50
Na ⁺ Dang ⁶	TIP3P	0.24	0.45	5.7	0.25/0.31	0.52
Na ⁺ Drude ^{20,46,47}	SWM4-NDP	0.13	0.27	n/a	0.24	0.35
K ⁺ experiment		0.28-0.29 ^a			0.260-0.295 ^c	
K ⁺ QM		0.264/0.265 ^b		6	0.274-0.276 ^b	
K ⁺ KB ⁵	SPC/E	0.25	0.46	n/a	0.260	0.320
K ⁺ HV ¹⁷	SPC/E	0.29	0.49	6.1	0.30/0.35	0.57
K ⁺ HV ¹⁷	TIP3P	0.29	0.50	7.2	0.30/0.35	0.58
K ⁺ Drude ^{20,46,47}	SWM4-NDP	0.26	0.43	n/a	0.27	0.51
Rb ⁺ experiment		0.300 ^a			0.291-0.293 ^b	
Rb ⁺ QM		0.277/0.286 ^b		6, 8	0.291-0.293 ^b	
Rb ⁺ KB ⁵	SPC	0.18	0.38	n/a	0.19	0.44
Rb ⁺ Drude ^{20,46}	SWM4-NDP	0.30	0.50	7.2	0.29	0.50
Cs ⁺ experiment		0.31-0.34 ^a			0.295-0.321 ^c	
Cs ⁺ QM		0.294/0.297 ^b		8	0.314-0.336 ^b	
Cs ⁺ KB ⁵	SPC/E	0.16	0.33	n/a	0.18	0.25
Cs ⁺ CHM ⁵⁸	SPC/E	0.30	0.49	9.3	0.32	n/a
Cs ⁺ CHM ⁵⁸	TIP3P	0.30	0.51	9.4	0.33	0.60
Cs ⁺ Drude ^{20,46}	SWM4-NDP	0.32	0.52	8.9	0.31	n/a

^aDatabase survey, see SI.

^bQM from this work.

^cRef¹²

Not available, i.e., no peak or no appropriate value

FIG. 1. Radial distribution functions of M^+ relative to acetate oxygen atoms simulated in 0.03 M (dotted lines), 0.1 M (dashed lines) and 1 M (solid lines) concentrations. Non-polarizable forcefields (simulations with SPC/E water) are shown in the left panels and polarizable forcefields in the panels to the right. The curves were smoothed by averaging the measurements over 20 steps to remove spurious jumps. The forcefield parameter sets are given in Table I.

TABLE V. Free energies of interaction (ΔG_{int}) between alkali ion-acetate and alkali ion-water in PCM, decomposed by FDA-PCM⁵⁴ into contributions from electrostatics (ΔG^{ele}), exchange (ΔG^{ex}), repulsion (ΔG^{rep}), polarization (ΔG^{pol}), desolvation (ΔG^{desol}) and dispersion (ΔG^{disp}). The values were obtained with MP2 and are given in kJ/mol.

Metal ion	Ligands	Basis set	ΔG^{tot}	ΔG^{ele}	ΔG^{ex}	ΔG^{rep}	ΔG^{pol}	ΔG^{desol}	ΔG^{disp}
Li ⁺ salt	acetate	aug-cc-pVTZ	-151	-791	-67	+201	-84	+577	+13
	acetate	def2-TVZPD ^b	-151	-795	-67	+201	-79	+582	+17
Li ⁺ hydr.	4 water ^a	aug-cc-pVTZ	-385	-473	-50	+142	-113	+88	+21
	5 water ^a	aug-cc-pVTZ	-272	-389	-59	+142	-50	+63	+17
Na ⁺ salt	acetate	aug-cc-pVTZ	-126	-519	-13	+29	-29	+397	+4
	acetate	def2-TVZPD ^b	-126	-519	-13	+29	-29	+397	+4
Na ⁺ hydr.	4 water ^a	aug-cc-pVTZ	-272	-389	-59	+142	-50	+63	+17
	5 water ^a	aug-cc-pVTZ	-259	-339	-42	+105	-59	+63	+13
	6 water ^a	aug-cc-pVTZ	-310	-381	-42	+105	-67	+63	+17
K ⁺ salt	acetate	TZV/aug-cc-pVTZ	-96	-561	-67	+134	-29	+410	+8
	acetate	def2-TVZPD	-113	-577	-75	+159	-42	+423	-4
K ⁺ hydr.	5 water ^a	TZV/aug-cc-pVTZ	-188	-377	-88	+176	-17	+109	+8
	6 water ^a	TZV/aug-cc-pVTZ	-234	-423	-84	+172	-21	+109	+8
	6 water	def2-TVZPD	-259	-427	-92	+192	-25	+105	-8
Rb ⁺ salt	acetate	def2-TVZPD	-100	-531	-75	+146	-42	+406	-4
Rb ⁺ hydr.	6 water	def2-TVZPD	-218	-393	-105	+201	-17	+109	-8
	8 water	def2-TVZPD	-186	-344	-94	+180	-21	+108	-16
Cs ⁺ salt	acetate	def2-TVZPD	-100	-515	-100	+180	-54	+389	-8
Cs ⁺ hydr.	6 water	def2-TVZPD	-188	-356	-117	+218	-17	+100	-21
	8 water	def2-TVZPD	-192	-339	-113	+209	-21	+100	-25

^a previous work⁴. ^b structure optimized with aug-cc-pVTZ.

TABLE V. Equilibrium constants (experimental $\log K_a$ and calculated $\log K_{CIP}$), free energies of complexation (ΔG), activity coefficients (γ) and interaction energies (ΔE) for the alkali ion–acetate and the alkali ion–water interactions in solutions at 298 K for different concentrations. Critical radii used in the calculations of $\log K$, ΔG and activity calculations are based on CIP distances (Table S3). For the non-polarizable forcefields, results are averages (standard deviations) of five simulations (100 ns each). The polarizable forcefield parameters were calculated from five 10 ns simulations.

Ion	Water model	Concentration (M)	log K		ΔG (kJ/mol)		γ		ΔE_{int} ion-acetate (kJ/mol)	ΔE_{int} ion-water (kJ/mol)
			MD	exp. ⁸⁴	MD	exp.	MD	exp.		
Li ⁺ HV ¹⁷	SPC/E	0.03	+0.17(13)		−1.05		0.96		−178	−240
		0.1	+0.00(3)	−0.11	0	+0.25	0.91	0.79		
		1	−0.09(3)		0		0.55	0.69		
Li ⁺ HV ¹⁷	TIP3P	0.03	+0.28(20)		−1.90		0.94		−218	−473 ^a
		0.1	−0.04(20)	−0.11	0	+0.25	0.91	0.79		
		1	+0.32(4)		−1.90		0.32	0.69		
Li ⁺ HV ¹⁷ scaled 0.4	TIP3P	0.03	−2.00(0)		+11.0		1.00		n/a	−629
		0.1	−2.50(4)	−0.11	+14.0	+0.25	1.00	0.79		
		1	+0.60(4)		−3.80		0.18	0.69		
Li ⁺ Å ¹⁸	SPC/E	0.03	+0.47(45)		−3.40		0.90		−206	−413
		0.1	+0.33(11)	−0.11	−2.30	+0.25	0.80	0.79		
		1	+0.33(2)		−1.85		0.32	0.69		
Li ⁺ Å ¹⁸	TIP3P	0.03	+0.57(44)		−4.00		0.87		−232	−495
		0.1	+0.70(13)	−0.11	−4.10	+0.25	0.66	0.79		
		1	+0.33(2)		−1.85		0.32	0.69		
Li ⁺ Drude ^{20,46}	SWM4-NDP	0.1	−2.00(100)	−0.11	+5.0	+0.25	0.99	0.79		
		1	−0.22(10)		+1.2		0.62	0.69		
Na ⁺ WS ⁶²	SPC/E	0.03	−0.93(30)		+4.80		1.00		−134	−340
		0.1	−0.96(11)	−0.26	+5.40	+0.65	0.99	0.79		
		1	−1.07(2)		+6.10		0.92	0.75		
Na ⁺ WS ⁶²	TIP3P	0.03	−0.96(46)		+4.55		1.00		−178	−424
		0.1	−0.91(14)	−0.26	+5.10	+0.65	0.99	0.79		
		1	−0.93(1)		+5.30		0.90	0.75		
Na ⁺ Dang ⁶	SPC/E	0.03	−0.29(14)		+1.60		0.98		−124	−285
		0.1	−0.39(8)	−0.26	+2.20	+0.65	0.96	0.79		
		1	−0.47(1)		+2.65		0.75	0.75		
Na ⁺ Dang ⁶	TIP3P	0.03	−0.41(26)		+1.90		0.99		−188	−359
		0.1	−0.32(4)	−0.26	+1.85	+0.65	0.96	0.79		
		1	−0.32(1)		+1.85		0.68	0.75		
Na ⁺ Drude ^{20,46,47}	SWM4-NDP	0.1		−0.26		+0.65		0.79		
		1	Cluster formation					0.75		
K ⁺ HV ¹⁷	SPC/E	0.03	−0.41(6)		+2.40		0.99		−60	
		0.1	−0.52(3)	−0.41	+2.95	+1.00	0.97	0.79		
		1	−0.66(0)		+3.75		0.82	0.78		
K ⁺ HV ¹⁷	TIP3P	0.03	−0.74(15)		+4.05		0.99		−89	
		0.1	−0.68(2)	−0.41	+3.90	+1.00	0.98	0.79		
		1	−0.73(1)		+4.20		0.84	0.78		
K ⁺ Drude ^{20,46,47}	SWM4-NDP	0.1	+1.30(23)	−0.41	−7.5	+1.00	0.36	0.79		
		1	+1.20(11)		−7.0		0.06	0.78		
Rb ⁺ Drude ^{20,46}	SWM4-NDP	0.1	−0.32(13)	−0.35	+1.70	+0.85	0.95	0.78		
		1	−0.44(2)		+2.50		0.74	0.79		
Cs ⁺ CHM ⁵⁸	SPC/E	0.03	−0.40(11)		+2.15		0.95		−53	
		0.1	−0.38(2)	−0.31	+2.15	+0.75	0.96	0.79		
		1	−0.55(6)		+3.10		0.78	0.80		
Cs ⁺ CHM ⁵⁸	TIP3P	0.03	−0.56(10)		+3.15		0.99		−79	
		0.1	−0.58(2)	−0.31	+3.30	+0.75	0.98	0.79		
		1	−0.63(1)		+3.60		0.81	0.80		
Cs ⁺ Drude ^{20,46}	SWM4-NDP	0.1	−0.29(7)	−0.31	+1.65	+0.75	0.95	0.79		
		1	−0.44(1)		+2.55		0.74	0.80		

^a Interaction with 5 water molecules

CONCLUSIONS

Extensive simulations of alkali-acetate solutions were performed with different polarizable and non-polarizable forcefield parameters. Observables were calculated from the simulations and compared to experimental measurements that are relevant to simulations of proteins in solutions. QM EDA calculations were performed in order to estimate the contributions of polarizability and non-classical contributions to the interaction energies between the ions and acetates. Some of the parameters did not reproduce the correct rdf structures for the solutions. For all alkali ions except Li^+ , good agreement between calculated and experimentally observed activity coefficients was obtained in 1 M concentrated solutions by at least one of the tested parameter sets. Activity coefficients were overestimated for the non- Li^+ ions when simulated in 0.1 M solutions. On the other hand, calculated complexation free energies were in most cases within few kJ/mol or less of the experimental values, and the simulations reproduced the higher propensity to observe ion-acetate complexes in lower concentrations in density-normalized rdf. EDA calculations revealed that although the contribution of polarization with respect to the overall interaction energy between the ions and the acetates was significant, it was much smaller than the electrostatic contribution. Polarization, however, was shown to be important for Li^+ -water interactions. Differences between the non-polarizable forcefield parameters for Na^+ appeared to be due to the interactions between the cations and the water, and point out that further tuning the ion-water interactions may be important to achieve better agreement with the experiment when interactions with carboxylates are considered.

Overestimation of the activity coefficients in 0.1 M solutions of non- Li^+ alkali ions was systematic, and stood in contrast to the agreement between simulation and experiment in 1 M solutions. Since none of the water models that were employed in the simulations overestimated the dielectric constant of the water, it is not likely that the screening of the charge-charge interactions was the source of this discrepancy. Instead, it may well be that the simulation protocol, which uses finite interaction cutoff was the source of this artifact. It can be expected that this would be less pronounced on the surface of proteins, when the acetates are more static and the Coulomb cage extends to a larger volume^{3,15}.

Simulations of Li^+ -acetate solutions did not achieve an overall good agreement with the experiment. The polarizable parameters reproduced all observables well when the solution concentration was 1 M, but when it was smaller. The Åqvist parameters with SPC/E water yielded activity coefficients that were close to the experimental values for 0.1 M solutions, but were too low for 1 M solutions, whereas calculations of the activity coefficient were closer to the experimental value when carried out with the HV parameter set in a 1 M Li-acetate solution. Since the simulation protocol was similar for the

different alkali ions, agreement with the experiment at 0.1 M may be due to cancellation of errors (the forcefields overestimated the anion-cation interactions, which compensated for the opposite effect introduced by the Coulomb cutoff). EDA calculations revealed that the contributions of the exchange interaction to the overall free energy of interaction between Li^+ and water or acetate was not higher than for other ions, whereas polarization was important for Li^+ -water interactions. Thus, developing forcefield parameters that could represent the interactions between Li^+ , carboxylates and water more realistically should be achievable, but may require a polarizable model.

VI. SUPPLEMENTARY MATERIAL

See supplementary material for CGenFF acetate parameters and parameters for all ions for the polarizable force field, critical radius values and equilibrium constants for SIP, diffusion constants and distribution of crystallographic distances between carboxylate oxygens and alkali cations.

ACKNOWLEDGMENTS

Some of the simulations were performed on resources provided by the Swedish National Infrastructure for Computing (SNIC) at the center for scientific and technical computing at Lund University (LUNARC), project SNIC 2016/1-518. This study was supported in part by the Swedish Research Council, grant number VR 2014-04406. JZS thanks the Brazilian National Council for Scientific and Technological Development for a scholarship (CNPq-305626/2013-2).

- ¹R. Friedman, E. Nachliel, and M. Gutman, *Bioch. Biophys. Acta.* **1710**, 67 (2005).
- ²M. Gutman, E. Nachliel, and R. Friedman, *Photochem. Photobiol. Sci.* **5**, 531 (2006).
- ³R. Friedman, *J. Phys. Chem. B* **115**, 9213 (2011).
- ⁴O. Becconi, E. Ahlstrand, A. Salis, and R. Friedman, *Israel J. Chem.* **57**, 403 (2017).
- ⁵B. Klasczyk and V. Knecht, *J. Chem. Phys.* **132**, 024109 (2010).
- ⁶L. X. Dang, *J. Am. Chem. Soc.* **117**, 6954 (1995).
- ⁷P. Jungwirth and D. J. Tobias, *Chem. Rev.* **106**, 1259 (2006).
- ⁸E. F. Aziz, N. Ottosson, S. Eisebitt, W. Eberhardt, B. Jagoda-Cwiklik, R. Vcha, P. Jungwirth, and B. Winter, *J. Phys. Chem. B* **112**, 12567 (2008).
- ⁹R. Friedman, *J. Chem. Edu.* **90**, 1018 (2013).
- ¹⁰T. X. Dang and E. W. McCleskey, *J. Gen. Physiol.* **111**, 185 (1998).
- ¹¹E. Project, R. Friedman, E. Nachliel, and M. Gutman, *Biophys. J.* **90**, 3842 (2006).
- ¹²H. Ohtaki and T. Radnai, *Chem. Rev.* **93**, 1157 (1993).
- ¹³H. I. Okur, J. Kherb, and P. S. Cremer, *J. Am. Chem. Soc.* **135**, 5062 (2013).
- ¹⁴R. Friedman, E. Nachliel, and M. Gutman, *J. Biol. Phys.* **31**, 433 (2005).
- ¹⁵R. Friedman, E. Nachliel, and M. Gutman, *Biophys. J.* **89**, 768 (2005).

- ¹⁶E. Project, E. Nachliel, and M. Gutman, PLoS One **6**, 21364983 (2011).
- ¹⁷B. Hess and N. F. van der Vegt, Proc. Natl. Acad. Sci. U.S.A. **106**, 32296 (2009).
- ¹⁸J. Åqvist, J. Chem. Phys. **94**, 8021 (1990).
- ¹⁹B. Roux and M. Karplus, J. Phys. Chem. **95**, 4856 (1991).
- ²⁰H. Yu, T. W. Whitfield, E. Harder, G. Lamoureux, I. Vorobyov, V. M. Anisimov, A. D. MacKerell, and B. Roux, J. Chem. Theory Comput. **6**, 774 (2010).
- ²¹L. X. Dang and T.-M. Chang, J. Chem. Phys. **106**, 8149 (1997).
- ²²D. Jiao, C. King, A. Grossfield, T. A. Darden, and P. Ren, J. Phys. Chem. B **110**, 18553 (2006).
- ²³N. Gresh, G. A. Cisneros, T. A. Darden, and J.-P. Piquemal, J. Chem. Theory Comput. **3**, 1960 (2007).
- ²⁴B. de Courcy, J.-P. Dognon, C. Clavaguéra, N. Gresh, and J.-P. Piquemal, Int. J. Quant. Chem. **111**, 1213 (2011).
- ²⁵M. Soniat and S. W. Rick, J. Chem. Phys. **140**, 184703 (2014).
- ²⁶T. Dudev, M. Devereux, M. Meuwly, C. Lim, J. P. Piquemal, and N. Gresh, J. Comput. Chem. **36**, 285 (2015).
- ²⁷G. E. Marlow and B. M. Pettitt, Biopolymers **60**, 134 (2001).
- ²⁸L. Vrbka, P. Jungwirth, P. Bauduin, D. Touraud, and W. Kunz, J. Phys. Chem. B **110**, 7036 (2006).
- ²⁹S. J. Lee, Y. Song, and N. A. Baker, Biophys. J. **94**, 3565 (2008).
- ³⁰J. Heyda, J. Pokorná, L. Vrbka, R. Vácha, B. Jagoda-Cwiklik, J. Konvalinka, P. Jungwirth, and J. Vondrásek, Phys. Chem. Chem. Phys. **11**, 7599 (2009).
- ³¹D. Horinek, S. I. Mamatkulov, and R. R. Netz, J. Chem. Phys. **130**, 124507 (2009).
- ³²S. Pokorna, P. Jurkiewicz, L. Cwiklik, M. Vazdar, and M. Hof, Faraday Discuss. **160**, 341 (2013).
- ³³P. Ganguly, T. Hajari, and N. F. A. van der Vegt, J. Phys. Chem. B **118**, 5331 (2014).
- ³⁴F. R. Beierlein, T. Clark, B. Braunschweig, K. Engelhardt, L. Glas, and W. Peukert, J. Phys. Chem. B **119**, 5505 (2015).
- ³⁵L. Pineda De Castro, M. Dopson, and R. Friedman, J. Phys. Chem. B **120**, 10628 (2016).
- ³⁶G. Lamoureux, A. D. M. Jr., and B. Roux, J. Chem. Phys. **119**, 5185 (2003), <http://dx.doi.org/10.1063/1.1598191>.
- ³⁷B. R. Brooks, R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan, and M. Karplus, J. Comp. Chem. **4**, 187 (1983).
- ³⁸B. R. Brooks, C. L. Brooks, A. D. MacKerell, L. Nilsson, B. Roux, Y. Won, G. Archontis, C. Bartels, S. Boresch, A. Caffisch, L. Caves, Q. Cui, A. Dinner, S. Fischer, J. Gao, M. Hodoseck, K. Kuczera, T. Lazaridis, J. Ma, E. Paci, R. W. Pastor, C. B. Post, M. Schaefer, B. Tidor, R. W. Venable, H. L. Woodcock, X. Wu, and M. Karplus, J. Comp. Chem. **30**, 1545 (2009).
- ³⁹J. A. Lemkul, B. Roux, D. van der Spoel, and A. D. MacKerell, J. Comput. Chem. **36**, 1473 (2015).
- ⁴⁰H. J. C. Berendsen, D. van der Spoel, and R. Vandrunen, Comput. Phys. Commun. **91**, 43 (1995).
- ⁴¹D. van der Spoel, E. Lindahl, B. Hess, G. Groenhof, A. E. Mark, and H. J. C. Berendsen, J. Comput. Chem. **26**, 1701 (2005).
- ⁴²M. J. Abraham, T. Murtola, R. Schulz, S. Páll, J. C. Smith, B. Hess, and E. Lindahl, SoftwareX **12**, 19 (2015).
- ⁴³W. Jiang, D. J. Hardy, J. C. Phillips, A. D. MacKerell, K. Schulten, and B. Roux, J. Phys. Chem. Lett. **2**, 87 (2011), <http://dx.doi.org/10.1021/jz101461d>.
- ⁴⁴J. C. Phillips, R. Braun, W. Wang, J. Gumbart, E. Tajkhorshid, E. Villa, C. Chipot, R. D. Skeel, L. Kalé, and K. Schulten, J. Comput. Chem. **26**, 1781 (2005).
- ⁴⁵H. V. Annappureddy and L. X. Dang, J. Phys. Chem. B **116**, 7492 (2012).
- ⁴⁶Y. Luo, W. Jiang, H. Yu, A. D. MacKerell, and B. Roux, Faraday Discuss. **160**, 135 (2013).
- ⁴⁷H. Li, V. Ngo, M. C. Da Silva, D. R. Salahub, K. Callahan, B. Roux, and S. Y. Noskov, J. Phys. Chem. B **119**, 9401 (2015).
- ⁴⁸S. B. Rempe, L. R. Pratt, J. D. Kress, R. L. Martin, and A. Redondo, J. Am. Chem. Soc. **122**, 966 (2000).
- ⁴⁹S. B. Rempe and L. R. Pratt, Fluid Phase Equilibria **183-184**, 121 (2001).
- ⁵⁰K. Leung, S. B. Rempe, and O. A. von Lilienfeld, J. Chem. Phys. **130**, 204507 (2009).
- ⁵¹C. N. Rowley and B. Roux, J. Chem. Theory. Comput. **8**, 3526 (2012).
- ⁵²A. Y. Mehandzhyski, E. Riccardi, T. S. van Erp, T. T. Trinh, and B. A. Grimes, J. Phys. Chem. B **119**, 10710 (2015).
- ⁵³J.-P. Piquemal, L. Perera, G. A. Cisneros, P. Ren, L. G. Pedersen, and T. A. Darden, J. Chem. Phys. **125**, 054511 (2006).
- ⁵⁴P. Su, H. Liu, and W. Wu, J. Chem. Phys. **137**, 034111 (2012).
- ⁵⁵K. Vanommeslaeghe, E. Hatcher, C. Acharya, S. Kundu, S. Zhong, J. Shim, E. Darian, O. Guvench, P. Lopes, I. Vorobyov, and A. D. Mackerell, J. Comput. Chem. **31**, 671 (2010).
- ⁵⁶A. D. MacKerell, D. Bashford, M. Bellott, R. L. Dunbrack, J. D. Evanseck, M. J. Field, S. Fischer, J. Gao, H. Guo, S. Ha, D. Joseph-McCarthy, L. Kuchnir, K. Kuczera, F. T. K. Lau, C. Mattos, S. Michnick, T. Ngo, D. T. Nguyen, B. Prodhom, W. E. Reiher, B. Roux, M. Schlenkerich, J. C. Smith, R. Stote, J. Straub, M. Watanabe, J. Wiorkiewicz-Kuczera, D. Yin, and M. Karplus, J. Phys. Chem. B **102**, 3586 (1998).
- ⁵⁷A. D. Mackerell, M. Feig, and C. L. Brooks, J. Comput. Chem. **25**, 1400 (2004).
- ⁵⁸P. Bjelkmar, P. Larsson, M. A. Cuendet, B. Hess, and E. Lindahl, J. Chem. Theory Comput. **6**, 459 (2010).
- ⁵⁹H. J. C. Berendsen, J. R. Grigera, and T. Straatsma, J. Phys. Chem. **91**, 6269 (1987).
- ⁶⁰H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, and J. Hermans, *Interaction models for water in relation to protein hydration*, Intermolecular Forces. (D. Reidel Publishing Company Dordrecht, 1981).
- ⁶¹E. Ahlstrand, D. Spångberg, K. Hermansson, and R. Friedman, Int. J. Quant. Chem. **113**, 2554 (2013).
- ⁶²S. Weerasinghe and P. E. Smith, J. Chem. Phys. **119**, 11342 (2003).
- ⁶³B. Hess, H. Bekker, H. J. C. Berendsen, and J. G. E. M. Fraaije, J. Comp. Chem. **18**, 1463 (1997).
- ⁶⁴S. Miyamoto and P. A. Kollman, J. Comp. Chem. **13**, 952 (1992).
- ⁶⁵G. Bussi, D. Donadio, and M. Parrinello, J. Chem. Phys. **126**, 014101 (2007).
- ⁶⁶M. Parrinello and A. Rahman, J. Appl. Phys. **52**, 7182 (1981).
- ⁶⁷T. Darden, D. York, and L. Pedersen, J. Chem. Phys. **98**, 10089 (1993).
- ⁶⁸S. Jo, T. Kim, V. G. Iyer, and W. Im, J. Comput. Chem. **29**, 1859 (2008).
- ⁶⁹P. E. M. Lopes, J. Huang, J. Shim, Y. Luo, H. Li, B. Roux, and A. D. MacKerell, J. Chem. Theory Comput. **9**, 5430 (2013).
- ⁷⁰G. Lamoureux, E. Harder, I. V. Vorobyov, B. Roux, and A. D. M. Jr., Chem. Phys. Lett. **418**, 245 (2006).
- ⁷¹E. Ahlstrand, K. Hermansson, and R. Friedman, J. Phys. Chem. A **121**, 2643 (2017).
- ⁷²S. Peifeng and L. Hui, J. Chem. Phys. **131**, 014102 (2009).
- ⁷³M. W. Schmidt, K. K. Baldrige, J. A. Boatz, S. Elbert, M. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis, and J. A. Montgomery, J. Comput. Chem. **14**, 1347 (1993).
- ⁷⁴H. Li and J. H. Jensen, J. Comput. Chem. **25**, 1449 (2004).
- ⁷⁵C. Möller and M. Plesset, Phys. Rev. **46**, 0618 (1934).
- ⁷⁶D. Rappoport and F. Furche, J. Chem. Phys. **133**, 134105 (2010).
- ⁷⁷D. Feller, J. Comput. Chem. **17**, 1571 (1996).
- ⁷⁸K. L. Schuchardt, B. T. Didier, T. Elsethagen, L. Sun, V. Gurmooorthi, J. Chase, J. Li, and T. L. Windus, J. Chem. Info. Model. **47**, 1045 (2007).
- ⁷⁹T. Leininger, A. Nicklass, W. Kuchle, H. Stoll, M. Dolg, and A. Bergner, Chem. Phys. Lett. **255**, 274 (1996).
- ⁸⁰A. Bondi, J. Phys. Chem. **68**, 441 (1964).
- ⁸¹E. Project, E. Nachliel, and M. Gutman, J. Comput. Chem. **29**, 1163 (2008).
- ⁸²N. Bjerrum, Danske Vidensk. Selskab **7**, 1 (1926).
- ⁸³R. A. Robinson and R. H. Stokes, *Electrolyte solutions* (Butterworths, London, U.K., 1965).

ACCEPTED MANUSCRIPT