

Solvent Electronic Polarization Effects on $\text{Na}^+ - \text{Na}^+$ and $\text{Cl}^- - \text{Cl}^-$ Pair Associations in Aqueous Solution

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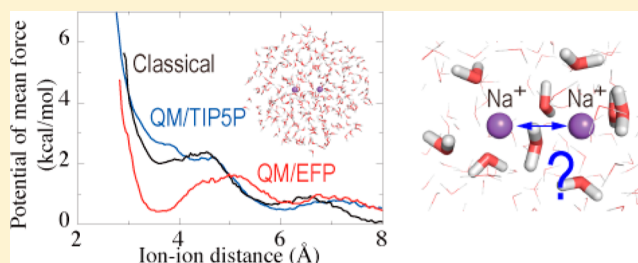
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S Supporting Information

ABSTRACT: The formation of like-ion pairs, $\text{Na}^+ - \text{Na}^+$ and $\text{Cl}^- - \text{Cl}^-$, in aqueous solution was studied by high-level ab initio methods, classical molecular dynamics (MD), QM/TIP5P, and QM/EFP MD (quantum mechanics/effective fragment potential molecular dynamics). Ab initio calculations on model clusters revealed that the $\text{Na}^+(\text{H}_2\text{O})_n\text{Na}^+$ ($n = 2-4$) clusters were significantly more stabilized by bridged waters than the corresponding $\text{Cl}^-(\text{H}_2\text{O})_n\text{Cl}^-$ clusters. QM/EFP MD simulations in solution also predicted a clear local minimum near 3.6 Å only for the $\text{Na}^+ - \text{Na}^+$ pair, suggesting that $\text{Na}^+ - \text{Na}^+$ pairs may be more likely to form than $\text{Cl}^- - \text{Cl}^-$ pairs in solution. Analysis of the hydration structures further showed that two-water bridged $\text{Na}^+ - \text{Na}^+$ pairs were dominant at the local minimum. The preferred formation of Na^+ like-ion pairs in solution appeared to come from significant short-range effects, in particular, charge delocalization (polarization) between the bridged oxygen p and the vacant valence Na^+ orbitals.



1. INTRODUCTION

The interaction of ions in solution is fundamentally important in various chemical and biological processes.¹⁻⁴ Such interactions play a vital role in determining the structure and function of proteins⁴ and in ion selectivity of ion channels in biological membranes.^{5,6} An interesting phenomenon of ion interactions is the possibility of like-charge ion pairing, which has been observed in a wide range of polyelectrolyte systems.⁷⁻⁹ There is also accumulated structural evidence for the association of like-charge ions, such as anions bound to anionic protein surfaces^{10,11} or arginine-arginine pairing.¹² This indicates that such ion pairs may be significant for affecting the structure and association of proteins. X-ray diffraction¹³ and neutron scattering experiments^{14,15} provide further evidence for the existence of halide ion pairs in solution. These experiments are usually performed at high salt concentration, and, consequently, partial ion-ion structures are not easily accessible. Recently, Zangi¹⁶ proposed possible mechanisms of reduced like-ion repulsion in solution.

Since the first theoretical studies on like-ion pairings in solution,^{17,18} past studies were mostly based on classical force fields, resulting in conflicting conclusions. The stabilization of $\text{Cl}^- - \text{Cl}^-$ pairs has been ascribed to the presence of water molecules that bridge the two ions through strong ion-water

hydrogen bond interactions ($\text{Cl}^- - \text{H}$).¹⁹⁻²⁵ Pettitt and Rossky²⁶ reported a deep minimum of the potential of mean force (PMF) at short $\text{Cl}^- - \text{Cl}^-$ separation using integral equation methods. Subsequent molecular dynamics (MD) simulations supported the existence of stable $\text{Cl}^- - \text{Cl}^-$ pairs that form either a direct contact^{19,20,27} or a solvent-separated ion pair.²¹ In contrast, Zhong and Friedman²⁸ found that the calculated diffusion coefficient of a $\text{Cl}^- - \text{Cl}^-$ pair based on an attractive PMF disagreed with experiment. Yu et al.²² also obtained a shallow minimum in the $\text{Cl}^- - \text{Cl}^-$ PMF using integral equation methods but with a different ion-ion potential from what was used by Pettitt and Rossky.²⁶ MD simulations using flexible and/or polarizable potentials also show a shallow minimum for the $\text{Cl}^- - \text{Cl}^-$ pair.²⁹⁻³¹ The stability of ion pairs also appears to be sensitive to the treatment of long-range interactions.³²⁻³⁴ MD simulations using Ewald summation or a spherical solvent boundary potential showed no deep minimum for the $\text{Cl}^- - \text{Cl}^-$ pairing.³⁵⁻³⁷ This is in contrast with the results from earlier MD simulations using truncation methods. A study using a

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three-dimensional reference interaction site model provided similar results.²³

Theoretical results on cation pairs in solution also remain conflicting. $\text{Na}^+ - \text{Na}^+$ PMFs obtained from simulations commonly exhibit no clear minimum at short $\text{Na}^+ - \text{Na}^+$ separation distances but show only a damped oscillatory feature.^{20,26,37–39} However, Guardia et al.²⁹ found a distinct minimum for the $\text{Na}^+ - \text{Na}^+$ pairing when a flexible water model was used. Zhu and Robinson³¹ reported a similar result using a flexible/polarizable five-site water model. The size or even the presence of minima was largely dependent on the force fields and/or models used.³⁹

The significance of many-body effects especially in ion solvation is well-known.⁴⁰ Such nonadditivity is an essential part of intermolecular interactions. It is customary to decompose the interaction energy into the usual terms based on the theory of intermolecular forces: exchange, induction (polarization and charge transfer), electrostatic, and dispersion.⁴¹ The zeroth- and first-order terms are usually considered together as the self-consistent field (SCF) energy, which may be further decomposed into the Heitler–London and SCF deformation interactions. At long-range, the latter can be asymptotically described by a classical polarization model, while the Heitler–London term may be further divided into electrostatic and exchange interactions. Many-body effects have been mostly described by elaborated classical polarization models.^{42–44} Therefore, molecular mechanics (MM) techniques based on classical force fields generally do not attempt to reproduce individual exchange–repulsion contributions and resort instead to Lennard-Jones-like van der Waals (vdW) terms that reproduce the exchange term along with dispersion and other mixed terms. At the same time, it has been recognized that the exchange interactions are an important source of many-body interactions.^{42,45–51} Recently, Chaudret et al.⁵² showed that the magnitude of exchange–repulsion is strongly cation-dependent, ranging from close to 0 for some alkali metal complexes to about 6 kcal/mol for the hexahydrated Zn^{2+} complex. As compared to ion solvation, it is expected that the accurate prediction of like-ion pairings in solution requires even more special consideration in terms of model parametrization.

Although various experiments have confirmed like-ion association in aqueous solution, a clear theoretical consensus on such pairings has not been well established. A main objective of the current study is to have better understanding of these intriguing phenomena in aqueous solution by adopting high-level ab initio theories and advanced quantum mechanical MD.

2. COMPUTATIONAL DETAILS

In order to capture the fundamental aspects of ion pairings, ab initio calculations of the model clusters $\text{Na}^+(\text{H}_2\text{O})_n\text{Na}^+$ and $\text{Cl}^-(\text{H}_2\text{O})_n\text{Cl}^-$ ($n = 2–4$) were conducted. Full geometry optimizations were performed at the MP2/aug-cc-pVTZ level without frozen core approximations. Additional single-point energy calculations were performed using the CCSD(T)/aug-cc-pVTZ method at the optimized geometries to improve the energetics. The charge distribution was analyzed by using the recently developed MGC (mean gradient charge)⁵³ method together with conventional charge models for comparison. The former charge is relatively invariant with respect to molecular rotation, to the choices of the basis set, and even to correlation treatments. The interaction energies were analyzed by using LMO-EDA (localized molecular orbital-energy decomposition

analysis).⁵⁴ All ab initio calculations were performed using the GAMESS program package.⁵⁵

We adopted a hybrid scheme of quantum mechanics and the EFP1-HF (effective fragment potential 1-Hartree–Fock) water model⁵⁶ for the simulations in solution. The EFP1-HF model is a quantum mechanical rigid and polarizable force field for water with fitted exchange–repulsion corrections. It was designed to reproduce Hartree–Fock results in water cluster calculations. The applicability of the hybrid QM/EFP⁵⁶ to a long-time MD simulation of chemical reaction in aqueous solution has been examined recently,⁵⁷ where it was demonstrated that the QM/EFP-MD approach yields accurate free-energy changes and barriers associated with the zwitterion to neutral tautomerization of glycine in aqueous solution. The same approach has also been utilized successfully for NaCl association/dissociation dynamics,⁵⁸ for hydrophobic association of a methanol dimer,⁵⁹ and for anharmonic vibrational properties⁶⁰ in aqueous solution.

PMFs of two like-ion pairs were obtained from QM/EFP MD simulations of the spherical systems of $\text{Na}^+ - \text{Na}^+$ and $\text{Cl}^- - \text{Cl}^-$ pairs surrounded by 292 water molecules. Two ions were treated quantum mechanically at the HF/6-31G(d) level. All of the water molecules were represented by EFPs. The spherical boundary potential (SBP) was applied in order to maintain the solvent sphere. The umbrella sampling (US) technique was used to obtain the PMFs of two like-ion pairs. The ion–ion distance was used as the primary reaction coordinate. A force constant of 2 kcal/mol/Å² was used for both SBP and the US restraints. We performed QM/EFP MD simulations for seven windows covering ion–ion distances from 3.0 to 9.0 Å with a spacing of 1.0 Å. Initially, classical MD simulations in the NVT ensemble at 300 K were performed on each of the seven windows. Then, QM/EFP MD simulations were performed for 140 ps from the final structures of the classical MD simulations. The time step was set to 1 fs. Finally, the weighted histogram analysis method (WHAM)⁶¹ was used to obtain the PMFs for the like-ion pairs. The ion–water radial distribution functions, $g(r)$, calculated at the largest ion separation (9 Å) (see Figure S1 in the Supporting Information) are in agreement with those obtained from the CPMD simulations.^{62,63} For comparison, QM/TIP3P MD simulations, in which solvent waters were described by the TIP3P model,⁵⁹ were also carried out to obtain corresponding PMFs. In the QM/TIP3P MD simulations, the interaction between the QM and TIP3P regions was modeled by using effective Gaussian repulsion potentials similar to those used in the EFP1-HF model. We used a modified version of GAMESS⁵⁵ in which the SBP and the harmonic restraint potentials were implemented for the purpose of this study.

Conventional MD simulations of the same systems were performed using the ion parameters from Roux et al.⁶⁴ and the TIP3P model⁶⁵ for waters, respectively. The particular values of Na^+ ($\sigma = 2.43$ Å, $\epsilon = 0.047$ kcal/mol) and Cl^- ($\sigma = 4.045$ Å, $\epsilon = 0.015$ kcal/mol) were used. The MD simulations were carried out using Langevin dynamics at 300 K with a friction constant corresponding to a relaxation time of 5 ps^{−1}, which was applied to all non-hydrogen atoms. The water geometries were fixed by SHAKE⁶⁶ during the simulations. The center of mass of the two ions was harmonically constrained to the center of the sphere by using the GEO command in CHARMM. An integration time step of 1 fs was used. The systems were pre-equilibrated for 50 ps. For each umbrella window, an NVT run

for 200 ps was performed at 300 K. CHARMM (version 35b2)⁶⁷ was used to run the classical MD simulations.

3. RESULTS AND DISCUSSION

A. Energies and Structures of $\text{Na}^+(\text{H}_2\text{O})_n\text{Na}^+$ and $\text{Cl}^-(\text{H}_2\text{O})_n\text{Cl}^-$ ($n = 2-4$). We first performed ab initio calculations at the CCSD(T)/aug-cc-pVTZ//MP2/aug-cc-pVTZ level on the model clusters of $\text{Na}^+(\text{H}_2\text{O})_n\text{Na}^+$ and $\text{Cl}^-(\text{H}_2\text{O})_n\text{Cl}^-$ ($n = 2-4$) and found that both water-bridged clusters are stable. Figure 1 shows the optimized structures and the predicted stabilization energies (ΔE) as obtained with the following equation

$$\Delta E = E(\text{X}(\text{H}_2\text{O})_n\text{X}) - 2E(\text{X}) - nE(\text{H}_2\text{O})$$

($\text{X} = \text{Na}^+, \text{Cl}^-$) (1)

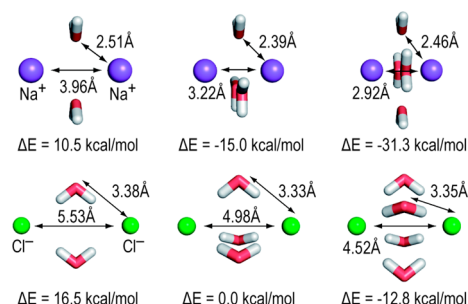


Figure 1. Optimized structures and stabilization energies of $\text{X}(\text{H}_2\text{O})_n\text{X}$ ($\text{X} = \text{Na}^+$ and Cl^- , $n = 2-4$) clusters obtained from ab initio calculations at the CCSD(T)/aug-cc-pVTZ//MP2/aug-cc-pVTZ level with no frozen core approximation.

Our current results are consistent with previous calculations on Cl^- clusters done by Gao et al.²² Structurally, the Na^+ ions are interacting with the oxygen side of water, while Cl^- ions are interacting with water hydrogens. As a result, the Na^+-Na^+ distances are expected to be shorter than those of Cl^--Cl^- pairs. The Cl^--Cl^- distances with two, three, and four waters are predicted to be 5.53, 4.98, and 4.52 Å, respectively. The corresponding Na^+-Na^+ distances are 3.96, 3.22, and 2.92 Å. Therefore, from a simple electrostatic point of view, the Na^+-Na^+ clusters are experiencing stronger electrostatic repulsion. Despite such unfavorable repulsions, exothermic stabilizations occurred with more than three bridging waters in both Na^+ and Cl^- clusters. Furthermore, the overall exothermicities of $\text{Na}^+(\text{H}_2\text{O})_n\text{Na}^+$ clusters are significantly greater than those of the Cl^- clusters (Figure 1). Especially in the case of four-water

bridged structures, the relative stability of $\text{Na}^+(\text{H}_2\text{O})_4\text{Na}^+$ is greater than that of $\text{Cl}^-(\text{H}_2\text{O})_4\text{Cl}^-$ by about 20 kcal/mol.

The high stability of Na^+ pairs may be attributed to the electron density delocalization between the oxygen p orbital and the two vacant valence Na^+ orbitals, making its HOMO electrons more delocalized over the cation clusters. In the case of anion pairs, such strong orbital overlap is not possible. To quantify the charge delocalization, the atomic charges on ions in the clusters were calculated at the MP2/aug-cc-pVTZ level and are summarized in Table 1. Due to the geometric symmetries of all model clusters, the charges on the two ions were identical within a given cluster. The charges in Table 1 are the net charges of one of these two ions. In general, the amount of charge delocalization increased with an increasing number of bridged waters. However, various charge models exhibit inconsistent predictions with each other. Results from Mulliken analysis and from the recently developed MGC⁵³ method show that the net amount of charge transfer of Na^+ clusters is larger than that of Cl^- clusters. This is consistent with the concept of larger orbital overlap between the oxygen p orbital and the two vacant valence Na^+ orbitals. However, the other charge models exhibit an opposite trend. In any event, the amount of charge transfer, as predicted by various models, does not seem to be large enough to fully explain the high stability of Na^+ pairs.

In order to quantify the individual interaction terms, LMO-EDA⁵⁴ using MP2/aug-cc-pVTZ was performed on the above clusters. Each system was divided into two regions ($2\text{Na}^+/2\text{Cl}^-$ and $(\text{H}_2\text{O})_n$ ($n = 2-4$)), and the interactions between them were decomposed into electrostatic (ES), exchange (EX), repulsion (REP), and polarization (POL) contributions. In LMO-EDA, the ES, EX, and REP terms are isolated according to Hayes and Stone's method⁶⁸ from the Heitler–London interaction energy derived from an antisymmetric product of the monomer Hartree–Fock spin orbitals. In Kitaura and Morokuma's method,⁶⁹ exchange and repulsion are not separated. Separating exchange and repulsion terms can often provide a better understanding of the interaction, especially many-body effects. The details of the LMO-EDA method can be found elsewhere.⁵⁴ The LMO-EDA results are presented in Table 2. The electrostatic attractions of Na^+ clusters were greater than those of Cl^- clusters by about 20 kcal/mol. Furthermore, the electrostatic attraction increased with the number of waters. As compared to the negative Cl^- ions, the electron density of the positive Na^+ ions was tight and compact, which can yield an enhanced electrostatic attraction. The sum of exchange and repulsion terms for Cl^- clusters was greater than that of Na^+ clusters, which had net destabilizing effects. While the magnitude of EX+REP is rather insensitive to the number of waters for Na^+ clusters, it is greatly increased as a

Table 1. Atomic Charges (e) on Ions Calculated with Several Charge Models:^a Atoms in Molecule (AIM), Mulliken, Natural Population Analysis (NPA), ChelpG^b, and MGCs (q_{MG})^c

	AIM	Mulliken	NPA	ChelpG	q_{MG}
$\text{Cl}^-(\text{H}_2\text{O})_2\text{Cl}^-$	−0.9692	−0.9535	−0.9923	−0.9406	−0.9965
$\text{Cl}^-(\text{H}_2\text{O})_3\text{Cl}^-$	−0.9443	−0.9275	−0.9443	−0.8896	−0.9833
$\text{Cl}^-(\text{H}_2\text{O})_4\text{Cl}^-$	−0.9309	−0.9154	−0.9309	−0.8578	−0.9745
$\text{Na}^+(\text{H}_2\text{O})_2\text{Na}^+$	0.9768	0.8989	0.9907	0.9539	0.9663
$\text{Na}^+(\text{H}_2\text{O})_3\text{Na}^+$	0.9638	0.8424	0.9737	0.9294	0.9448
$\text{Na}^+(\text{H}_2\text{O})_4\text{Na}^+$	0.9609	0.7928	0.9567	0.9476	0.9428

^aAll calculations were done at the MP2-aug-cc-pVTZ level. The values correspond to the net charges of one of the two ions due to the geometric symmetry. ^bCharges from electrostatic potentials using a grid-based method. ^cReference 53.

Table 2. Results of LMO-EDA Analysis:^a Decomposition of Ion–Water Interaction Energies into ES, EX, REP, and POL Contributions

	ES	EX	REP	POL
$\text{Cl}^-(\text{H}_2\text{O})_2\text{Cl}^-$	−44.90	−28.64	48.61	−11.85
$\text{Cl}^-(\text{H}_2\text{O})_3\text{Cl}^-$	−73.82	−53.15	90.08	−22.52
$\text{Cl}^-(\text{H}_2\text{O})_4\text{Cl}^-$	−98.68	−69.29	115.76	−30.02
$\text{Na}^+(\text{H}_2\text{O})_2\text{Na}^+$	−60.35	−4.37	10.36	−11.99
$\text{Na}^+(\text{H}_2\text{O})_3\text{Na}^+$	−97.28	−8.38	19.89	−23.86
$\text{Na}^+(\text{H}_2\text{O})_4\text{Na}^+$	−122.04	−8.30	19.76	−33.54

^aAll calculations were done at the MP2-aug-cc-pVTZ level.

function of the number of waters for the Cl^- clusters. It appears that the EX+REP contribution also strongly depends on the diffuseness of the ion electron density. Quantum mechanically, the repulsions arise from the avoided electron density because of mixing between different parts of a system. When the electron density is diffuse, as seen in Cl^- clusters, the repulsion terms appear to be large. This observation indicates that the EX+REP term tends to prevent the formation of Cl^- clusters with a larger number of waters. The POL contribution was rather similar in both Na^+ and Cl^- clusters, its magnitude increasing in both cases with the number of waters. Consequently, the overall comparatively larger stabilities of Na^+ clusters appear to be due to a larger electrostatic attraction and a smaller EX+REP repulsion.

The LMO-EDA analysis indicates significant polarization in the clusters, which is often missing in classical force fields. In addition, the exchange repulsions are usually replaced by classical Lennard-Jones in classical force fields. In order to assess the ability of the QM/EFP method to overcome these deficiencies, we performed QM/EFP calculations on the model clusters $\text{Na}^+(\text{H}_2\text{O})_n\text{Na}^+$ and $\text{Cl}^-(\text{H}_2\text{O})_n\text{Cl}^-$ ($n = 2-4$), where the two ions were treated quantum mechanically (HF/6-31G(d)) while waters were described using EFP. The results are listed in Table 3. QM/EFP reproduces MP2 geometries with a maximum deviation of 0.25 Å, and its energies agreed with the CCSD(T) results to within 3 kcal/mol on average.

The success of QM/EFP in the current cluster calculations can be attributed to the inclusion of induced dipole polarization, as well as sophisticated and balanced electrostatics and repulsion potentials in the EFP. In the EFP method, the quantum mechanical exchange–orthogonality interaction be-

tween QM and EFP is modeled by a repulsive effective Gaussian potential that is centered at atomic position in the water molecule and included in the one-electron Hamiltonian of the QM region. The fragment polarization energy of EFP is evaluated as an interaction of induced dipoles of each fragment with the static field due to the Coulomb multipoles and the induced field due to the induced dipoles of the other fragments. The induced dipoles originate at the centroids of LMOs, where (anisotropic) distributed polarizability tensors are placed.

B. PMFs as a Function of Ion Association in Solution.

Encouraged by the good agreement between the full quantum and QM/EFP cluster calculations, we performed comparative classical and QM/EFP MD simulations. Identical spherical systems of Na^+-Na^+ and Cl^--Cl^- pairs with 292 water molecules were prepared for the classical MD, QM/TIP5P MD, and QM/EFP MD simulations. The final PMFs from the classical, QM/TIP5P, and QM/EFP MD simulations are presented in Figure 2. These PMFs were sufficiently converged (see Figures S2 and S3, Supporting Information). The classical, QM/TIP5P, and QM/EFP PMFs were nearly identical to each other beyond 6 Å of ion separation regardless of ion type (Figure 2a and b). However, they differed significantly for distances below 5 Å. While the PMFs from the classical MD and QM/TIP5P MD simulations did not have a minimum at short distances, the QM/EFP MD results exhibited a clear local minimum near 3.6 Å for the Na^+-Na^+ pair (Figure 2b). The opposite trend can be seen for the Cl^--Cl^- pair (Figure 2a). The results with QM/EFP show no clear indication of a minimum between 4 and 6 Å of ion separation. However, classical and QM/TIP5P MD featured a local minimum at 5.0 Å, which is in agreement with other previous classical MD studies.^{20,21,25,27,70,71}

It appears that classical force fields as well as the QM/TIP5P potential may underestimate the attractive interactions between positive ions in solution, while they may overestimate the interactions between negative ions. The distinct differences in PMFs between classical, QM/TIP5P, and QM/EFP MD, especially for short ion–ion distances, can be attributed mostly to a missing POL contribution in the classical force fields, including the TIP5P model, as well as general inaccuracies in the potential describing the interaction between ions and water molecules. Our QM/EFP MD predicts that Na^+-Na^+ pairs are more likely to be observed than Cl^--Cl^- pairs. This is consistent with the higher stabilities of $\text{Na}^+(\text{H}_2\text{O})_n\text{Na}^+$ clusters.

The different hydration structures of Cl^--Cl^- and Na^+-Na^+ pairs give further insight into the mechanism of like-ion pair formation. Figure 2c and d shows the relative probabilities of the ion pairs bridged via different numbers of water molecules. We define water molecule bridges when the water oxygen atom (or two hydrogen atoms) is (are) within 2.8 Å of both Na^+ (Cl^-) ions. In the case of Na^+-Na^+ , one-, two-, and three-water bridged structures were present at short ion–ion distances (Figure 2d). The two-water bridged structures turned out to be the major species of Na^+-Na^+ at the local minimum near 3.6 Å. Three-water bridged structures become dominant for shorter ion–ion distances at around 3.3 Å. Single-water bridged structures also existed between 3 and 5 Å. However, the four-water bridged structures, which were predicted by cluster calculations, did not appear in the QM/EFP MD simulations. This is likely due to the large entropy cost of associating four waters in a highly compact structure. A typical snapshot for the two-water bridged Na^+-Na^+ ion pairs is shown in Figure 2d. The ion–water clusters are quite similar to the corresponding

Table 3. Optimized Structures and Stabilization Energies of $\text{X}(\text{H}_2\text{O})_n\text{X}$ Clusters Using a Hybrid QM/EFP^a

		X = Na^+		X = Cl^-	
$n = 2$	$r_{\text{ion-ion}}$	3.98	(0.02) ^b	5.78	(0.25)
	$r_{\text{ion-water}}$	2.58	(0.07)	3.52	(0.14)
	ΔE	11.5	(1.0)	13.2	(−3.3)
$n = 3$	$r_{\text{ion-ion}}$	3.44	(0.22)	5.21	(0.23)
	$r_{\text{ion-water}}$	2.55	(0.16)	3.45	(0.12)
	ΔE	−15.2	(−0.2)	−4.7	(−4.7)
$n = 4$	$r_{\text{ion-ion}}$	3.08	(0.16)	4.77	(0.25)
	$r_{\text{ion-water}}$	2.59	(0.13)	3.46	(0.11)
	ΔE	−33.3	(−2.0)	−19.2	(−6.4)

^aHF/6-31G(d) and EFP were used for X and waters, respectively.

^bNumbers in parentheses show the deviations from the full ab initio results at the CCSD(T)/aug-cc-pVTZ//MP2-aug-cc-pVTZ level. Distances and stabilization energies (ΔE) are given in Å and kcal/mol, respectively.

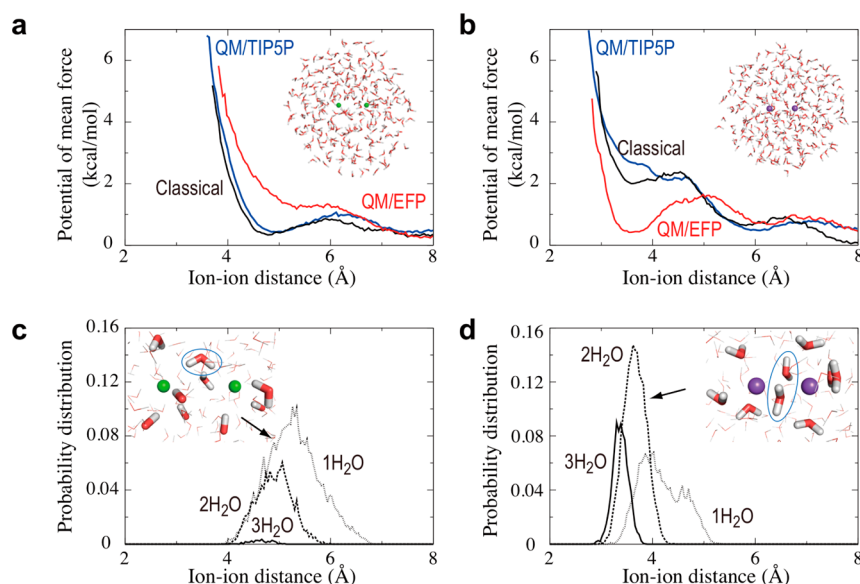


Figure 2. PMFs obtained with QM/EFP (HF/6-31G(d) for QM) and classical MD for (a) Cl^- – Cl^- and (b) Na^+ – Na^+ pairs. Relative probabilities of ion pairs with one, two, and three bridged water molecules for Cl^- – Cl^- (c) and (d) Na^+ – Na^+ pairs.

structures of the $\text{Na}^+(\text{H}_2\text{O})_n\text{Na}^+$ ($n = 2, 3$) clusters obtained from the gas-phase ab initio calculations. A strong correlation between the maximum probability positions of bridged water structures and the ion–ion distance is seen in the Na^+ – Na^+ simulation, indicating that the hydration structure of Na^+ – Na^+ like-ion pairs is largely determined by their local bridged waters. On the other hand, only one- and two-water bridged ion pairs are observed for the Cl^- – Cl^- pairs (Figure 2c). Unlike the Na^+ – Na^+ ion pairs, one-water bridged structures dominate over the entire range of Cl^- – Cl^- distances, implying a weak dependency of ion pair structures on locally bridged waters.

Our QM/EFP MD results might depend on the accuracy of the computational methodology. However, the good agreement between the QM/EFP calculations and full quantum calculations shown in Table 3 suggests that additional electron correlation effects that are missing in our QM/EFP model may not significantly affect the results. Another point of validation is that QM/EFP MD yielded correct radial distribution functions of water–ion structures (see Figure S1, Supporting Information). A common concern in MD simulations is related to the use of spherical cutoffs for the water solvent environment. The use of larger water spheres with radii of 15, 20, and 25 Å led to an increased stabilization of the contact ion pair by $\sim 1RT$ for the Na^+ – Na^+ pair (see Figure S4, Supporting Information). However, this is a relatively minor effect that does not change the qualitative conclusions of our study. We also confirmed that MD simulations with either the SBP or the periodic boundary condition give consistent results (Figure S5, Supporting Information). Finally, we note that the same protocol that was used here was used previously to obtain quantitatively accurate solvation free energies of amino acid side-chain analogues, thereby supporting the use of SBP in the present simulations.⁷² Therefore, even with those caveats, the general conclusions obtained with the QM/EFP MD simulations presented here should remain valid.

4. CONCLUSION

In summary, our combined studies of ab initio and MD simulations have provided new insight into like-ion attractions.

In particular, we find that Na^+ – Na^+ pairs can be preferentially formed in solution. The QM/EFP MD simulations predict that two-water bridged Na^+ – Na^+ pairs are the major species at the local contact minimum. Our analysis further revealed that electronic polarization effects may play a critical role in short-distance ion–ion interactions via bridged waters. This contribution is missing in classical nonpolarizable force fields.

As a way of introducing polarization effects to MD simulations, we demonstrated that the combination of QM/EFP and additional MD techniques could yield a promising quantum mechanical molecular dynamics method.

■ ASSOCIATED CONTENT

Supporting Information

Ion–water radial distribution functions $g(r)$, convergence, and boundary effects on the calculated PMFs. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Schultz, P. G. Catalytic Antibodies. *Acc. Chem. Res.* **1989**, *22*, 287–294.

- (2) Horovitz, A.; Serrano, L.; Avron, B.; Bycroft, M.; Fersht, A. R. Strength and Cooperativity of Contributions of Surface Salt Bridges to Protein Stability. *J. Mol. Biol.* **1990**, *216*, 1031–1044.
- (3) Perutz, M. F. Electrostatic Effects in Proteins. *Science* **1978**, *201*, 1187–1191.
- (4) Warshel, A. Electrostatic Basis of Structure–Function Correlation in Proteins. *Acc. Chem. Res.* **1981**, *14*, 284–290.
- (5) Berneche, S.; Roux, B. Energetics of Ion Conduction through the K^+ Channel. *Nature* **2001**, *414*, 73–77.
- (6) Roux, B.; Berneche, S.; Egwolf, B.; Lev, B.; Noskov, S. Y.; Rowley, C. N.; Yu, H. B. Ion Selectivity in Channels and Transporters. *J. Gen. Physiol.* **2011**, *137*, 415–426.
- (7) Kirkwood, J. G.; Shumaker, J. B. Forces between Protein Molecules in Solution Arising from Fluctuations in Proton Charge and Configuration. *Proc. Natl. Acad. Sci. U.S.A.* **1952**, *38*, 863–871.
- (8) Angelini, T. E.; Liang, H.; Wriggers, W.; Wong, G. C. L. Like-Charge Attraction between Polyelectrolytes Induced by Counterion Charge Density Waves. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 8634–8637.
- (9) Lau, A. W. C.; Lukatsky, D. B.; Pincus, P.; Safran, S. A. Charge Fluctuations and Counterion Condensation. *Phys. Rev. E* **2002**, *65*, 051502/1–051502/7.
- (10) Vyas, N. K.; Vyas, M. N.; Quirocho, F. A. Crystal Structure of M-Tuberculosis Abc Phosphate Transport Receptor: Specificity and Charge Compensation Dominated by Ion–Dipole Interactions. *Structure* **2003**, *11*, 765–774.
- (11) Auffinger, P.; Bielecki, L.; Westhof, E. Anion Binding to Nucleic Acids. *Structure* **2004**, *12*, 379–388.
- (12) Vondrasek, J.; Mason, P. E.; Heyda, J.; Collins, K. D.; Jungwirth, P. The Molecular Origin of Like-Charge Arginine–Arginine Pairing in Water. *J. Phys. Chem. B* **2009**, *113*, 9041–9045.
- (13) Smith, L. S.; Wertz, D. L. Solute Structuring in Aqueous Lanthanum(III) Chloride Solutions. *J. Am. Chem. Soc.* **1975**, *97*, 2365–2368.
- (14) Copestake, A. P.; Neilson, G. W.; Enderby, J. E. The Structure of a Highly Concentrated Aqueous-Solution of Lithium-Chloride. *J. Phys. C: Solid State Phys.* **1985**, *18*, 4211–4216.
- (15) Collins, K. D.; Neilson, G. W.; Enderby, J. E. Ions in Water: Characterizing the Forces That Control Chemical Processes and Biological Structure. *Biophys. Chem.* **2007**, *128*, 95–104.
- (16) Zangi, R. Attraction between Like-Charged Monovalent Ions. *J. Chem. Phys.* **2012**, *136*, 184501/1–184501/11.
- (17) Chandrasekhar, J.; Spellmeyer, D. C.; Jorgensen, W. L. Energy Component Analysis for Dilute Aqueous-Solutions of Li^+ , Na^+ , F^- , and Cl^- Ions. *J. Am. Chem. Soc.* **1984**, *106*, 903–910.
- (18) Fries, P. H.; Patey, G. N. The Relative Motion of Ions in Solution. I. Microdynamical Models and Intermolecular Dipolar Spin Relaxation. *J. Chem. Phys.* **1984**, *80*, 6253–6266.
- (19) Dang, L. X.; Pettitt, B. M. Solvated Chloride-Ions at Contact. *J. Chem. Phys.* **1987**, *86*, 6560–6561.
- (20) Dang, L. X.; Pettitt, B. M. A Theoretical-Study of Like Ion-Pairs in Solution. *J. Phys. Chem.* **1990**, *94*, 4303–4308.
- (21) Buckner, J. K.; Jorgensen, W. L. Energetics and Hydration of the Constituent Ion-Pairs of Tetramethylammonium Chloride. *J. Am. Chem. Soc.* **1989**, *111*, 2507–2516.
- (22) Yu, H. A.; Roux, B.; Karplus, M. Solvation Thermodynamics — An Approach from Analytic Temperature Derivatives. *J. Chem. Phys.* **1990**, *92*, 5020–5032.
- (23) Kovalenko, A.; Hirata, F. Potentials of Mean Force of Simple Ions in Ambient Aqueous Solution. I. Three-Dimensional Reference Interaction Site Model Approach. *J. Chem. Phys.* **2000**, *112*, 10391–10402.
- (24) Gao, J.; Boudon, S.; Wipff, G. Abinitio and Crystal-Structure Analysis of Like-Charged Ion-Pairs. *J. Am. Chem. Soc.* **1991**, *113*, 9610–9614.
- (25) Keasler, S. J.; Nellas, R. B.; Chen, B. Water Mediated Attraction between Repulsive Ions: A Cluster-Based Simulation Approach. *J. Chem. Phys.* **2006**, *125*, 144520/1–144520/5.
- (26) Pettitt, B. M.; Rossky, P. J. Alkali-Halides in Water — Ion Solvent Correlations and Ion Ion Potentials of Mean Force at Infinite Dilution. *J. Chem. Phys.* **1986**, *84*, 5836–5844.
- (27) Dang, L. X.; Pettitt, B. M. Chloride-Ion Pairs in Water. *J. Am. Chem. Soc.* **1987**, *109*, 5531–5532.
- (28) Zhong, E. C.; Friedman, H. L. Self-Diffusion and Distinct Diffusion of Ions in Solution. *J. Phys. Chem.* **1988**, *92*, 1685–1692.
- (29) Guardia, E.; Rey, R.; Padro, J. A. Na^+Na^+ and Cl^-Cl^- Ion-Pairs in Water — Mean Force Potentials by Constrained Molecular-Dynamics. *J. Chem. Phys.* **1991**, *95*, 2823–2831.
- (30) Karim, O. A. Potential of Mean Force for an Aqueous Chloride-Ion Pair — Simulation with a Polarizable Model. *J. Chem. Phys.* **1992**, *96*, 9237–9238.
- (31) Zhu, S. B.; Robinson, G. W. Molecular-Dynamics Computer-Simulation of an Aqueous NaCl Solution - Structure. *J. Chem. Phys.* **1992**, *97*, 4336–4348.
- (32) Levy, R. M.; Gallicchio, E. Computer Simulations with Explicit Solvent: Recent Progress in the Thermodynamic Decomposition of Free Energies and in Modeling Electrostatic Effects. *Annu. Rev. Phys. Chem.* **1998**, *49*, 531–567.
- (33) Bader, J. S.; Chandler, D. Computer-Simulation Study of the Mean Forces between Ferrous and Ferric Ions in Water. *J. Phys. Chem.* **1992**, *96*, 6423–6427.
- (34) Rozanska, X.; Chipot, C. Modeling Ion–Ion Interaction in Proteins: A Molecular Dynamics Free Energy Calculation of the Guanidinium–Acetate Association. *J. Chem. Phys.* **2000**, *112*, 9691–9694.
- (35) Hummer, G.; Soumpasis, D. M.; Neumann, M. Computer-Simulations Do Not Support Cl–Cl Pairing in Aqueous NaCl Solution. *Mol. Phys.* **1994**, *81*, 1155–1163.
- (36) Maksimiak, K.; Rodziewicz-Motowidlo, S.; Czaplowski, C.; Liwo, A.; Scheraga, H. A. Molecular Simulation Study of the Potentials of Mean Force for the Interactions between Models of Like-Charged and between Charged and Nonpolar Amino Acid Side Chains in Water. *J. Phys. Chem. B* **2003**, *107*, 13496–13504.
- (37) Masunov, A.; Lazaridis, T. Potentials of Mean Force between Ionizable Amino Acid Side Chains in Water. *J. Am. Chem. Soc.* **2003**, *125*, 1722–1730.
- (38) Kovalenko, A.; Hirata, F. Potentials of Mean Force of Simple Ions in Ambient Aqueous Solution. II. Solvation Structure from the Three-Dimensional Reference Interaction Site Model Approach, and Comparison with Simulations. *J. Chem. Phys.* **2000**, *112*, 10403–10417.
- (39) Dang, L. X.; Pettitt, B. M.; Rossky, P. J. On the Correlation between Like Ion-Pairs in Water. *J. Chem. Phys.* **1992**, *96*, 4046–4047.
- (40) Elrod, M. J.; Saykally, R. J. Many-Body Effects in Intermolecular Forces. *Chem. Rev.* **1994**, *94*, 1975–1997.
- (41) Szczesniak, M. M.; Chalasinski, G. Abinitio Calculations of Nonadditive Effects. *J. Mol. Struct.: THEOCHEM* **1992**, *93*, 37–54.
- (42) Gresh, N.; Cisneros, G. A.; Darden, T. A.; Piquemal, J. P. Anisotropic, Polarizable Molecular Mechanics Studies of Inter- and Intramolecular Interactions and Ligand–Macromolecule Complexes. A Bottom-Up Strategy. *J. Chem. Theory Comput.* **2007**, *3*, 1960–1986.
- (43) Ponder, J. W.; Wu, C. J.; Ren, P. Y.; Pande, V. S.; Chodera, J. D.; Schnieders, M. J.; Haque, I.; Mobley, D. L.; Lambrecht, D. S.; DiStasio, R. A.; et al. Current Status of the Amoeba Polarizable Force Field. *J. Phys. Chem. B* **2010**, *114*, 2549–2564.
- (44) Holt, A.; Bostrom, J.; Karlstrom, G.; Lindh, R. A Nemo Potential That Includes the Dipole–Quadrupole and Quadrupole–Quadrupole Polarizability. *J. Comput. Chem.* **2010**, *31*, 1583–1591.
- (45) Gordon, M. S.; Slipchenko, L.; Li, H.; Jensen, J. H. The Effective Fragment Potential: A General Method for Predicting Intermolecular Interactions. *Annual Reports in Computational Chemistry* Elsevier B. V.: Amsterdam, The Netherlands, 2007; Vol. 3, pp 117–193.
- (46) Piquemal, J. P.; Chevreau, H.; Gresh, N. Toward a Separate Reproduction of the Contributions to the Hartree–Fock and DFT Intermolecular Interaction Energies by Polarizable Molecular Mechanics with the Sibfa Potential. *J. Chem. Theory Comput.* **2007**, *3*, 824–837.

- (47) Soderhjelm, P.; Karlstrom, G.; Ryde, U. Comparison of Overlap-Based Models for Approximating the Exchange–Repulsion Energy. *J. Chem. Phys.* **2006**, *124*, 244101/1–244101/10.
- (48) Jensen, J. H.; Gordon, M. S. An Approximate Formula for the Intermolecular Pauli Repulsion between Closed Shell Molecules. II. Application to the Effective Fragment Potential Method. *J. Chem. Phys.* **1998**, *108*, 4772–4782.
- (49) Cisneros, G. A.; Piquemal, J. P.; Darden, T. A. Quantum Mechanics/Molecular Mechanics Electrostatic Embedding with Continuous and Discrete Functions. *J. Phys. Chem. B* **2006**, *110*, 13682–13684.
- (50) Stone, A. J.; Tong, C. S. Anisotropy of Atom–Atom Repulsions. *J. Comput. Chem.* **1994**, *15*, 1377–1392.
- (51) Piquemal, J. P.; Cisneros, G. A.; Reinhardt, P.; Gresh, N.; Darden, T. A. Towards a Force Field Based on Density Fitting. *J. Chem. Phys.* **2006**, *124*, 104101/1–104101/12.
- (52) Chaudret, R.; Gresh, N.; Parisel, O.; Piquemal, J. P. Many-Body Exchange–Repulsion in Polarizable Molecular Mechanics. I. Orbital-Based Approximations and Applications to Hydrated Metal Cation Complexes. *J. Comput. Chem.* **2011**, *32*, 2949–2957.
- (53) Choi, C. H. Mean Gradient Charge: A New Definition of Atomic Charge Using Induced Atomic Gradient. *Chem. Phys. Lett.* **2012**, *524*, 107–111.
- (54) Su, P. F.; Li, H. Energy Decomposition Analysis of Covalent Bonds and Intermolecular Interactions. *J. Chem. Phys.* **2009**, *131*, 014102/1–014102/15.
- (55) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; et al. General Atomic and Molecular Electronic-Structure System. *J. Comput. Chem.* **1993**, *14*, 1347–1363.
- (56) Day, P. N.; Jensen, J. H.; Gordon, M. S.; Webb, S. P.; Stevens, W. J.; Krauss, M.; Garmer, D.; Basch, H.; Cohen, D. An Effective Fragment Method for Modeling Solvent Effects in Quantum Mechanical Calculations. *J. Chem. Phys.* **1996**, *105*, 1968–1986.
- (57) Choi, C. H.; Re, S.; Feig, M.; Sugita, Y. Quantum Mechanical/Effective Fragment Potential Molecular Dynamics (QM/EFP-MD) Study on Intra-Molecular Proton Transfer of Glycine in Water. *Chem. Phys. Lett.* **2012**, *539*, 218–221.
- (58) Ghosh, M. K.; Re, S.; Feig, M.; Sugita, Y.; Choi, C. H. Interionic Hydration Structures of NaCl in Aqueous Solution: A Combined Study of Quantum Mechanical Cluster Calculations and QM/EFP-MD Simulations. *J. Phys. Chem. B* **2013**, *117*, 289–295.
- (59) Ghosh, M. K.; Uddin, N.; Choi, C. H. Hydrophobic and Hydrophilic Associations of a Methanol Pair in Aqueous Solution. *J. Phys. Chem. B* **2012**, *116*, 14254–14260.
- (60) Ghosh, M. K.; Lee, J.; Choi, C. H.; Cho, M. Direct Simulations of Anharmonic Infrared Spectra Using Quantum Mechanical/Effective Fragment Potential Molecular Dynamics (QM/EFP-MD): Methanol in Water. *J. Phys. Chem. A* **2012**, *116*, 8965–8971.
- (61) Kumar, S.; Rosenberg, J. M.; Bouzida, D.; Swendsen, R. H.; Kollman, P. A. Multidimensional Free-Energy Calculations Using the Weighted Histogram Analysis Method. *J. Comput. Chem.* **1995**, *16*, 1339–1350.
- (62) Heuft, J. M.; Meijer, E. J. Density Functional Theory Based Molecular-Dynamics Study of Aqueous Chloride Solvation. *J. Chem. Phys.* **2003**, *119*, 11788–11791.
- (63) Khalack, J. M.; Lyubartsev, A. P. Car–Parrinello Molecular Dynamics Simulations of Na⁺–Cl[−] Ion Pair in Liquid Water. *Condens. Matter Phys.* **2004**, *7*, 683–698.
- (64) Beglov, D.; Roux, B. Finite Representation of an Infinite Bulk System — Solvent Boundary Potential for Computer-Simulations. *J. Chem. Phys.* **1994**, *100*, 9050–9063.
- (65) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. Comparison of Simple Potential Functions for Simulating Liquid Water. *J. Chem. Phys.* **1983**, *79*, 926–935.
- (66) Ryckaert, J. P.; Ciccotti, G.; Berendsen, H. J. C. Numerical-Integration of Cartesian Equations of Motion of a System with Constraints — Molecular-Dynamics of N-Alkanes. *J. Comput. Phys.* **1977**, *23*, 327–341.
- (67) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. Charmm — A Program for Macromolecular Energy, Minimization, and Dynamics Calculations. *J. Comput. Chem.* **1983**, *4*, 187–217.
- (68) Hayes, I. C.; Stone, A. J. An Intermolecular Perturbation-Theory for the Region of Moderate Overlap. *Mol. Phys.* **1984**, *53*, 83–105.
- (69) Kitaura, K.; Morokuma, K. New Energy Decomposition Scheme for Molecular-Interactions within Hartree–Fock Approximation. *Int. J. Quantum Chem.* **1976**, *10*, 325–340.
- (70) Hirata, F.; Rossky, P. J.; Pettitt, B. M. The Interionic Potential of Mean Force in a Molecular Polar-Solvent from an Extended Rism Equation. *J. Chem. Phys.* **1983**, *78*, 4133–4144.
- (71) Kusalik, P. G.; Patey, G. N. Theoretical Results for Dielectric and Structural-Properties of Aqueous-Electrolytes — The Influence of Ion Size and Charge. *J. Chem. Phys.* **1983**, *79*, 4468–4474.
- (72) Nina, M.; Berneche, S.; Roux, B. Anchoring of a Monotopic Membrane Protein: The Binding of Prostaglandin H-2 Synthase-1 to the Surface of a Phospholipid Bilayer. *Eur. Biophys. J.* **2000**, *29*, 439–454.