Dissociation of NaCl in water from \textit{ab initio} molecular dynamics simulations

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We perform \textit{ab initio} molecular dynamics simulations to study the dissociation of NaCl in water. The potential of mean force (PMF) between the two ions is determined using the constrained-force method. The simulation windows corresponding to the contact and solvent-separated minima, and the transition state in between, are further analyzed to determine the changes in the properties of hydration waters such as coordination number, dipole moment, and orientation. The \textit{ab initio} results are compared with those obtained from classical molecular dynamics simulations of aqueous NaCl using several common force fields. The \textit{ab initio} PMF is found to have a shallower contact minimum and a smaller transition barrier compared with the classical ones. Also the binding free energy calculated from the \textit{ab initio} PMF almost vanishes whereas it is negative for all the classical PMFs. Water dipole moments are observed to exhibit little change during dissociation, indicating that description of NaCl with a nonpolarizable force field may be feasible. However, overcoordination of the ion pair at all distances remains as a serious shortcoming of the current classical models. The \textit{ab initio} results presented here provide useful guidance for alternative parameters of the nonpolarizable force fields as well as the polarizable ones currently under construction. © 2010 American Institute of Physics. [doi:10.1063/1.3360310]

I. INTRODUCTION

Electrolyte solutions have been traditionally described using continuum theories as exemplified by those of Debye, Hückel, and Onsager.\textsuperscript{1–3} In recent years, however, there has been a steady shift toward microscopic theories urged by the more exacting demands from biochemistry and molecular biology. An accurate description of biomolecules requires atomic-level modeling using classical molecular dynamics (MD) simulations.\textsuperscript{4,5} Because water and ions are an integral part of a biomolecular simulation system—and in some cases directly involved in the function of a protein, e.g., ion channels—their accurate representation is also an important issue in MD simulations. The force fields currently used for description of water and ions typically consist of Coulomb and short-range Lennard-Jones (LJ) 6-12 interactions. For computational expediency, the polarization interaction has been left out, and its effect has been included in an average way by increasing the partial charges on atoms. This prescription is used in all major force fields such as AMBER,\textsuperscript{6} CHARMM,\textsuperscript{7} and GROMACS.\textsuperscript{8}

While the nonpolarizable force fields have been quite successful in description of biomolecules, closer scrutiny by comparing the MD results with \textit{ab initio} calculations\textsuperscript{9–12} or detailed experiment\textsuperscript{13–18} has revealed some discrepancies that may require inclusion of the polarization interaction for resolution. \textit{Ab initio} MD simulations provide the most direct tool for studying the role of polarization in biomolecular systems. Recent developments in parallel computing have made such investigations distinctly feasible. For example, the \textit{ab initio} methods have been used in description of enzyme reactions,\textsuperscript{19–23} computation of pK\textsubscript{a} values,\textsuperscript{24,25} and in guiding and testing of the classical force fields.\textsuperscript{26–29}

The question of the accuracy of the classical force fields for electrolyte solutions has been raised in some recent MD studies, where formation of NaCl and KCl clusters was observed in long MD simulations.\textsuperscript{30–34} While this behavior appears to be specific to the AMBER force field, it has nevertheless started a debate on how to construct more reliable force fields for ions.\textsuperscript{35–37} Force field optimization typically involves fitting the two LJ parameters for an ion to the experimental solvation free energy and the ion-water radial distribution function (RDF). Not surprisingly all force fields reproduce these quantities very well despite a considerable variation among the parameter values. Where the force fields differ most are the ion-ion RDFs for which there are no experimental data.\textsuperscript{38} Thus the \textit{ab initio} computation of the potential of mean force (PMF) between two ions would provide additional constraints in optimizing the force fields. An advantage of using the \textit{ab initio} results as a guide in optimizing the force fields is that it shifts the focus from global to microscopic solvation properties. This will be especially useful in constraining the polarizable force fields currently under construction\textsuperscript{28,30} because it enables a detailed comparison of the polarization properties of water in the solvation shell of ions.

Here we present the results of an \textit{ab initio} computation for the dissociation of aqueous NaCl obtained from the Car–Parrinello MD (CPMD) simulations.\textsuperscript{40} We use the constrained-MD method\textsuperscript{41} to determine the PMF between the Na\textsuperscript{+} and Cl\textsuperscript{−} ions from the contact-ion pair (CIP) position to...
the solvent-separated-ion pair (SSIP) position and beyond. The ab initio PMF is compared with the classical ones obtained using several common force fields. To shed further light on the differences between the ab initio and classical PMF results, we analyze the solvation structures at the CIP and SSIP positions and the transition state (TS) in between them. The coordination number, dipole moment, and orientation of water molecules in the solvation shell are calculated at those window positions and compared with the similar quantities obtained using the CHARMM force field.

As far as we are aware, this is the first ab initio calculation of the PMF for the dissociation of the Na\(^+\)--Cl\(^-\) ions in solution (or any other ion pair). In a previous CPMD simulation of the aqueous NaCl system, the ions were separated by 8 Å and their effect on the hydrogen bond network was investigated via the water dipole moments.\(^{42}\) At that distance, the ion-ion PMF vanishes and they essentially move independent of each other.

II. COMPUTATIONAL METHODS

A. PMF calculations

If simulation time is not a concern, the most straightforward way to calculate the PMF between two ions in a salt solution is to perform a sufficiently long simulation of the system and determine the RDF \(g(r)\) of the two ions from the trajectory data. The PMF \(W(r)\) is then obtained from the RDF using

\[
W(r) = -k_B T \ln g(r),
\]

where \(k_B\) is the Boltzmann constant, \(T\) is the temperature, and \(r\) is the ion-ion separation which is the reaction coordinate. We use this method to determine the Na\(^+\)--Cl\(^-\) PMF in classical MD simulations.

For ab initio simulations, the above method is clearly not feasible at present, and a method with biasing is required to enable a faster sampling of the system along the reaction coordinate. The two main methods available for this purpose are constrained MD (Ref. 41) and umbrella sampling.\(^{43}\) Test calculations performed for the PMF of methane-methane association indicate that force averaging with constraint biasing has better convergence properties compared with configuration sampling with an umbrella potential.\(^{44}\) Indeed the former method has been employed in a recent ab initio calculation of the PMF\(^{10}\) between a methane pair in the framework of the CPMD simulations.\(^{10}\) Therefore, we also choose the constrained-MD method in the present ab initio PMF calculations. Here the ion-ion distance is fixed at certain separations \(r\), and the average effective force \(\bar{F}(r)\) is determined from the time average of the constraint force sampled during the CPMD simulations. Fixing the ion-ion distance reduces their entropy, which is equivalent to an entropic force of magnitude \(-2k_B T/r\). This volume-entropy force needs to be taken into account when relating the average effective force to the PMF\(^{10}\)

\[
-\frac{dW(r)}{dr} = \bar{F}(r) - \frac{2k_BT}{r}.
\]

Integration of Eq. (2) yields for the PMF

\[
W(r) = -\int_{r_0}^{r} \bar{F}(r') dr' + 2k_BT \ln r + C,
\]

where \(r_0\) is a reference point for the PMF and \(C\) is a constant of integration chosen such that \(W(r)\) vanishes at large ion-ion separations.

The PMF is useful for detailed comparisons of the ab initio and classical results but it does not tell whether the ion pair can bind or not. For that purpose one needs the binding free energy of the ion pair, which can be calculated from the volume integral of the PMF

\[
G_b = -k_B T \ln \left[ \frac{4\pi}{V} \int_0^{r_c} \exp \left( \frac{-W(r)}{k_B T} \right) r^2 dr \right],
\]

where \(V=4\pi r_c^3/3\) is the volume occupied by the ion pair. A negative \(G_b\) value would signal ion clustering problems in MD simulations—the larger the \(G_b\) is (in absolute value), the faster the clustering is likely to occur.

B. Ab initio simulations

The ab initio MD simulations of the NaCl solution are performed using the CPMD code.\(^{45}\) Here the electronic structure is determined from the density functional theory (DFT) by solving the Kohn–Sham equations,\(^{46}\) and the nuclei propagate in this ab initio potential according to Newton’s equation of motion. Only the valence electrons of each atomic species are included in the DFT calculations while the interaction of the core with the valence electrons is described by pseudopotentials. We use norm-conserving Goedecker-type pseudopotentials\(^{47}\) for Na and Cl and Troullier–Martins\(^{38}\) pseudopotentials for O. For H, a von Barth–Car analytical pseudopotential\(^{49}\) is employed. The 2s and 2p semicore states of Na and 3s and 3p states of Cl are treated explicitly as valence states. For the exchange-correlation functional in DFT we choose BLYP,\(^{50,51}\) which remains as one of the best choices for ab initio simulations of aqueous systems.\(^{52–56}\) The valence electrons in the Kohn–Sham equations are expanded in a plane-wave basis set with an energy cutoff of 80 Ry. The CPMD equations are integrated using the Verlet algorithm with a time step of 4 a.u. (\(\sim 0.1\) fs) and using a fictitious mass of 400 a.u. for the electrons. Periodic boundary conditions are applied using the simple cubic symmetry for the cell images. The temperature is maintained at 300 K using a Nosé–Hoover thermostat chain for the ions with a frequency of 1200 cm\(^{-1}\).\(^{57,58}\)

The simulation system is constructed using a standard cubic box of size 12.5 Å containing 64 water molecules, which has a density of \(\sim 1\) g/cm\(^3\). A pair of water molecules near the center of the box is replaced with a Na\(^+\)--Cl\(^-\) ion pair, resulting in an \(\sim 0.9\) M salt solution. Initially the ion-ion separation is fixed at \(r=2.7\) Å, corresponding to the CIP position. This system is subjected to energy minimization and then equilibrated for 100 ps using classical MD simulations. The resulting atomic coordinates are used as a starting configuration for the ab initio calculations. The system is first quenched to its Born–Oppenheimer energy surface, followed by CPMD simulations where the ion-ion separation is
increased or decreased at a constant rate to create windows for sampling of the constraint force. Because the force rapidly increases when the ions are pushed together, the window positions are taken at 0.1 Å steps from \( r = 2.7 \) to 2.2 Å. The force is better behaved when the ions are pulled apart, hence the window positions are taken at 0.2 Å steps between 2.7 and 5.7 Å. At 4.7 Å, which corresponds to the SSIP position, the system is again quenched to its Born–Oppenheimer energy surface before continuing with the pulling of the ions. In this way, a total of 21 windows is generated for force sampling. The maximum pulling distance is limited to about half of the box size to avoid potential artifacts due to the image ions getting too close to the sampled ions (this is justified below). For each window, the CPMD simulations are carried out for 6 ps while keeping the reaction coordinate \( r \) fixed. This simulation time was found to be sufficient for the convergence of the PMF in the \textit{ab initio} calculations for a methane pair.\(^9\) The constraint force required to fix the distance between the ions is recorded at each time step, and the effective force acting on the ions at the window position is determined from the average of these data. Finally the resulting average effective force is integrated according to Eq. (3) to determine the \textit{ab initio} \( \text{Na}^+–\text{Cl}^- \) PMF.

### C. Classical simulations

For comparison purposes we have also calculated the \( \text{Na}^+–\text{Cl}^- \) PMF for five sets of classical force field parameters, including those used in the current versions of the CHARMM (version 27), AMBER (version 9), and GROMACS (version 3) force fields as well as the parameters determined by Smith and Dang\(^59\) and Joung and Cheatham.\(^35\) We note that in the recently released version of AMBER, the parameters of Joung and Cheatham\(^35\) have been adapted. All the AMBER results here are obtained using version 9, which has led to the clustering problems mentioned in the Sec. I. The TIP3P model\(^60\) is used for water molecules in all cases except in GROMACS which uses the SPC model.\(^61\) Classical MD simulations are performed using version 2.6 of the NAMD code.\(^62\) The simulation system consists of 3780 water molecules and 71 \( \text{Na}^+–\text{Cl}^- \) ion pairs in a cubic box of side length of 50 Å, which corresponds to a 1 M salt solution. An NpT ensemble is used with periodic boundary conditions. The temperature is maintained at 300 K through Langevin damping with a coefficient of 5 ps\(^{-1}\). Similarly the pressure is kept at 1 atm using the Langevin piston method with a damping coefficient of 5 ps\(^{-1}\).

Electrostatic interactions are computed using the particle-mesh Ewald algorithm with 50 grid points along each direction, corresponding to a grid spacing of 1 Å. The list of nonbonded interactions is truncated at 13.5 Å. The short-range LJ interactions are switched off in the range of 10–12 Å using a smooth switching function. A time step of 2 fs is employed in the MD simulations, and the trajectory data are written at 0.1 ps intervals during the production runs. For each force field the system is first energy minimized and then equilibrated for 500 ps. After this, production data are collected for 10 ns. The \( \text{Na}^+–\text{Cl}^- \) RDF is determined from the ion trajectory data, which is then used in Eq. (1) to calculate the \( \text{Na}^+–\text{Cl}^- \) PMF.

To study the finite size effects and justify the choice of the maximum \( \text{Na}–\text{Cl} \) distance in the \textit{ab initio} PMF, we have also calculated the classical PMF (for the CHARMM force field) in a small box using the same system as in the CPMD simulations. The PMF obtained from the small box overlaps with the one obtained from the large box up to 5.5 Å and starts deviating from it afterward. At 5.7 Å, the deviation is still small enough. This indicates that the CPMD results presented in Figs. 1 and 3 are not influenced much by the finite size effects.

The CIP and SSIP configurations are well populated in free MD simulations but not the TS in between them. In order to collect sufficient data for comparisons of the \textit{ab initio} and classical solvation structures, we have performed an additional MD simulation with the CHARMM force field where the ion-ion separation is restrained to 3.6 Å. For this purpose a smaller system (54 water molecules with one \( \text{NaCl} \) pair) is used and data are collected during a 5 ns production run.

### D. Solvation structure and dipole moments

An advantage of the MD simulations is that one obtains detailed data on the microscopic solvation structure of the ion pair at various separations. Comparison of the solvation structures obtained from the \textit{ab initio} and classical MD simulations could provide useful insights on how to improve the classical force fields. To this end, we consider three ion-ion configurations that are of particular importance: CIP and SSIP positions and the TS in between them. For the \textit{ab initio} data we use the windows from the CPMD simulations that are closest to these positions. The classical data are gathered from the free MD simulations for the CIP and SSIP positions using a bin of size 0.1 Å centered at those positions, and from the constrained MD simulations for the TS as mentioned above. Using the trajectory data, we calculate the hy-

![FIG. 1. Convergence of the \textit{ab initio} PMF. The dashed lines show the individual PMFs obtained from 1 ps blocks of data (numbered from 1 to 6 sequentially). The solid line shows the PMF obtained from the production run (2–6 ps).](image)
paration numbers for each ion as well as the number of bridging waters that coordinate both ions at each ion-ion position. The average orientations of the water molecules in the coordination shells are also computed and compared.

The dipole moments of water molecules are fixed in the classical force fields, but in reality they could vary with the ion-ion distance. If substantial changes were to occur in the dipole moments of the hydration waters during dissociation, it would be very difficult to describe this process using a nonpolarizable force field. To check against this possibility, we calculate the dipole moments of hydration waters from the CPMD data for the three positions considered above. The dipole moments are calculated using the maximally localized Wannier function (MLWF) analysis. The MLWF orbitals are obtained from the Bloch orbitals available from the DFT calculations via a unitary transformation and their spread is minimized iteratively. Using the centers of the MLWFs and the charges associated with them, the dipole moment can be calculated from the classical formula

$$\mu = \sum_n Z_{ne} \mathbf{R}_n - \sum_i 2e \mathbf{r}_i,$$

where the first sum is over the O and two H atoms in water which are at positions \( \mathbf{R}_n \) and have ionic charges \( Z_{ne} \), and the second sum is over the four MLWF centers in water at positions \( \mathbf{r}_i \) with charges \(-2e\). The MLWF analysis has been used in numerous \textit{ab initio} calculations of the dipole moments previously.\textsuperscript{11,12,42,52,53} Also this method has been successful in reproducing the dipole moment of water clusters (\( n=1, \ldots, 5 \)) where experimental data exist.\textsuperscript{54}

III. RESULTS AND DISCUSSION

A. \textit{Ab initio} PMF for NaCl dissociation

The results of the \textit{ab initio} PMF calculations for the dissociation of NaCl are displayed in Fig. 1. To address the equilibration and convergence issues, we have divided the 6 ps of CPMD data into 1 ps blocks and determined the corresponding PMF for each block. These are labeled from 1 to 6 in Fig. 1. The advantage of the block representation of the data compared with the cumulative one is that the equilibration phase can be more clearly identified. The inspection of the individual PMFs shows that the equilibration of the CIP configuration is almost instantaneous but the SSIP configuration takes about 2 ps to equilibrate. Therefore, we have excluded the first 2 ps of data as equilibration and constructed a final PMF from the remaining 4 ps of production data (thick curve in Fig. 1). The individual PMFs from three to six are seen to fluctuate around this final PMF. The faster equilibration in the NaCl PMF is reasonable because equilibration is expected to take less time for a charged pair compared with a neutral pair.

It is also worthwhile to look at the constraint force at several distances and check the convergence of its cumulative average. This is done in Fig. 2, where the constraint force (gray points) and its cumulative average (lines) are plotted against the simulation time for three ion-ion separations, \( r=3.1, 3.9, \) and \( 4.7 \) Å. To show the effect of the equilibration, we present the cumulative average force for both the production data (2–6 ps, solid line in Fig. 2) and the whole CPMD data (0–6 ps, dashed line in Fig. 2). The constraint force is seen to exhibit large fluctuations around a baseline, and it would be very difficult to make a decision on the equilibration time on the basis of these data. The cumulative forces, in contrast, converge rather quickly and remain more or less flat in the last 2 ps. However, they are seen to converge to different values in two cases, highlighting the importance of choosing the correct equilibration time. Because the CPMD simulations are computationally expensive, an optimal choice for the equilibration time is very important. The block-data analysis of the PMF curves in Fig. 1 is visually very clear in this respect, hence it provides a valuable guidance for separating the equilibration phase from the production data.

B. Polarization of hydration waters during dissociation

In classical nonpolarizable models, water molecules have a fixed dipole moment, e.g., in the TIP3P model, \( \mu=2.35 \) D. In reality, however, water molecules have a fairly large polarizability, and their dipole moments could change substantially with the environment.\textsuperscript{11,12} Thus the first question to ask in assessing the viability of using nonpolarizable models in the description of NaCl dissociation is whether the dipole moments of hydration waters change significantly during dissociation. For this purpose, we have calculated the average dipole moment of hydration waters from the CPMD production data using Eq. (5). The data are sampled at 50 fs intervals, and the average dipole moment is obtained from the analysis of 80 frames. The results for the CIP, TS, and SSIP positions—corresponding to the ion-ion separations, \( r=2.68, 3.38, \) and \( 4.74 \) Å—are shown in Table I. For comparison, we show the bulk results for each ion in the last
the column of the table, which were computed using similar systems and the BLYP functional. Because polarizability of water changes with the ion type, we have calculated the dipole moment of hydration waters separately for Na$^+$ and Cl$^-$ ions. The last row shows the result for the bridging waters that belong to the hydration shell of both ions simultaneously.

Inspection of Table I shows that the variation in the dipole moments of hydration waters with ion-ion distance is quite small and certainly within the accuracy of the calculations. Distributions of the dipole moments for each ion are also found to be similar to those of the bulk calculations. Overall the results in Table I indicate that variations in water polarization is not expected to play a significant role in dissociation of aqueous NaCl. The reduction in the dipole moments of the shared water appears counterintuitive—the electric field is twice as large at the middle of the ions compared with a single ion—and therefore requires some explanation. The average number of shared waters is about 0.5 in the CIP and about 1 in the TS and SSIP positions. The position and orientation of this water indicate that it is mainly in the coordination shell of the Na$^+$ ion in the CIP and TS positions. For example, in the CIP position, the shared water is in the coordination shell of the Na$^+$ ion 100% of the time but moves in and out of the coordination shell of Cl$^-$ ion resulting in a coordination number of 0.5. The presence of the Cl$^-$ ion actually hinders the polarization of the shared water in the CIP and TS configurations, which partly explains the smaller values of the dipole moments for the shared waters. A more interesting situation occurs in the SSIP position where both ions are equally well coordinated by the shared water molecule. Yet the dipole moment of this water still remains well below the bulk value of 3.0 D. Inspection of the hydrogen bonds of the shared water from the CPMD data helps to explain this counterintuitive result. The shared water makes a hydrogen bond with a neighboring water molecule 74% of the time (38% donor, 36% acceptor, and 26% none). This is far below the ideal situation where the shared water would have one donor and one acceptor. Each hydrogen bond contributes about 0.2 D to the dipole moment of water. Thus due to geometrical restrictions, the average number of hydrogen bonds the shared water makes is reduced from the possible 2 to 0.74, which appears to be sufficient to cancel any polarization gains from the simultaneous presence of the Na$^+$ and Cl$^-$ ions.

C. Comparison of ab initio and classical PMFs

The ab initio PMF for the dissociation of NaCl is compared with the classical PMFs for several force fields in Fig. 3. The classical PMFs are determined to distances $r=10$ Å. Because all the classical PMFs are flat beyond 8 Å, the region $8–10$ Å is used to set the zero of the potential, and thus align the PMFs. Due to computational limitations, the ab initio PMF could not be extended to this asymptotic region. We have therefore aligned the ab initio PMF with the classical ones for $r>5$ Å, where all PMFs bunch together and tend to zero. This choice affects the binding energy but not the other properties discussed in the paper. To make the comparison of PMFs easier, we also list in Table II the main properties of each PMF, namely, the CIP, TS, and SSIP positions, the barrier height relative to the CIP minimum, and the binding free energy obtained from Eq. (4). Because the

![PMF comparison](image_url)

**FIG. 3.** Comparison of the ab initio PMF (CPMD) for dissociation of NaCl with the classical ones obtained using the force fields AMBER, CHARMM, GROMACS, Smith and Dang, and Joung and Cheatham.

### Table I. Average dipole moments of the water molecules (in units of Debye, D) coordinating the Na$^+$ ion only, the Cl$^-$ ion only, and both ions simultaneously (shared) at the CIP, TS, and SSIP positions. The corresponding bulk values are taken from Ref. 65 for Na$^+$ and Ref. 66 for Cl$^-$. 

<table>
<thead>
<tr>
<th></th>
<th>CIP</th>
<th>TS</th>
<th>SSIP</th>
<th>Bulk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$^+$</td>
<td>2.89</td>
<td>2.87</td>
<td>2.77</td>
<td>2.81</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>2.93</td>
<td>2.86</td>
<td>2.90</td>
<td>2.87</td>
</tr>
<tr>
<td>Shared</td>
<td>2.79</td>
<td>2.77</td>
<td>2.81</td>
<td></td>
</tr>
</tbody>
</table>

**Table II.** Positions of the first minimum (CIP), the maximum (TS), and the second minimum (SSIP) in the ab initio and the classical PMFs. The column $U_B$ shows the barrier height relative to the CIP minimum, and $G_B$ gives the binding free energy obtained from the integration of the PMFs via Eq. (4).

<table>
<thead>
<tr>
<th></th>
<th>CIP (Å)</th>
<th>TS (Å)</th>
<th>SSIP (Å)</th>
<th>$U_B$ (kcal/mol)</th>
<th>$G_B$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPMD</td>
<td>2.68</td>
<td>3.38</td>
<td>4.74</td>
<td>1.40 ± 0.28</td>
<td>$-$0.03 ± 0.07</td>
</tr>
<tr>
<td>AMBER</td>
<td>2.76</td>
<td>3.82</td>
<td>5.40</td>
<td>3.56</td>
<td>$-$0.43</td>
</tr>
<tr>
<td>CHARMM</td>
<td>2.62</td>
<td>3.58</td>
<td>5.10</td>
<td>3.49</td>
<td>$-$0.16</td>
</tr>
<tr>
<td>GROMACS</td>
<td>2.67</td>
<td>3.63</td>
<td>5.21</td>
<td>3.32</td>
<td>$-$0.13</td>
</tr>
<tr>
<td>Smith and Dang</td>
<td>2.81</td>
<td>3.67</td>
<td>5.27</td>
<td>2.70</td>
<td>$-$0.09</td>
</tr>
<tr>
<td>Joung and Cheatham</td>
<td>2.71</td>
<td>3.63</td>
<td>5.19</td>
<td>3.16</td>
<td>$-$0.12</td>
</tr>
</tbody>
</table>
*ab initio* simulations are quite short, we have included the error bars in the *ab initio* calculations of free energies, which are obtained from the block data in Fig. 1.

Figure 3 shows that qualitatively the *ab initio* PMF is very similar to the classical ones—a well defined CIP minimum is separated from a broader SSIP minimum by a TS barrier. However, as is clear from Fig. 3 and quantified in Table II, there are sizable differences between the *ab initio* and classical PMFs with respect to both the positions of the extremum points and their energies. The CIP distance is well constrained from the ionic sizes so there is a little problem there, but the TS and SSIP distances are markedly larger in the classical PMFs. In this regard, AMBER shows the maximum deviation from the *ab initio* PMF while the others are quite similar, with CHARMM being the closest to the *ab initio* results. The shorter TS and SSIP distances in the *ab initio* simulations are presumably due to the fact that water molecules are both flexible and polarizable, which is not the case in the classical models. More important differences occur in free energies. First, the CIP minimum is relatively shallower and the TS barrier is much lower in the *ab initio* PMF. As a result, the TS barrier height relative to the CIP minimum is more than doubled in the classical PMFs compared with the *ab initio* PMF. Second the CIP and SSIP minima are nearly degenerate in the *ab initio* PMF, whereas the CIP minimum is always lower than that of SSIP in the classical PMFs, which could be seen as a harbinger of clustering problems. Inspection of Fig. 3 and Table II shows that AMBER exhibits the largest deviation in free energies with a distinctly lower CIP minimum and the highest TS barrier. However, as is clear from Fig. 3 and quantified in Table II, there are sizable differences between the *ab initio* and classical PMFs with respect to both the positions of the extremum points and their energies. The CIP distance is well constrained from the ionic sizes so there is a little problem there, but the TS and SSIP distances are markedly larger in the classical PMFs. In this regard, AMBER shows the maximum deviation from the *ab initio* PMF while the others are quite similar, with CHARMM being the closest to the *ab initio* results. The shorter TS and SSIP distances in the *ab initio* simulations are presumably due to the fact that water molecules are both flexible and polarizable, which is not the case in the classical models. More important differences occur in free energies. First, the CIP minimum is relatively shallower and the TS barrier is much lower in the *ab initio* PMF. As a result, the TS barrier height relative to the CIP minimum is more than doubled in the classical PMFs compared with the *ab initio* PMF. Second the CIP and SSIP minima are nearly degenerate in the *ab initio* PMF, whereas the CIP minimum is always lower than that of SSIP in the classical PMFs, which could be seen as a harbinger of clustering problems. Inspection of Fig. 3 and Table II shows that AMBER exhibits the largest deviation in free energies with a distinctly lower CIP minimum and the highest TS barrier.

The contrast between the *ab initio* and classical PMFs is succinctly summarized by the binding free energy calculations presented in the last column of Table II. Experimentally, the solubility limit of the aqueous NaCl at room temperature is 5.4 M.67 Thus no clustering should occur for the ~1 M NaCl solutions considered here. The binding free energy is very small (in absolute value) in the *ab initio* case, which more or less ensures this. But in all the classical models a substantially larger binding free energy is obtained, which will lead to some degree of clustering depending on the simulation time. AMBER by far yields the largest binding free energy, so it is not surprising that clustering has first been observed for this force field in multinanosecond MD simulations. For the other force fields, the binding free energy is relatively smaller, hence clustering is expected to occur in a much longer time scale.

Table III gives the average coordination numbers obtained from the *ab initio* (CPMD) and classical (CHARMM) MD simulations at each of these three positions. The cutoff values are determined from the first minimum in the ion-oxygen RDF as 3.2 Å for Na+ and 3.9 Å for Cl−. To help with the visualization of the results, we show in Fig. 4 typical snapshots from the *ab initio* and classical simulations for each configuration. Because the sampling time in the *ab initio* simulations is much shorter than the classical ones, there are considerable uncertainties in the *ab initio* results. Thus while they provide useful insights for classical force fields, it is important that they are confirmed in future *ab initio* studies with longer simulation times.

D. Solvation structure during dissociation

To see how the solvation structure changes with the ion-separation in the *ab initio* MD simulations, we have examined the coordination shells of each ion at the CIP, TS, and SSIP positions. For comparison, similar calculations are performed in classical MD simulations using the CHARMM force field. Table III gives the average coordination numbers for Na+ and Cl− ions in *ab initio* simulations and contrast them with the *ab initio* calculations. The snapshots in Fig. 4 depict this situation, which is further analyzed in

<table>
<thead>
<tr>
<th>CPMD</th>
<th>CIP</th>
<th>TS</th>
<th>SSIP</th>
<th>Bulk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+</td>
<td>2.8</td>
<td>3.2</td>
<td>4.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Cl−</td>
<td>4.0</td>
<td>5.0</td>
<td>4.3</td>
<td>6.0</td>
</tr>
<tr>
<td>Shared</td>
<td>0.5</td>
<td>1.1</td>
<td>1.1</td>
<td>…</td>
</tr>
<tr>
<td>Total</td>
<td>7.3</td>
<td>9.3</td>
<td>9.6</td>
<td>11.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHARMM</th>
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<th>TS</th>
<th>SSIP</th>
<th>Bulk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+</td>
<td>1.8</td>
<td>3.3</td>
<td>4.3</td>
<td>5.7</td>
</tr>
<tr>
<td>Cl−</td>
<td>5.3</td>
<td>6.1</td>
<td>6.4</td>
<td>7.5</td>
</tr>
<tr>
<td>Shared</td>
<td>2.2</td>
<td>2.0</td>
<td>1.0</td>
<td>…</td>
</tr>
<tr>
<td>Total</td>
<td>9.3</td>
<td>11.4</td>
<td>11.7</td>
<td>13.2</td>
</tr>
</tbody>
</table>
Table IV below. Thus it is more realistic to include the shared coordination number in that of Na⁺ when comparing the CIP and TS results. With this provision, we can summarize the results in Table III as follows. (i) At the CIP and TS positions, both ions are overcoordinated by about one water molecule in classical MD relative to \textit{ab initio} MD. (ii) At the SSIP position, the Na⁺ and shared coordination numbers match but the Cl⁻ ion is overcoordinated by two water molecules in classical MD. (iii) Remarkably, while the total coordination number for the NaCl system increases with ion-ion separation, the classical system remains overcoordinated by two water molecules compared with the \textit{ab initio} results at all distances. This suggests that more attention should be paid in getting the coordination numbers right in the parametrization of the classical force fields.

Orientation of the dipole moments of the hydration waters is clearly an important consideration in deciphering the changes in the microscopic solvation structure during NaCl dissociation. In Table IV we compare the orientations of water molecules obtained from \textit{ab initio} and classical MD simulations in the same way as the coordination numbers in Table III. The angles plotted in Table IV are as follows. For Na⁺ the angle between the Na⁺–O vector and the water-dipole vector and for Cl⁻ the angle between the Cl⁻–H vector and the H–O vector, where H is the water-hydrogen closest to the Cl⁻ ion. The same angles are calculated for the shared waters for Na⁺ and Cl⁻ coordination separately. Overall there is a reasonable agreement between the \textit{ab initio} and classical results, with the Cl⁻ ion results faring slightly better than those of Na⁺. In both \textit{ab initio} and classical cases, there is quite a good alignment between the H–O and Cl⁻–H vectors, and this hardly changes with distance. The slightly higher angle found in CHARMM is presumably due to the constraints imposed by the higher coordination number. For the Na⁺ ion, CPMD predicts larger angles compared with CHARMM, and there is some variation in the dipole orientations with distance, which is not observed in CHARMM. The largest difference between the \textit{ab initio} and classical models occurs for the shared water, especially in the SSIP position. In CPMD, the shared water’s coordination of the Cl⁻ ion improves with distance whereas no change is observed in CHARMM. This may have contributed to the smaller CIP well obtained in the \textit{ab initio} PMF compared with the classical PMFs. These results suggest that the dipole orientations could also be helpful in understanding the differences between the \textit{ab initio} and classical PMFs, and as such could play a role in constraining the force field parameters.

Table IV: Average angular orientations of the dipole moments (in degrees) of the coordinating waters obtained from the \textit{ab initio} and classical MD simulations. The last two rows give the same orientations for the shared waters which coordinate both ions simultaneously. Standard deviations are given in brackets. See the text for the definition of the angles.

<table>
<thead>
<tr>
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<th>CPMD</th>
<th>CHARMm</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CIP</td>
<td>TS</td>
</tr>
<tr>
<td>Na⁺</td>
<td>41 (21)</td>
<td>51 (20)</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>6 (4)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Shared Na⁺</td>
<td>48 (22)</td>
<td>58 (22)</td>
</tr>
<tr>
<td>Shared Cl⁻</td>
<td>14 (1)</td>
<td>12 (4)</td>
</tr>
</tbody>
</table>

IV. CONCLUSIONS

In this paper, we have presented the first \textit{ab initio} calculation of the PMF for the dissociation of aqueous NaCl. Because the PMF (or the corresponding RDF) is not a measurable quantity, it has not been used in parametrization of the classical force fields in the past. Detailed comparisons of the \textit{ab initio} PMF with the classical PMFs obtained using several force fields show that they have problems with regard to both the free energy profiles (roughly doubled) and positions of the extremum points (further away). This results in appreciable binding free energies in all classical force fields, which could cause clustering of NaCl in long MD simulations in contradiction with experimental solubility results. To get a better understanding of the causes of these discrepancies, we have investigated the microscopic solvation structure in the \textit{ab initio} MD simulations—i.e., coordination numbers, dipole moments, and orientations—and compared them with similar quantities obtained from the classical MD simulations. No significant variations have been observed in dipole moments of hydration waters with ion-ion distance,
which suggests that NaCl dissociation may be described using nonpolarizable force fields.

As pointed out in previous comparisons of \textit{ab initio} and classical MD results, \cite{66} overcoordination of ions is a significant problem for the current classical force fields. Here we have shown that this problem persists in the aqueous NaCl system at various ion-ion separations. It is possible that the problems found in the classical PMFs are also caused by overcoordination. For example, a larger number of water molecules in the coordination shell could push the extremum points (TS and SSIP) further away and also result in a more stable CIP configuration. Therefore, it is important to consider this possibility in future developments of force fields and devise ways to incorporate the coordination numbers in the parametrization process. If such attempts fail to produce a nonpolarizable force field consistent with the experiments and the \textit{ab initio} results, then inclusion of polarization will be essential for description of NaCl dissociation. The \textit{ab initio} results presented here will be especially useful in guiding the efforts in construction of such polarizable force fields.

**ACKNOWLEDGMENTS**

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