Computational investigation of the hydration of alkyl diammonium cations in water clusters

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ABSTRACT

The hydration behavior of α,ω-alkyl diammonium cations of varying alkyl chain length in water clusters has been investigated with molecular dynamics simulations. The OPLS force field was validated against high-level quantum-chemistry results and experimental data and subsequently used to describe the interatomic interactions in the simulations. The results were further validated with simulations performed with approximate density-functional theory (DFTB3). Surface solvation structures are found to be the most stable, accompanied by considerable ion conformational changes, especially in the case of longer dications. This work demonstrates that, depending on their structure, doubly charged cations may have a high affinity towards aqueous interfaces.

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1. Introduction

The hydration of ions has been extensively investigated due to their ubiquity in nature [1,2]. Such investigations have provided useful information about the structural and thermodynamic aspects of ion hydration which could be used to obtain insight into the nature of important chemical phenomena [3,4]. In particular, the hydration extent of ions, which reflects their propensity to locate well beneath the first few interfacial layers of the solvent molecules (interior solvation) *vs.* in the first interfacial layer of the solvent molecules (surface solvation), and their effect on the orientation of surrounding water molecules, usually referred to as the structure-making or structure-breaking effect [5], have been used to explain the behavior of ions in electrolyte solutions [5,6]. In this respect, recent computational and experimental investigations have demonstrated that some singly charged anions tend to locate in higher concentrations at aqueous interfaces [7,8]. However, the affinity for surface solvation of cations and doubly charged ions has been only rarely reported [9–11].

Ionic groups such as ammonium play an essential role in the hydration of peptides, proteins and other biomolecules as they are one of the primary binding targets of water molecules [12,13]. Sequential hydration analysis of peptides and other biomolecules reveals that the hydration extent of ammonium groups is affected by their surrounding organic domain which regulates their level

of exposure to the aqueous phase [12]. The extent of the interactions between water and such ionic groups is key in explaining the structural and thermodynamic aspects of the hydration of large and complex biomolecules [13,14].

The hydration of the ammonium cation and ammonium groups attached to different hydrophobic domains has been previously investigated using both experimental [15–19] and computational [20–25] methods. In particular, α,ω-alkyl diammonium dications lend themselves as paradigms for investigating the effect of the aliphatic domain – and its size – on the hydration of the ammonium group in a systematic manner [17,18]. The hydration extent and the water-induced conformational change of these ions upon sequential addition of water molecules may provide insight into the hydration of more complex biological molecules such as peptides and proteins [26,27] and also help to understand the hydration behavior of neighboring charged groups in multiply charged molecules [12,13]. Such information is also useful to explain the 'specific effect' of ions on the solubility and stability of biomolecules in electrolyte solutions [14]. In this respect, the specific hydration behavior of alkyl diammonium salts has been used to design environmental-friendly switchable water solvents [9,28,29].

The stepwise ion–water binding energies of α,ω-alkyl diammonium dications in clusters with up to six water molecules have been measured by Kebarle and co-workers, revealing that the α and ω terminal sites are hydrated sequentially [17,18]. However, infrared photodissociation experiments show that, upon increasing the number of water molecules, the $NH_3(CH_2)_7NH_3{}^{2+}$ dication folds and the water molecules form a single cluster which hydrates both terminal groups [19]. We note that analogous hydration

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behavior and conformational change upon addition of water molecules has been reported for a dicarboxylate dianion [11,30]. However, no systematic and rigorous (computational) investigation of $NH_3(CH_2)_mNH_3^{2+}$ dication hydration has been reported to date.

In this Letter, we report an investigation of the cluster hydration of α,ω-alkyl diammonium cations with an alkyl chain of 5–10 carbon atoms from molecular dynamics (MD) simulations. The objective is to address the hydration extent of the dications as a function of the alkyl chain length in order to shed light onto their affinity for the surface *vs.* the cluster interior, and in particular to characterize the factors that determine the ultimate hydration extent of these ions. In this respect, the effects of both conformational changes of the dications upon sequential addition of water molecules and cluster size on the hydration extent of the dications are investigated. For this purpose, accurate two-dimensional potentials of mean force (free energy surfaces) and their corresponding probability distributions are computed to quantify the hydration extent and conformational stability of the dications in water clusters of varying size.

This Letter is organized as follows: computational details of the simulations are described in Section 2, results are presented, discussed and compared with available experimental and high-level computational data in Section 3 while concluding remarks follow in Section 4.

2. Computational procedure

Simulations were performed for water clusters containing 10–40 water molecules and each of the $NH_3(CH_2)_{5-10}NH_3^{2+}$ dications in order to compute the potential of mean force (PMF) as a function of the distance between the dication terminal nitrogen atoms (r_{NN}) upon sequential addition of water molecules. To further characterize the relation between the hydration extent of the dications and their conformational change, two-dimensional PMFs were calculated as a function of both the latter coordinate and the distance between the ions and the cluster centers of mass (r_{cm}) for clusters containing 200 water molecules.

The optimized potentials for liquid simulations (OPLS) [31] model was used to describe interatomic interactions in the MD simulations together with a modified transferable interaction potential with three points (TIP3P) [32] for water molecules. This initial choice of force field was guided by its success in reproducing size-selected cluster data from infrared photodissociation experiments for the hydrated $NH_3(CH_2)_7NH_3^{2+}$ dication [19]. On occasion, approximate density-functional theory, namely the self-consistent-charge density-functional tight-binding model [33] with its third-order extension (DFTB3) [34], was also used as an alternative to the force-field approach. It should be noted that both OPLS and DFTB3 have been successfully used to investigate the hydration of ammonium-based cations in several previous studies [19,35,36].

In order to validate the accuracy of the models, various geometric and energetic properties of small ion–water clusters were calculated and compared with *ab initio* results and available experimental data. *Ab initio* quantum chemistry calculations were performed with second-order Møller-Plesset perturbation theory (MP2) [37] and Dunning's augmented correlation consistent aug-cc-pVDZ and aug-cc-pVTZ [38] basis sets. Thermal corrections were calculated under the rigid rotor-harmonic oscillator approximations. The *ab initio* binding energies were corrected for basis set superposition error using the counterpoise method of Boys and Bernardi [39].

PMF calculations were performed with the umbrella sampling [40] method to increase the efficiency of sampling and the unbiased free energies and probability distributions were obtained with

the weighted histogram analysis method (WHAM) [41]. Restraining harmonic potentials with force constant values of 10.0 and 5.0 kcal/mol/$\mathring{A}^2$ were applied at 0.25 and 0.5 $\mathring{A}$ intervals to restrain the r_{NN} and r_{cm} values, respectively. All PMFs were corrected for the effects of increased conformational space with increase of the intermolecular distance [42]. The OPLS-MD simulations were performed for water clusters of varying size containing each of the ions investigated, with spherical boundary conditions [43] to prevent cluster evaporation, at a constant temperature of 250 K. The simulations were performed with a time step of 1 fs for 2 ns, with the first half of the simulation for equilibration and the second half for data collection. The DFTB3-MD simulations were performed for clusters containing the $NH_3(CH_2)_5NH_3^{2+}$ dication, also with spherical boundary conditions [43] at a constant temperature of 250 K. Simulations were performed for 120 ps with a time step of 1 fs; the simulations were equilibrated for 60 ps and data was collected for the last 60 ps. Overall, over 3.5 ns of MD simulations were performed with DFTB3 and over 13 μs with OPLS.

The GAUSSIAN09 [44] suite of programs was used for all *ab initio* quantum chemistry calculations. The DFTB+ code was used for DFTB3 calculations and the Modes program was used to calculate the DFTB3 vibrational frequencies [45]. The *DFTB3 parameters for organic and biological applications* (3OB) [46] were used for all DFTB3 calculations. The DFTB3-MD simulations were performed with our in-house MD engine coupled with the DFTB+ [45] program, while the NAMD [47] software package was used for OPLS-MD simulations. The WHAM [48] code was used to obtain the final PMFs.

3. Results and discussion

3.1. Method validation

Selected geometrical parameters predicted by various models are listed in Table 1 for $NH_3(CH_2)_{5-10}NH_3^{2+}(H_2O)$ clusters. The DFTB3 and OPLS hydrogen bond lengths deviate from the *ab initio* values by 0.024 and 0.060 $\mathring{A}$, on average, and both models overestimate the *ab initio* hydrogen bond angles by average values of 1.7° and 4.4°, respectively. Overall, the geometrical parameters predicted by DFTB3 and OPLS deviate by only 1–3% from the *ab initio* data.

Thermodynamic properties of $NH_3(CH_2)_{5-10}NH_3^{2+}(H_2O)_{1,2}$ clusters are listed in Table 2. The *ab initio* and DFTB3 binding enthalpies are in a very good agreement with the experimental values with a deviation of 0.2–0.4 kcal/mol (*cf.* Table 2). The OPLS model overestimates the experimental values by about 3.3 kcal/mol for the first hydration step while the average deviation decreases to 2.2 kcal/mol for addition of the second water molecules (*cf.* Table 2).

Comparing the structural and thermodynamic properties of small cluster minimum-energy structures by no means provide a thorough validation of the interaction models, and we now turn our attention to the validation of OPLS-MD results against those

Table 1
Hydrogen-bonding geometrical characteristics of $NH_3(CH_2)_mNH_3^{2+}(H_2O)$ clusters.

	Bond length ($\mathring{A}$)			Bond angle (°)		
	OPLS	DFTB3	Ab initio[a]	OPLS	DFTB3	Ab initio[a]
$m = 5$	1.626	1.690	1.668	179.6	176.8	174.3
$m = 6$	1.626	1.704	1.681	180.0	176.3	174.5
$m = 7$	1.633	1.714	1.690	178.4	176.3	174.5
$m = 8$	1.633	1.721	1.697	178.4	176.0	174.6
$m = 9$	1.633	1.726	1.702	178.5	176.1	174.6
$m = 10$	1.633	1.730	1.706	178.5	176.0	174.7
Δ[b]	0.060	0.024		4.4	1.7	

[a] *Ab initio* = MP2/aug-cc-pVDZ.
[b] Δ is the absolute mean deviation of OPLS and DFTB3 data from *ab initio* data in $\mathring{A}$ and° for bond lengths and angles, respectively.