Correlating structure and thermodynamics of hydrophobic–hydrophilic ion pairs in water

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ABSTRACT

The hydration structure and thermodynamics associated with the ion pairing between a halide anion and the tetramethyl ammonium cation in water are investigated by molecular dynamics simulations. Correlating the potential of mean force and different energy terms with the structure of the ion pair as a function of the interionic distance provides molecular level insight into recent experiments that shows increased affinity between a larger anion and the hydrophobic cation.

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1. Introduction

There is considerable interest in elucidating the structure and energetics involved in the interaction between ions and hydrophobic interfaces, such as membrane surfaces, large hydrophobic molecules and oil. These interactions underline phenomena such as protein folding and stability in salty solutions [1], phase transfer catalysis [2], separation phenomena and formulations of pharmaceuticals [3]. The simple picture of ions being expelled from a low dielectric medium region has been revised in recent years, as experimental and theoretical studies have suggested that large polarizable anions may actually be attracted to such interfaces [4–7].

A closely related issue, which is the subject of this work, is the ion pairing between hydrophilic and hydrophobic ions in an aqueous solution. This pairing, in particular, between nucleophilic anions and tetraalkylammonium cations (TAA), plays an important role in the operation of TAAs as phase transfer catalysts. The relative stability of the ion pair at the water/oil interface enables the catalyst to transfer the nucleophile to the organic phase, where it reacts with a substrate [8]. Salts of TAA have been the focus of many experimental and theoretical studies because of issues such as hydration water structure and dynamics [9,10] and its relation to the hydrophobic effect [11], protein stability and more. For example, Jungwirth and coworkers have used molecular dynamics simulations to show that while the affinity of halide anions to NH_4^+ decreases with increasing ionic size (follows the Hofmeister series), the anionic order is reversed for binding to hydrated TAA cations [12].

Recently, Ben-Amotz and coworkers have used Raman spectroscopy to directly determine the affinity of F^-, Cl^- and I^- anions to hydrated TMA^+ (and other hydrophobic cations) through the shift in the CH stretching frequency [13,14]. They concluded, in agreement with simulations, that the local anion concentration in the first hydration shell of TMA^+ increases with increasing anion size, but typically remains lower than that in the surrounding solution, with the possible exception of I^- (whose local concentration may slightly exceed that in the surrounding solution).

In this letter, our aim is to gain insight into the nature of the reversed binding affinity of halide ions to TMA^+ by correlating the structure (probed by calculating the radial distribution function) with the thermodynamics (potential of mean force and binding energy) of the ion pairing.

2. Systems and methods

The system we study includes a TMA^+–X^- (X = F, Cl, I) ion pair and 960 water molecules in a truncated octahedron box whose enclosing cube has an initial size of 39.11 Å. (The volume of the TO box is half the volume of the defining cube.) The actual size slightly varies with the system and time to maintain a fixed pressure of 1 atm [15]. The TMA^+ and water models used are fully flexible. The intramolecular potential for water is a power series fitted to spectroscopic data [16]. For TMA^+, the united atom model for the methyl group is used, and the intramolecular potential energy function includes harmonic-bond stretching and angle bending. The total intermolecular potential energy is a sum of atom-based Lennard–Jones plus Coulomb terms for the TMA^+ the water and the ions, and all the interactions between them. The Lennard–Jones parameters for interactions between unlike atoms are determined from the standard (Lorentz–Berthelot) mixing rules

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[17]. The Lennard–Jones parameters, charges and intramolecular parameters for all atoms are given elsewhere [8,18]. While other choices of the potential energy functions are possible, the potential energy used here gives reasonable agreement with the experimental free energy of hydration of TMA$^+$ [8] and of the halide ions [18]. In particular, the intermolecular potential energy functions used here are pair-wise additive with the polarizable nature of the solvent and the ions being effectively included by the proper adjustment of the Lennard–Jones parameters and the point charges. Many-body polarizable effects have been shown to be important for ions at hydrophobic interfaces [19–22] and could be important here as well.

The ion-pair potentials of mean force $W(r)$ are calculated using umbrella sampling [23] along r, and using ten 1 Å-wide windows with a 0.5 Å overlap between adjacent windows and a 2 ns trajectory at each window 'i':

$$W_i(r) = -RT \ln P_i(r)$$

$$P_i(r) = \frac{\int \delta(x - r) e^{-\beta H} d\mathbf{x}}{\int e^{-\beta H} d\mathbf{x}}, \tag{1}$$

where R is the gas constant, $\beta = 1/RT$, T is the temperature and $\mathbf{x}$ represents all nuclear positions. Note that direct, unconstrained sampling of r, which is the normal procedure for calculating the ion–ion pair correlation function $g(r)$ and thus $W(r) = -RT \ln g(r) + C$, does not give statistically accurate results and requires simulations of concentrated solutions.

The calculations in the gas phase and at the repulsive side of the PMF utilize non-Boltzman sampling using the biasing potential $U_b(r) = -A/r$, which is added to the Hamiltonian to obtain a flat distribution in each window by an iterative search of the constant A, greatly improving the statistical accuracy [24]. Once the $W_{biased}(r)$ is determined from the biased distribution, the correct $W(r)$ is determined by subtracting $U_b(r)$. Finally, the entropic contribution $2RT \ln r$ is added (accounting for phase space volume when the three-dimensional distribution is projected onto one dimension). For a description of other methodologies and interpolation procedures for rapid determination of PMF, as well as references to many earlier papers on calculations of PMF, the reader should consult a recent paper by Dill and coworkers [25].

The calculations are done (using in-house developed molecular dynamics code) at a constant temperature of $T = 298$ K, using a combination of the Andersen stochastic method and the Nose–Hoover thermostat [26]. The integration time-step is 0.5 fs for all systems, using the velocity version of the Verlet algorithm [24]. System size effects are minimized by using a molecule-centered gradual switching of the forces at the maximum possible switching distance consistent with the boundary conditions, using a switching function with continuous derivatives at the boundaries.

3. Results and discussion

Figure 1 presents the calculated potential of mean force (PMF) in the gas phase in order to provide quantitative information about the distance of optimal approach of the ions, taking into account steric/repulsive interactions and ions' polarizabilities. This distance corresponds to the location of the minima in the PMFs, which are at 3.40 Å, 4.10 Å and 4.45 Å for the ion pair formed between TMA$^+$ and F$^-$, Cl$^-$ and I$^-$, respectively. Asymptotic extrapolation of the curves to infinite separation gives for the free energy difference between the minima and the fully dissociated ion pairs the values 89.7 kcal/mol, 77.5 kcal/mol and 72.7 kcal/mol for F$^-$, Cl$^-$ and I$^-$, respectively.
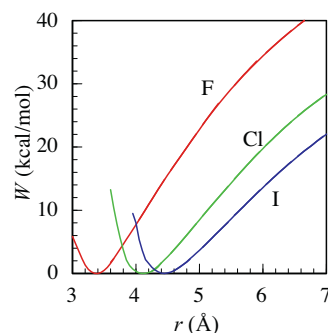

Figure 1. The potential of mean force for the tetramethyl ammonium (TMA) cation–halide ion pairs in vacuum at 298 K. r is the distance between the halide ion and the nitrogen atom of TMA.

The PMFs calculated in bulk water (including the entropic correction mentioned above) for these three ion pairs are depicted in Figure 2. $W = 0$ is taken to be the complete dissociative state for each ion pair. Clearly, the significant hydration of the halide ions in water completely changes the shape of the free energy profile, making the dissociative state more stable and removing the deep minimum observed in Figure 1. However, while the TMA$^+$–F$^-$ PMF in bulk water is purely repulsive, the TMA$^+$–Cl$^-$ exhibits a broad plateau/inflection point at a distance that is 1–1.5 Å outside the location of the PMF minimum in a vacuum, and the TMA$^+$–I$^-$ PMF exhibits a small barrier at a distance that is about 1.3 Å outside the location of the PMF minimum in a vacuum. Clearly, this suggests some weak affinity between the TMA$^+$ and the larger halide ions, consistent with the experimental observations [13]. The observation that the local minimum in $W(r)$ is positive suggests that the contact ion pair is less stable than the dissociated ions, so that the concentration of the halide ions near the cation is less than in the surrounding solution. We note that in a recent detailed study of halide anions pairing with NH$_4^+$ and with alkylated ammonium cations in water, Jungwirth and coworkers calculated the TMA$^+$–X$^-$ (X = F, Cl, Br, I) pair correlations $g_{TMA-X}(r)$ in finite concentration solutions [12] and found a significant peak in $g_{TMA-X}(r)$ at around 5 Å in the case of X = Cl, Br, I. While the PMFs in Figure 2 also suggest affinity for pairing, it is somewhat weaker. In the case of iodine, the free energy difference between the contact ion pair and the dissociated state is +1 kcal/mol, while the values inferred from the $g(r)$ given in Ref. [12] is −1 kcal/mol. This could be due to the different potential energy functions used, specifically the non-polarizable model of the iodine ion. Similar results were found in an earlier study of a finite concentration of tetraalkylammonium bromide and chloride by Slusher and Cummings [27] and more recently by Krienke et al. [28] (who have used the ion–ion pair correlations to estimate the PMF using an implicit solvent approach). Earlier study
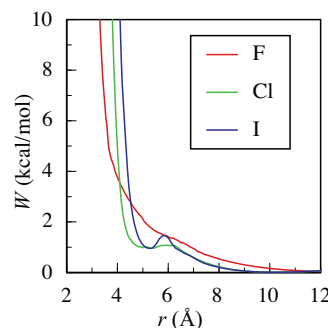

Figure 2. The potential of mean force for several TMA–halide ion pairs in water at 298 K. r is the distance between the halide ion and the nitrogen atom of TMA.