Solvation structure and dynamics of ions in concentrated urea solution

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A B S T R A C T

The solvation structure and dynamics of ions and a neutral hydrophobic solute in aqueous urea solutions are investigated using classical molecular dynamics simulations. Our results are analyzed in terms of varying concentrations ranging from pure water to ~6.9 M solution of urea. It is found that except K^+, other ions prefer to interact with water molecules in the solution irrespective of their charge and size whereas the neutral solute does not prefer to interact either with water or urea. The calculated diffusion coefficient values show comparatively slower dynamics for ions than the neutral solute in aqueous urea mixtures. The residence time of ions in water is found to be increased with increasing urea concentration whereas for the neutral solute it remains same for the entire range of urea concentration. There is no significant change observed for the structural relaxation time and lifetime of hydrogen bonded water molecules in the solution.

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1. Introduction

Urea is a product of nitrogen metabolism [1] and is accumulated by some species as a major blood and intracellular osmolyte. Some animals even accumulate a considerably high amount of urea as an osmotic adaptation in response to the decreased water availability in the environment [2]. The actions of urea on the macromolecules are fundamentally driven by the microscopic and macroscopic properties of aqueous urea. Hence, the curiosity in knowing this mechanism has triggered a lot of rigorous studies on the properties of aqueous urea [3–21]. The solubility of urea in water was explained by its ability to form hydrogen bonds which counts up to eight in number with water molecules [22]. It was suggested by Mountain and Thirumalai, through the analysis of urea–water pair functions that the nitrogen on urea will be unable to participate in hydrogen bonding (due to excluded volume) and hence the charge on nitrogen has no direct significance in urea solvation in water [22]. Using the polarization-resolved mid-infrared pump-probe spectroscopy, it was shown that there is a slower anisotropy decay with the increase in the concentration of urea and it was postulated to be the effect of immobilized water molecules that are doubly hydrogen bonded to urea [23]. But recently, simulation studies of Skinner et al. revealed that the slowdown was rather due to the excluded volume effect [24]. According to the MD simulations of Kuharski and Rossky, there is just a minor difference between water in the bulk and in the vicinity of urea, which showed that there is hardly any urea induced water–water interaction [25]. Though the local structural properties of water within the solvation shell of urea were investigated extensively by using both experiments and computer simulation studies, still there

are controversies in the understanding of the role of urea in aqueous urea solution. Some studies suggested that urea enhances water structure [19,26] whereas many others concluded that urea has negligible effects on water structure [27–29], as also suggested by IR experiments [23,30]. It has also been reported that urea induces a distortion of the tetrahedral arrangements of water molecules [31]. Recently, Chowdhuri et al. [32] studied the effects of co-solutes concentration on the hydrogen bonding structure and dynamics of aqueous N-methyl acetamide (NMA) solution. It was observed that, though the number of four-hydrogen-bonded water molecules decreases significantly in concentrated urea solution but the change in lifetime and structural relaxation times of water–water and water–urea hydrogen bonds are not significant when compared with other co-solutes, like tetramethyl urea (TMU) and trimethylamine N-oxide (TMAO).

Since water–urea mixtures are important solvent media in both chemistry and biochemistry, it is also important to understand that how the solute particles of different charge and size will behave in these mixed solvents. Like urea mediated destabilization of proteins, the kosmotropic (structure making) and chaotropic (structure breaking) effect of ions have been studied widely and is often correlated to protein stability. According to the Hofmeister series [33], which assists in predicting the minimum concentration of the ion that causes precipitation of a protein, some ions (e.g. K^+, Na^+, Mg^{2+}, Ca^{2+}, Cl^- etc.) have destabilizing effect on macromolecules [2]. So, the fundamental knowledge of the ion solvation in water–urea mixture would be useful in the study of their destabilizing effect on macromolecules. Using RISM theory and MD simulations study, Patey et al. [34] reveals several interesting facts about the preferential solvation of urea. Both TIP4P [35] and SPC/E [36] water models are used along with the OPLS potential parameter of urea, and it was observed that the hydration structure in the water–urea mixtures is insensitive to the water model. The study suggested that

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urea favors interaction with the electrically positive parts in the amino acid residues of native protein and thus denaturation process get started.

In this work, apart from the solvation behavior of ions, we also address the dynamical properties by investigating the tracer diffusion coefficients and residence times of five biologically important ionic solutes (Na^+, K^+, Ca^{2+}, Mg^{2+} and Cl^-) and a neutral hydrophobic solute (Cl^0) for many different composition of the water–urea mixtures ranging from pure water to ~6.9 M aqueous urea solution. Clearly, the present study can be considered as complementary to the earlier theoretical work on ion solvation in a water–urea mixture [34], where these dynamical properties of the solutes in the mixtures were not addressed.

2. Models and simulation details

Our calculations are based on multisite interaction models of urea and water molecules, and each solute particle consists of a single interaction site. In this model, the interactions between atomic sites of two molecules or between a solute and an atomic site are expressed as

$$u(r_i, r_j) = 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^6\right] + \frac{q_i q_j}{r_{ij}} \quad (1)$$

where, q_i is the charge of the i-th atom. The Lennard–Jones parameters σ_{ij} and ε_{ij} are obtained by using the combination rules $\sigma_{ij} = (\sigma_i + \sigma_j)/2$ and $\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}$, where σ_i and ε_i are the Lennard–Jones diameter and well-depth parameter for i-th atom. In the case of urea, we have used OPLS potential parameters proposed by Duffy et al. [37] For water, the extended simple point charge (SPC/E) potential [36] is considered where each water molecule consists of a Lennard–Jones interaction site located on oxygen and three charge interaction sites located on oxygen and two hydrogen atoms. The ionic solutes (Na^+, K^+, Ca^{2+}, Mg^{2+} and Cl^-) are considered as charged Lennard–Jones particles [38, 39] whereas the neutral hydrophobic solute (Cl^0) is modeled simply as a Lennard–Jones particle. The values of the potential parameters q_i, σ_i, and ε_i for solvents (urea and water) and solutes are available in the literature and also summarized in Table 1.

The simulations were carried out in a cubic box with a total of 255 solvent particles of urea and water along with a single solute. In the present study, for each solute, we have considered six different values of urea concentration: C_{urea} (mole/l) = 0.0, 1.052, 2.057, 3.741, 5.455 and 6.867 M. In addition, we have also simulated two different systems, a single Mg^{2+} dissolved in 8.336 M concentrated urea solution, and a single urea in water. Thus, altogether we have simulated 38 different systems in this present study. In all the simulations, the minimum image convention for calculation of the short range Lennard–Jones interactions were employed. The long range electrostatic interactions were treated using the Ewald method [40]. We employed the quaternion formulation of the equations of rotational motion and for the

integration over time, we adapted the leap-frog algorithm with time step of 10^{-15} s (1 fs). In order to find the appropriate box size for a given pressure and temperature, we first carried out MD runs of 600–800 ps at constant pressure by employing the weak coupling scheme of Berendsen et al. [41] During this initial phase of the simulations, the volume of the simulation box was allowed to fluctuate and the average volume was determined at the end of the simulation. Subsequently, we carried out simulations in microcanonical ensemble keeping the box size fixed at the average value obtained previously for a given system at a given temperature and pressure. While carrying out the simulations in microcanonical ensemble, each system was equilibrated for 2–3 ns and the simulations were run for another 8–10 ns for the calculation of the structural and dynamical quantities. The average values of the pressure and temperature of a system during the production phase of each simulation were found to be very close to the previously chosen pressure and temperature for that particular system. Some of the simulation results of ionic aqueous urea solution, such as density, volume, average pressure and potential energy are given in Table 2.

3. Results and discussion

3.1. Structure of solvation shell and translational diffusion of ions

The structure of the solvation shell of different solutes in aqueous urea solution is investigated by calculating radial distribution functions of various atomic sites of urea and water molecules around solutes. We have calculated these quantities for all ionic and neutral solutes for all different urea concentrations. Although we have calculated all possible radial distribution functions between solutes and different atomic sites of the solvents, here we present only very few of them which reveal a clear picture of concentration dependent distribution of water and urea molecules around the solutes. These are the Na^+-oxygen (water) and Na^+-oxygen (urea) shown in Fig. 1, K^+-oxygen (water) and K^+-oxygen (urea) shown in Fig. 2, Cl^--hydrogen (water) and Cl^--hydrogen (urea) shown in Fig. 3, Mg^{2+}-oxygen (water) and Mg^{2+}-oxygen (urea) shown in Fig. 4, Ca^{2+}-oxygen (water) and Ca^{2+}-oxygen (urea) shown in Fig. 5, and finally for neutral solute the distribution functions Cl-oxygen (water) and Cl-oxygen (urea) are shown in Fig. 6. It is observed that either for ionic or neutral solutes, as urea is added to the solution, the peak height of the ion–oxygen (water) and ion–hydrogen (water) radial distribution function increases but the position of the peak remains unchanged. The fact indicates that the water molecules have preference over urea for staying in the vicinity of the ions. It is found that ions, either positive or negative, form a strong first solvation shell surrounded by the opposite charge site of the solvent molecules and the presence of second solvation shell at around 4.5–5.0 Å, is also significant due to the formation of hydrogen bonds between the water and urea molecules. Almost all cases, monovalent ions (Na^+, K^+ and Cl^-), show strong affinity towards urea with increasing urea concentration in the solution, and particularly it is quite significant in case of potassium ion. The well-defined second maxima at r = 3.65 Å for anion–hydrogen (water) radial distribution function shown in Fig. 3(a), indicates that the solvation structure is extended with well-defined second coordination sphere preferably by water molecules for

Table 1
Values of Lennard–Jones and electrostatic interaction potential parameters for urea, water and ions, e represents the magnitude of electronic charge.

Name	Atom/Ion	σ (Å)	ε (kJ/mol)	Charge (e)
Urea	C	3.75	0.4396	0.142
	O	2.96	0.8793	−0.390
	N	3.25	0.7118	−0.542
	H	0.0	0.0	0.333
Water	O	3.166	0.6502	−0.8476
	H	0.0	0.0	+0.4238
Ion	Na^+	2.583	0.4184	+1.0
	K^+	3.331	0.4184	+1.0
	Cl^-	4.401	0.4184	−1.0
	Cl	4.401	0.4184	0.0
	Ca^{2+}	2.869	0.4184	+2.0
	Mg^{2+}	1.885	0.4184	+2.0

Table 2
The density, average volume (V), pressure (P) and potential energy (PE) of ionic aqueous urea solutions. The average value is calculated here with respect to monovalent ions (e.g. Na^+, K^+ and Cl^-), and the standard deviation is included due to different solutes.

Conc^n. (M)	Density (gm/cm^3)	V ($\times 10^{-6}$ m^3)	P (MPa)	PE (kJ/mol)
0.0	0.9907	18.110	0.43 ± 3.8	−47.05 ± 0.18
1.052	1.0112	18.556	2.27 ± 3.8	−47.73 ± 0.17
2.057	1.0317	18.983	6.60 ± 3.2	−48.45 ± 0.18
3.741	1.0618	19.836	4.37 ± 3.3	−49.78 ± 0.18
5.455	1.0935	20.764	4.38 ± 3.38	−51.35 ± 0.19
6.867	1.1189	21.614	2.77 ± 3.20	−52.81 ± 0.18