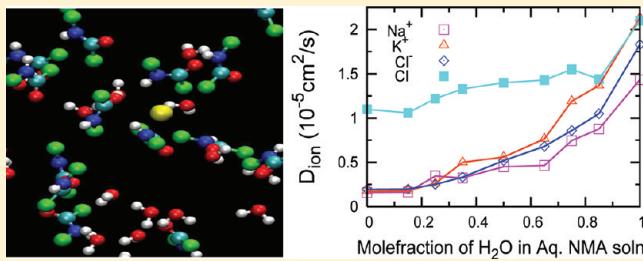


Effect of Water on Solvation Structure and Dynamics of Ions in the Peptide Bond Environment: Importance of Hydrogen Bonding and Dynamics of the Solvents

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ABSTRACT: The solvation structure and dynamics of ions in aqueous *N*-methylacetamide (NMA) solutions are calculated using classical molecular dynamics simulations. Our results are analyzed in terms of varying composition ranging from pure NMA to pure water. We also examined the effect of varying water content on the structure and dynamics of a neutral solute. Altogether we have simulated 38 different systems in the present work. It is found that water molecules have preference over NMA for the ions irrespective of their charge and size, whereas the neutral solute is preferably solvated by methyl groups of NMA. The calculated self-diffusion coefficient values show comparatively slower dynamics for ions than the neutral solute which can be attributed to the stronger solvation of ions in aqueous NMA mixtures. Various dynamical properties associated with translational and rotational motion of solvents are also calculated, and similar slower dynamics of solvents is observed which can be attributed to the enhanced stability of the hydrogen bonds and formation of interspecies complexes in the mixtures.



1. INTRODUCTION

Proteins are polymers of amino acids that attain well-defined three-dimensional structures both in solution and in biological cells. The *N*-methylacetamide (NMA) molecule contains a single amide group and can represent the protein as a model peptide group linkage and has been the subject of extensive experimental^{1–6} and theoretical investigations.^{7–16} The strong hydrogen bond cooperativity in liquid NMA and its structure and dynamics at different thermodynamic conditions have also been studied previously.^{17–22} Recently, Chowdhuri and co-workers²⁰ have studied extensively the structure, dynamics, and hydrogen bond properties of liquid NMA at different temperatures ranging from 303.5 to 454 K with varying pressures from 0.1 to 300 MPa. It is observed that the number of hydrogen bonds increases with application of pressure at a given temperature, whereas the calculated hydrogen bond energy shows that the stability of the hydrogen bond decreases with an increase in pressure and temperature. The calculated self-diffusion coefficient of NMA is found to be in excellent agreement with the experiment, and the behavior is non-Arrhenius at low temperatures with application of pressures, whereas the orientation relaxation times follow the Arrhenius behavior. Currently, the group presented the behavior of alkali metal ions and some other cations, halide ions in liquid NMA²³ at 313 and 453 K. The calculated self-diffusion coefficient values from the simulations are in very good agreement with the experimental observations. In the present study, aqueous NMA solution is considered due to its importance for the interpretation of the properties of peptides in aqueous solutions. NMA is highly unusual with respect to many of its physical properties and especially when water mixtures are considered.^{24,25}

The density²⁵ of water–NMA mixtures shows a maximum and a minimum with respect to composition at 303 K, whereas the viscosity²⁵ exhibits a large maximum at approximately 0.5 mol fraction at temperatures of 303–313 K which suggests a high degree of association or complex formation between the peptide dipole and water. Since water–NMA mixtures are important polar solvent media in chemistry, it is also very important to understand how the solute particles of different nature behave in these mixed solvents. Also, for a better understanding of the structural and biological function of proteins, it is important to know how the aqueous environment is interacting with it through hydrogen bonding. There have been a number of papers published on NMA–water interactions in aqueous NMA solution.^{26–55} Panuszko et al.²⁷ studied the hydration behavior of different amides including NMA by means of FT-IR spectra and molecular dynamics simulation. It is observed that the energetic stability of water H-bonds in the NMA hydration sphere is higher compared to the other amides, such as *N,N*-dimethylacetamide, acetamide, *N*-methylformamide, *N,N*-dimethylformamide, and formamide. The experimental and theoretical evidence shows that the NMA and its hydrogen-bonded water molecules are vibrationally coupled.²⁸ The strength of hydrogen-bonded amide–amide is more than that for amide–water and water–water obtained by statistical mechanics calculations.²⁹ However, Mitchell and Price have shown that the amide–amide and amide–water interactions should be approximately isoenergetic.³⁰ On

Received: June 27, 2011

Revised: September 26, 2011

Published: October 05, 2011

the experimental side, there is evidence that the amide–water interactions are stronger than the water–water interactions.^{31,32} UV Raman studies^{33,34} and normal coordinates analysis³⁵ have shown that water molecules are hydrogen bonded to the amide hydrogen and the carbonyl oxygen of NMA. Heat of solution and partial-pressure measurements indicate that the hydrogen bonding to the carbonyl oxygen is stronger than that of amide hydrogen.^{31–36} Guo and Karplus³⁷ studied several NMA water complexes by using ab initio quantum mechanical methods. Water molecules cooperatively bind to the peptide group, and the hydrogen bond increases the methyl rotational barriers. There are three hydrogen-bonding sites on an NMA molecule: two on the C=O group and one on the NH group.^{26,37} Four different conformers of *trans*-NMA exist in aqueous solution depending on their Ψ , Φ angle considering the rotation between the methyl groups.^{37–40} It is reported that among the four conformers the conformer with torsion angle $\Psi = 0^\circ$, $\Phi = 180^\circ$ is most stable in aqueous solution. To study the hydrogen bond interactions in the NMA–water mixtures, the potential energy surface is determined by the interactions of entire peptide groups or water molecules rather than by a single donor and acceptor groups.⁴¹ The majority of the works in aqueous NMA solution have been focused on how the amide vibrations of NMA can be changed by the interaction with surrounding solvent molecules.^{42–54} The recent realistic model^{53,54} which is a combination of the density functional theory and molecular dynamics can reproduce the observed temperature-dependent amide I vibration in aqueous NMA solution.⁵⁵ On the other hand, protein destabilization by various chemical agents (such as certain common salt solutions and one of the most denaturant, urea) is also a subject of interest. Recent studies have shown how the urea and other salt solutions in water interact with the protein backbone^{56–62} and with the aromatic side chain.^{63–69}

In the context of present study, we must include the work of Jungwirth and co-workers,⁷⁰ where the structure of the solvation shell of ions is investigated in concentrated salt solutions of aqueous NMA. It is found that irrespective of the charge and size the ionic solutes prefer water over NMA. It is also observed that, in comparison to K⁺, Na⁺ has a stronger affinity toward the carbonyl oxygen of the amide group, whereas none of the halide anions show any appreciable attraction for amide hydrogen. The structure and hydrogen bond properties of aqueous NMA solutions have been studied extensively by Allison and co-workers.⁷¹ It is suggested that water structure can be changed significantly by the addition of even small quantities of NMA. The weak C–H···O contacts in NMA dimers⁷² and between NMA and water in aqueous NMA solutions⁷³ were studied by molecular dynamics simulations and NMR experiment. The variation of rotational dynamics of NMA dissolves in water and CCl₄ studied as a function of concentration using optically heterodyne-detected optical Kerr-effect (OHD-OKE) and far-infrared spectroscopy.⁷⁴ The sudden decrease of rotational diffusion times of NMA is observed for both the solvents upon dilution. Rezus and Bakker⁷⁵ studied the orientational dynamics of water in aqueous NMA solution and found that the fraction of water molecules shows bulk-like orientational dynamics 2.5 ps, whereas immobilized water molecules show greater than 10 ps.

In this work, we have made an attempt to study the molecular dynamics simulations of a series of aqueous NMA systems including an ion or a neutral solute at varying composition ranging from pure NMA to pure water. The main purpose is to investigate the effects of solvent mixtures on the solvation structure

Table 1. Values of Lennard-Jones and Electrostatic Interaction Potential Parameters for NMA, Water, and Ions^a

name	atom/ion	σ (Å)	ε (kJ/mol)	charge (e)
NMA	C	3.75	0.4396	0.50
	CH ₃ (C)	3.91	0.6699	0.0
	O	2.96	0.8793	-0.50
	N	3.25	0.7118	-0.57
	CH ₃ (N)	3.80	0.7118	0.20
	H	0.0	0.0	0.37
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

^a e represents the magnitude of electronic charge.

and dynamics of solutes in a different nature. We have calculated the self-diffusion coefficient values for different solutes along with the radial distribution function of ion and different atomic sites of the solvents in aqueous NMA mixtures. In addition to that, we have also calculated intra- and interspecies hydrogen bonds and translational and rotational diffusion coefficients of solvents at varying composition.

The paper is organized as follows. In Section 2, we describe the model and simulation details. In Section 3.1, we present the structure of solvation shell and translational diffusion of ions. The hydrogen bond properties and translational and rotational diffusion of solvent molecules are presented in Section 3.2, whereas our conclusions are summarized in Section 4.

2. MODELS AND SIMULATION DETAILS

Our calculations are based on multisite interaction models of N-methylacetamide 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 $\varepsilon_{ij} = (\varepsilon_i \varepsilon_j)^{1/2}$, where σ_i and ε_i are the Lennard-Jones diameter and well-depth parameter for the i -th atom. We have used OPLS potential parameters for NMA.⁷⁶ The methyl group is assumed to be a single interaction site, and thus hydrogen atoms of the methyl group are not considered explicitly. For water, the extended simple point charge (SPC/E) potential⁷⁷ is considered where each water molecule consists of a Lennard-Jones interaction site located on oxygen and three charge interaction sites are located on oxygen and two hydrogen atoms. The rigid geometry and the values of the potential parameters q_p , σ_p , and ε_p are given in refs 76 and 77, respectively, for NMA and water and are also summarized in Table 1. The ionic solutes (Na⁺, K⁺, and Cl⁻) are considered as charged Lennard-Jones particles, whereas the neutral atomic solute (Cl) is modeled simply as a Lennard-Jones particle. The corresponding

Table 2. Average Potential Energy (PE), Average Volume (V), and Average Pressure (P) of Ionic Aqueous NMA Solutions

X_w	PE (kJ/mol)	$V (\times 10^{-6} \text{ m}^3)$	P (MPa)
0.0	-62.09 ± 0.15	77.016	0.34 ± 0.2
0.15	-59.45 ± 0.15	68.096	1.05 ± 0.5
0.25	-57.63 ± 0.14	62.240	0.40 ± 0.3
0.35	-56.08 ± 0.16	56.370	0.60 ± 0.4
0.50	-53.65 ± 0.13	47.306	0.70 ± 0.6
0.65	-51.51 ± 0.14	38.483	2.96 ± 1.5
0.75	-50.13 ± 0.15	32.781	1.60 ± 1.2
0.85	-48.71 ± 0.13	26.771	1.50 ± 1.3
1.0	-46.96 ± 0.15	18.103	0.95 ± 0.8

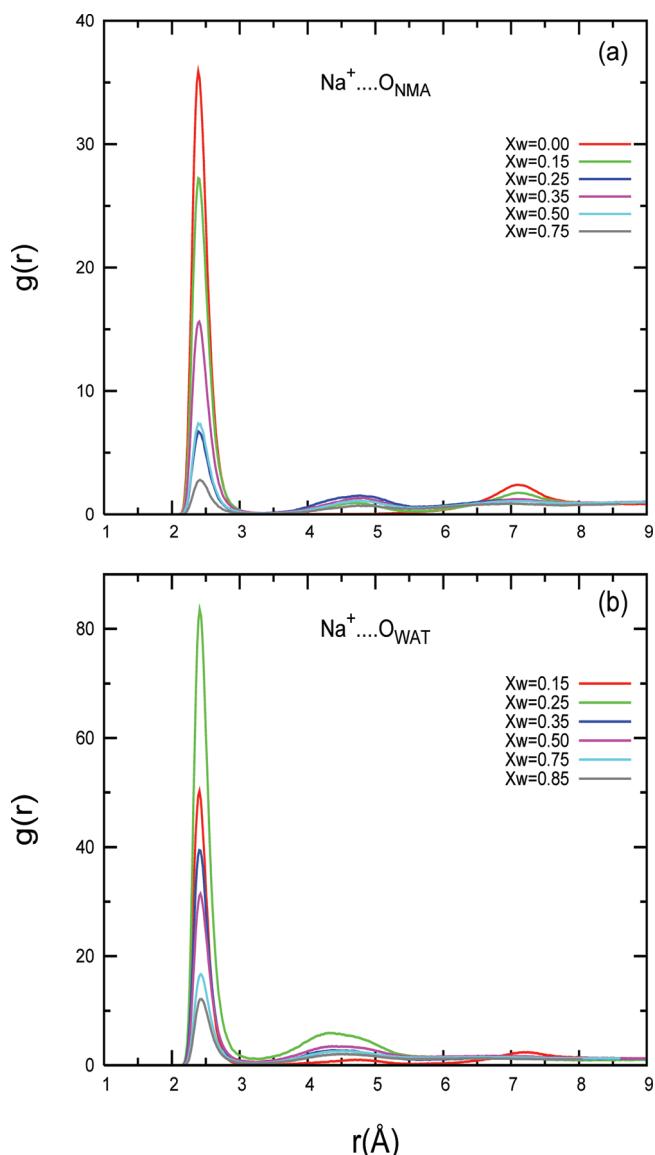


Figure 1. Na^+ –oxygen (NMA) and Na^+ –oxygen (water) radial distribution functions for varying composition of the NMA–water mixtures.

potential parameters for these solutes are available in refs 78 and 79 and also included in Table 1.

The simulations were carried out in a cubic box with a total of 255 solvent particles of *trans*-N-methyl acetamide and water along with a single solute. The composition of each solvent mixture is characterized by the mole fraction of water (X_w). In the present study, for each solute, we have considered nine different values of water mole fraction: $X_w = 0.0, 0.15, 0.25, 0.35, 0.50, 0.65, 0.75, 0.85$, and 1.0. In addition, we have also simulated two more systems with a single water dissolved in 255 NMA and a single NMA dissolved in 255 water molecules to calculate the dynamical properties of water and NMA in the limiting concentrations of $X_w = 0$ and 1.0, respectively. Thus, altogether we have simulated 38 different systems in this present study. In all the simulations, the minimum image conventions for calculation of the short-range Lennard-Jones interactions were employed. The long-range electrostatic interactions were treated using the Ewald method.⁸⁰ We employed the quaternion formulation of the equations of rotational motion, and for the integration over time, we adapted the leapfrog algorithm with time step of 10^{-15} s (1 fs). The production phase of all the simulations was run in a microcanonical ensemble but with varying box size. To find the appropriate box size for a desired pressure at a given temperature, we first carried out MD runs of 400–600 ps at constant pressure by employing the weak coupling scheme of Berendsen et al.⁸¹ 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 a 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 the microcanonical ensemble, each system was equilibrated for 400–800 ps, and the simulations were run for another 1.6–2 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 NMA systems, such as average potential energy, average volume, and pressure, are given in Table 2. The deviation indicated in Table 2 is due to the presence of different solute particles in the system.

3. RESULTS AND DISCUSSION

3.1. Structure of the Solvation Shell and Translational Diffusion of Ions. The structure of the solvation shell of different solutes in aqueous NMA solution is investigated by calculating radial distribution functions of various atomic sites of NMA and water molecules around solutes. We have calculated these quantities for all ionic and neutral solutes with different water–NMA composition. Although we have calculated all possible radial distribution functions between solutes and different atomic sites of the solvents, here we present only a very few of them which reveal a clear picture of composition dependence distribution of water and NMA molecules around the solutes. These are the Na^+ –oxygen (NMA) and Na^+ –oxygen (water) shown in Figure 1, Na^+ –hydrogen (NMA) and Na^+ –hydrogen (water) shown in Figure 2, K^+ –oxygen (NMA) and K^+ –oxygen (water) shown in Figure 3, K^+ –hydrogen (NMA) and K^+ –hydrogen (water) shown in Figure 4, Cl^- –oxygen (NMA) and Cl^- –oxygen (water) shown in Figure 5, and Cl^- –hydrogen (NMA) and Cl^- –hydrogen (water) shown in Figure 6, and finally for neutral solute the distribution functions $\text{Cl}-\text{CH}_3(\text{C})$ and $\text{Cl}-\text{CH}_3(\text{N})$

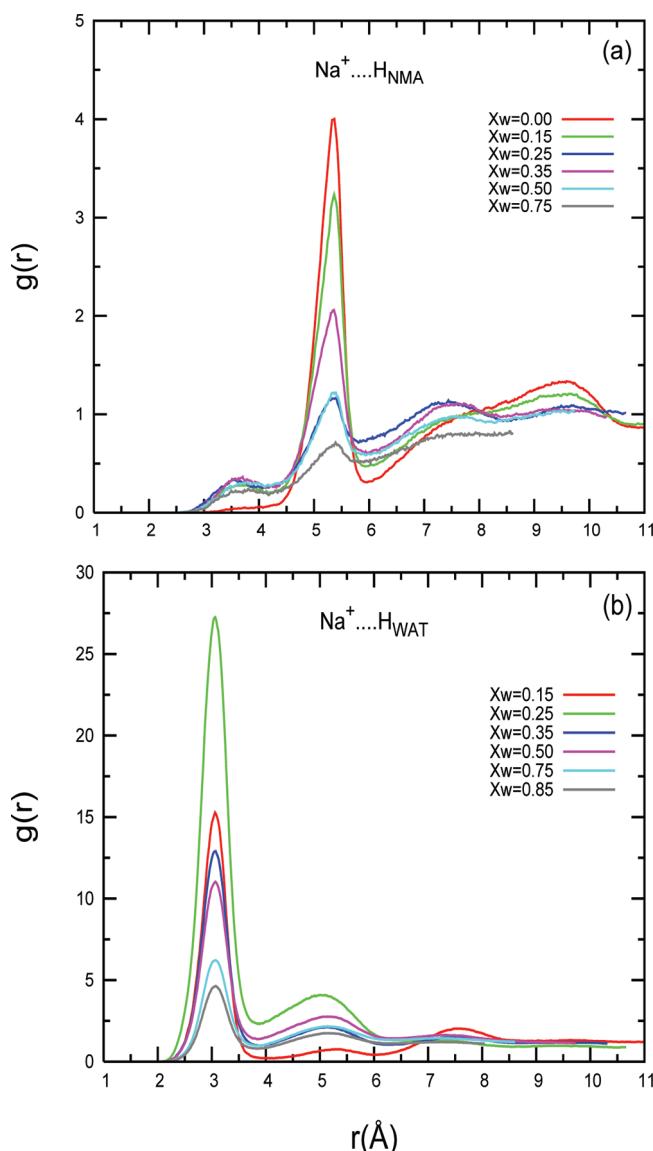


Figure 2. Na^+ –hydrogen (NMA) and Na^+ –hydrogen (water) radial distribution functions for varying composition of the NMA–water mixtures.

of NMA are shown in Figure 7. It is observed that for positive and negative ions, as water is added to NMA, the peak height of the ion–oxygen (NMA) and ion–hydrogen (NMA) radial distribution function decreases, but the positions of the peaks remain unchanged. A similar fashion is also observed for ion–oxygen (water) and ion–hydrogen (water) radial distribution functions when water is added to NMA but the peak heights are higher in value which indicates that the water molecules have preference over NMA for staying in the vicinity of the ions. In pure NMA, the ion forms a strong first solvation shell surrounded by the opposite charge site of the solvent molecules, and the presence of a second solvation shell at around 7 Å is also significant due to the formation of hydrogen bonds between the NMA molecules. Gradually, the water molecule will occupy this place when water is added to the system. The peak at around 7 Å will disappear, whereas a new peak will appear at around 5 Å due to NMA–water hydrogen bonds. Significantly, the higher peak particularly at $X_w = 0.25$ for Na^+ and $X_w = 0.35$ for K^+ indicates that the

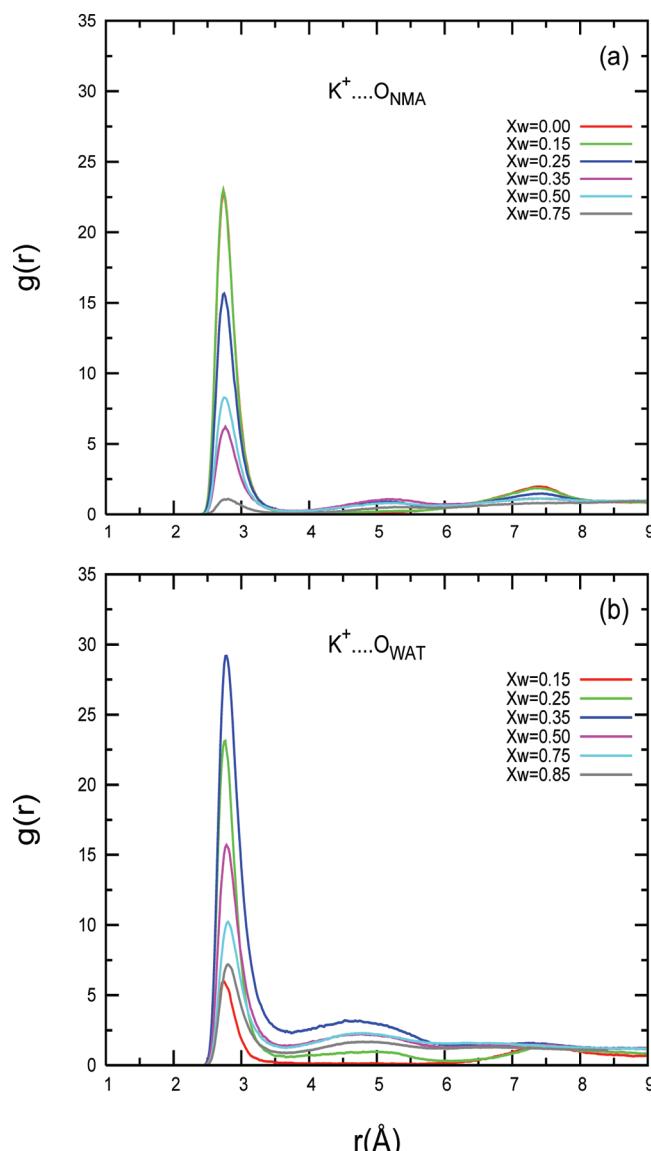


Figure 3. K^+ –oxygen (NMA) and K^+ –oxygen (water) radial distribution functions for varying composition of the NMA–water mixtures.

stronger water dominated the first solvation shell of the respective ions. The well-defined second maxima at $r = 3.62$ Å for the anion–hydrogen (water) radial distribution function shown in Figure 6(b) indicates that the solvation structure is extended with the well-defined second coordination sphere preferably by water molecules for all the compositions. On the other hand, the neutral solute is preferably solvated by methyl groups of NMA and is shown in Figure 7. The snapshot of a closer view of a solute in an aqueous NMA solution is shown in Figure 8.

The translational motion of ion in aqueous NMA solutions is analyzed using the velocity–velocity autocorrelation function (VAF), $C_v(t)$, defined by

$$C_v(t) = \frac{\langle \mathbf{v}_i(t) \cdot \mathbf{v}_i(0) \rangle}{\langle \mathbf{v}_i(0) \cdot \mathbf{v}_i(0) \rangle} \quad (2)$$

where $\mathbf{V}_i(t)$ is the velocity of an ion i at time t .⁸² The translational self-diffusion coefficient D_i of an ion i is calculated from the time

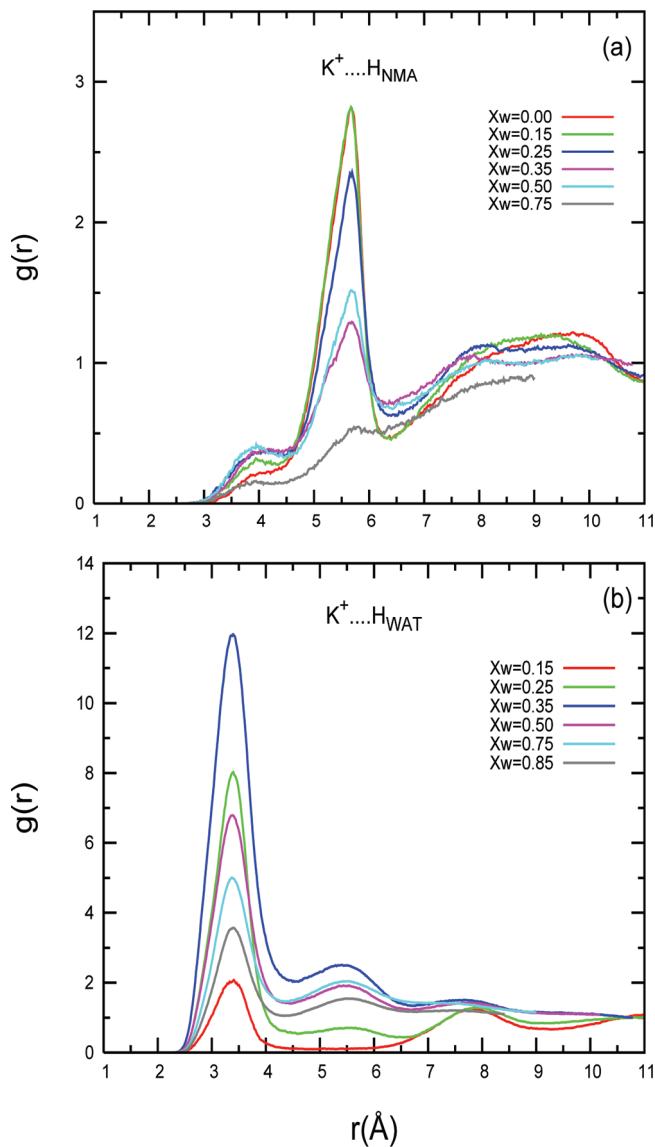


Figure 4. K^+ –hydrogen (NMA) and K^+ –hydrogen (water) radial distribution functions for varying composition of the NMA–water mixtures.

integral of the $C_\nu(t)$

$$D_i = \frac{k_B T}{m} \int_0^\infty C_\nu(t) dt \quad (3)$$

where k_B is the Boltzmann constant and m is the mass of ion i , by integrating $C_\nu(t)$ up to 2.5 ps with the time interval of 0.001 ps. In addition, the translational diffusion coefficient is calculated from the long-time limit of the mean-square displacement (MSD)

$$D_i = \lim_{t \rightarrow \infty} \frac{\langle |r(t) - r(0)|^2 \rangle}{6t} \quad (4)$$

where $r(t)$ is the position of NMA molecules at time t , by a least-squares fit of the MSD from simulation up to 30 ps. In Figures 9 and 10, we have shown the results of VAF and MSD for different solutes with varying compositions. The oscillatory behavior of the autocorrelation functions in Figure 9 is most manifest for Na^+ and less so for K^+ and Cl^- . Such behavior of the functions is

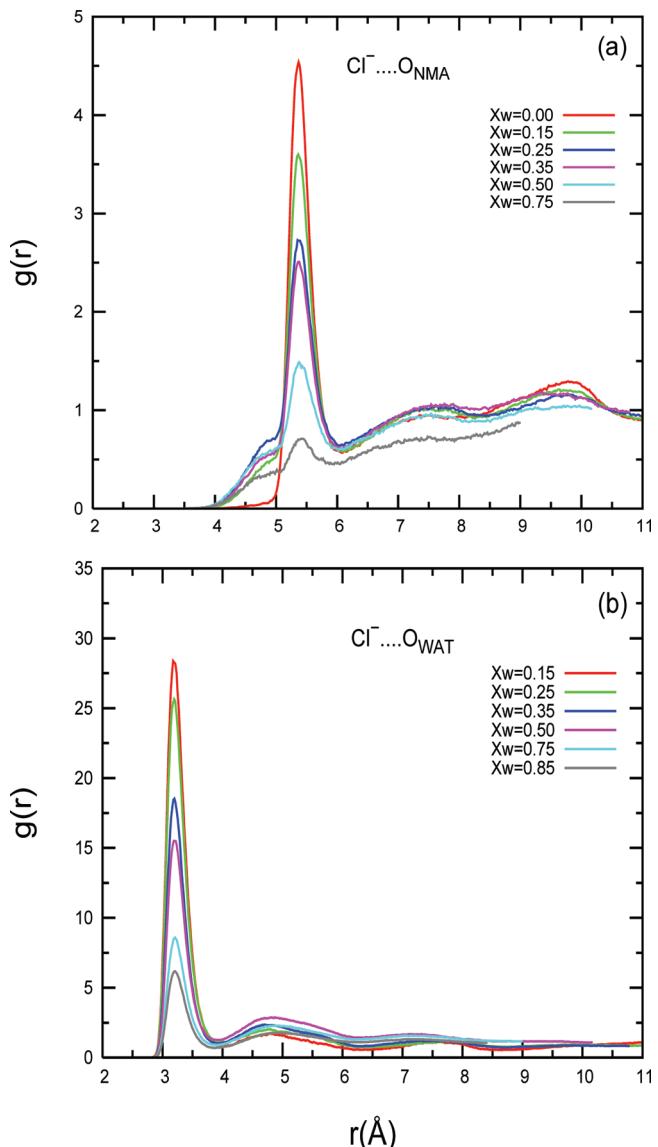


Figure 5. Cl^- –oxygen (NMA) and Cl^- –oxygen (water) radial distribution functions for varying composition of the NMA–water mixtures.

evidence of a strong influence of solvent molecules on the translational motions of Na^+ , K^+ , and Cl^- and strong coordinating ability of these ions. It can be concluded that strong dynamic cages of solvent molecules are formed around these ions. The diffusion coefficients calculated using VAF and MSD have been found to be quite close to each other, and we have taken the average of the values obtained from these two routes and shown them in Figure 11 (a). It is found that the self-diffusion coefficients of all solutes increases when water is added to the NMA, but overall increases of self-diffusion coefficients are not significant up to $X_w = 0.65$. The slower dynamics of ions in comparison with neutral solute can be explained by the stronger solvation behavior of ions in aqueous NMA solutions. To acquire a deeper understanding of the solute diffusion, the statistics and energetics of *intra* and *inter* species hydrogen bonds between the solvent molecules are known to be required, and in Section 4, we have calculated the number and energy of these different kinds of hydrogen bonds which exist in aqueous NMA solutions.

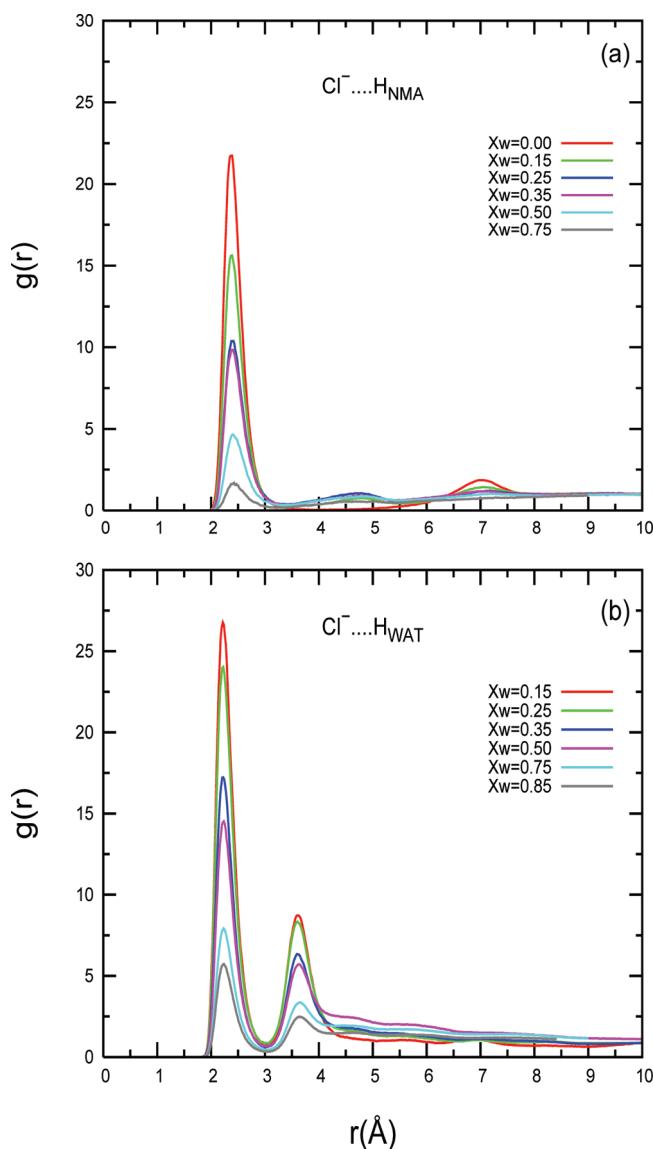


Figure 6. Cl^- -hydrogen (NMA) and Cl^- -hydrogen (water) radial distribution functions for varying composition of the NMA–water mixtures.

3.2. Self-Diffusion Coefficients and Orientational Relaxation Times of Solvent Molecules. The translational self-diffusion coefficient (D_{solv}) of the solvent molecules is calculated from the time integral of the velocity–velocity autocorrelation function as given in eq 3, where m is the mass of a solvent molecule. The integration value of $C_v(t)$ is taken up to 1.5 ps for water, whereas for NMA up to 2.5 ps is considered with the time interval of 0.001 ps. In addition, we have also calculated the translational diffusion coefficient from the long-time limit of the mean-square displacement (MSD) by a least-squares fit up to 100 ps. The diffusion coefficients calculated using these two different routes have been found to be quite close to each other, and we have taken the average of the values obtained from these two routes, which is shown in Figure 11(b). It is found that the self-diffusion coefficients of the solvent molecules decrease initially and then increase when water is added to the NMA. The standard deviation of the dynamical data presented here is about 4% of the average values for solutes and about 2% of the average values for solvent

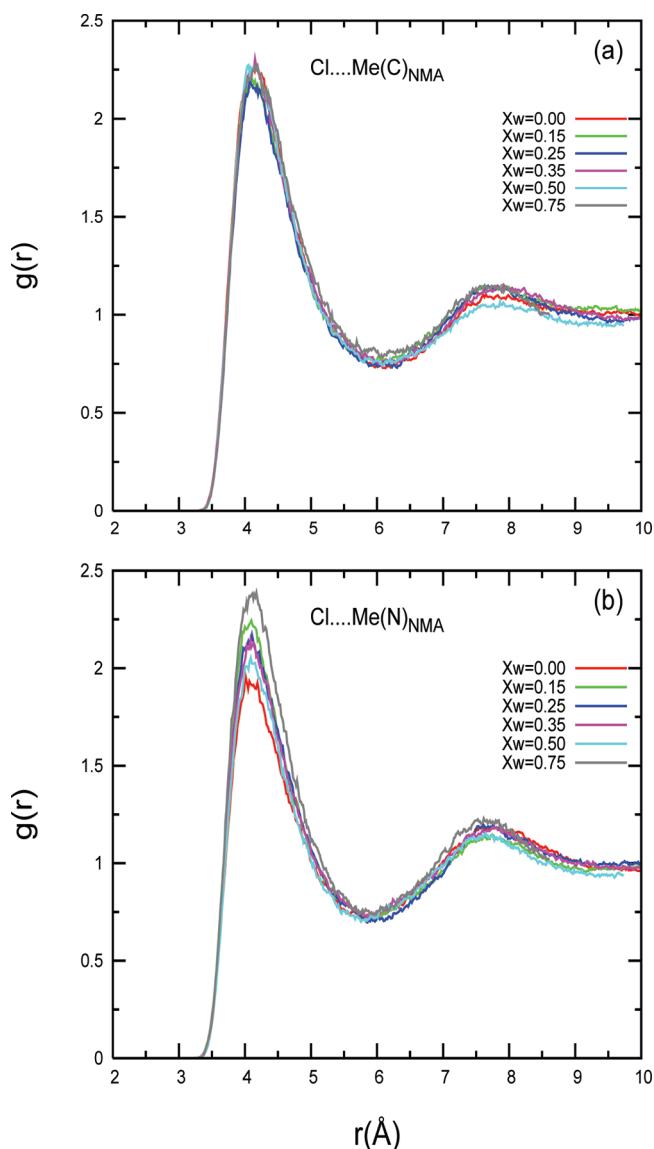


Figure 7. Cl –methyl group attached to the C atom of NMA and the Cl –methyl group attached to the N atom of NMA radial distribution functions for varying composition of the NMA–water mixtures.

molecules. The slower dynamics of the solvent molecules occur until $X_w = 0.5$, and at all compositions the water molecules diffuse faster than NMA, as expected for a smaller molecule. The slower diffusion of solvents was analyzed by calculating the number and energies of *intra* and *inter* species hydrogen bonds by using a set of geometric criteria^{20,83–88} where it is assumed that a hydrogen bond between two molecules exists, if the following distance and angular criteria are satisfied, i.e., $R_c^{(\text{OX})} < R_c^{(\text{OH})}, R_c^{(\text{OH})} < R_c^{(\text{OH})}$, and $\theta < \theta_c$. Here, $R^{(\text{OX})}$ and $R^{(\text{OH})}$ denote the oxygen (water)–nitrogen (NMA) and oxygen (water)–hydrogen(NMA) distances, and the corresponding quantities with subscript “c” denote the cutoff values. The angle $\theta (= \theta^{(\text{NOH})})$ is the nitrogen–oxygen–hydrogen angle, and the θ_c is the upper limit that is allowed for a hydrogen bond to exist between oxygen of water and the hydrogen of the NMA molecule. The cutoff values for O–N and O–H distances are determined from the positions of the first minimum of the corresponding radial distribution functions shown in Figure 12. A similar distance and angular criteria is

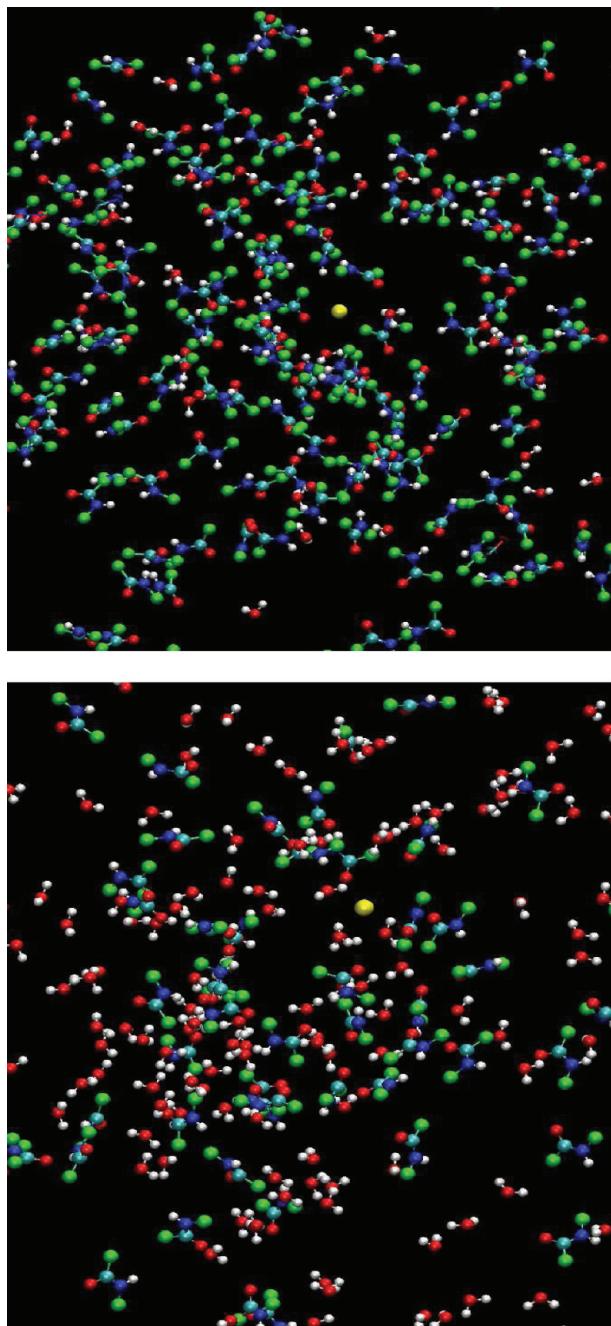


Figure 8. Snapshots of a closer view of a solute in NMA-rich (above) and water-rich (below) aqueous NMA solutions.

considered for the hydrogen bond between the carbonyl oxygen of NMA and hydrogen of a water molecule where $R^{(OX)}$ and $R^{(OH)}$ denote the oxygen (NMA)—oxygen (water) and oxygen (NMA)—hydrogen (water) distances and the corresponding cutoff values are taken from the O—O and O—H radial distribution functions shown in Figure 13. The angle θ ($=\theta^{(OOH)}$) is the oxygen—oxygen—hydrogen angle, and the θ_c is the upper limit that is allowed for a hydrogen bond to exist. Regarding the angular cutoff θ_c , we have calculated the corresponding probability $P(\cos \theta)$ for water—NMA pairs which satisfies the following distance criteria as mentioned before. In view of this distribution, we have used a cutoff of $\theta_c = 45^\circ$ both for the nitrogen—oxygen—hydrogen angle and the oxygen—oxygen—hydrogen

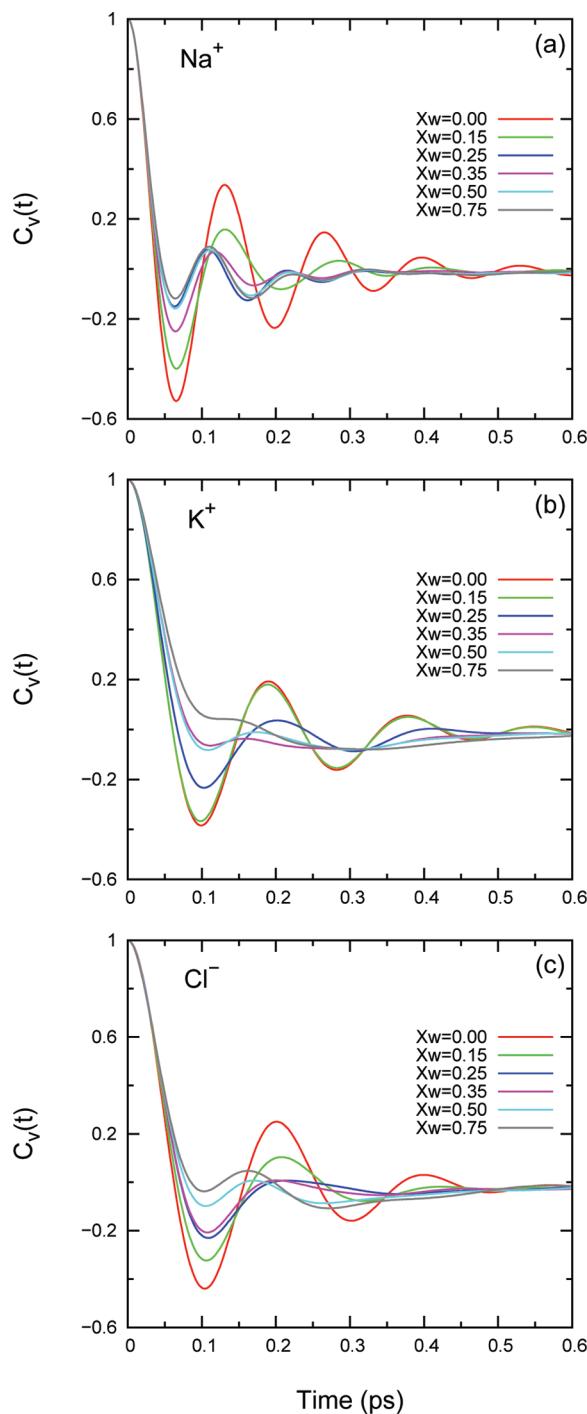


Figure 9. Time dependence of the velocity—velocity autocorrelation function of the Na^+ , K^+ , and Cl^- ions in NMA—water mixtures of varying mole fraction of water.

angle. It is found that the amide hydrogen is bonded with the oxygen of the water molecule, whereas the oxygen of the carbonyl group is hydrogen bonded with the two water molecules. So, we are expecting three *inter* molecular hydrogen bonds per NMA molecule. The distance and angular criteria for NMA—NMA²⁰ and water—water^{83,86} hydrogen bonds are taken from the earlier studies. In *geometric criteria*, generally the cutoff angle $\theta_c = 30^\circ$ is used, but to give more flexibility due to thermal motion we used the less strict definition with a cutoff angle

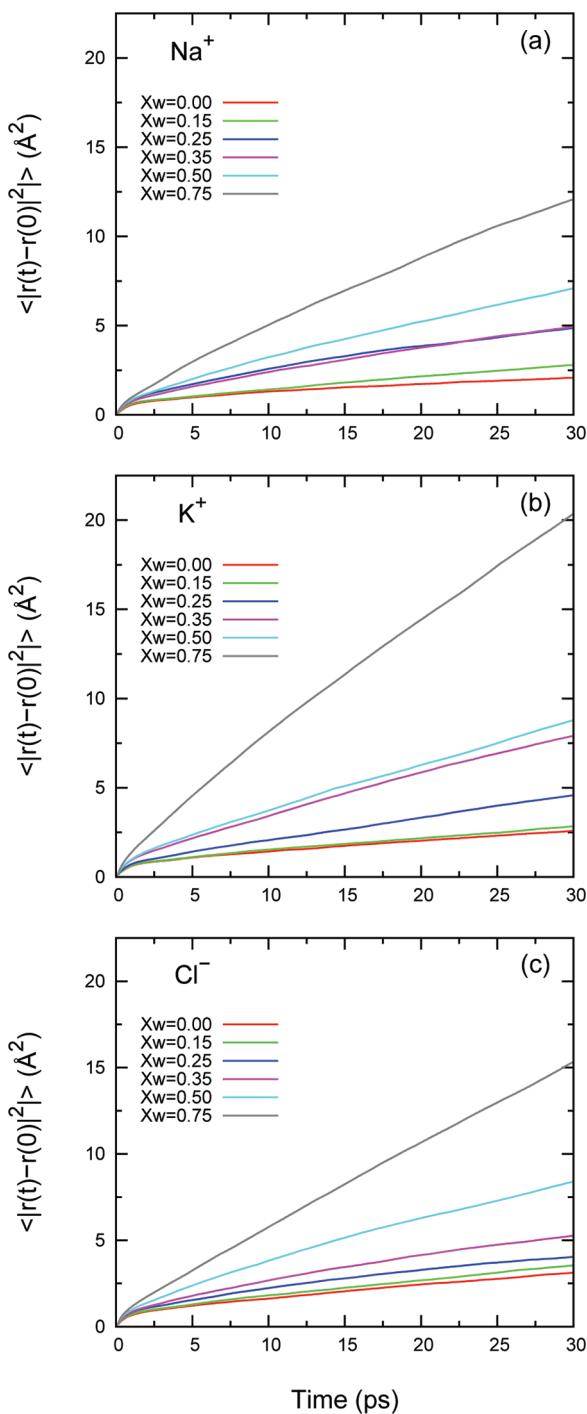


Figure 10. Time dependence of the mean-square displacement of the Na^+ , K^+ , and Cl^- ions in NMA–water mixtures of varying mole fraction of water.

$\theta_c = 45^\circ$ for the existence of the hydrogen bond along with the above-mentioned distance criteria. The details regarding the cutoff angle are discussed in earlier studies.^{83,84} Our calculated results for all *intra* and *inter* molecular hydrogen bonds are presented in Table 3. It is observed that the *intra* molecular hydrogen bonds per NMA decrease with dilution, whereas *inter* molecular hydrogen bonds between water and NMA increase on addition of water. At higher water concentration, the *intra* molecular hydrogen bonds per water molecule increase, but the stability of water–NMA hydrogen bonds is higher compared

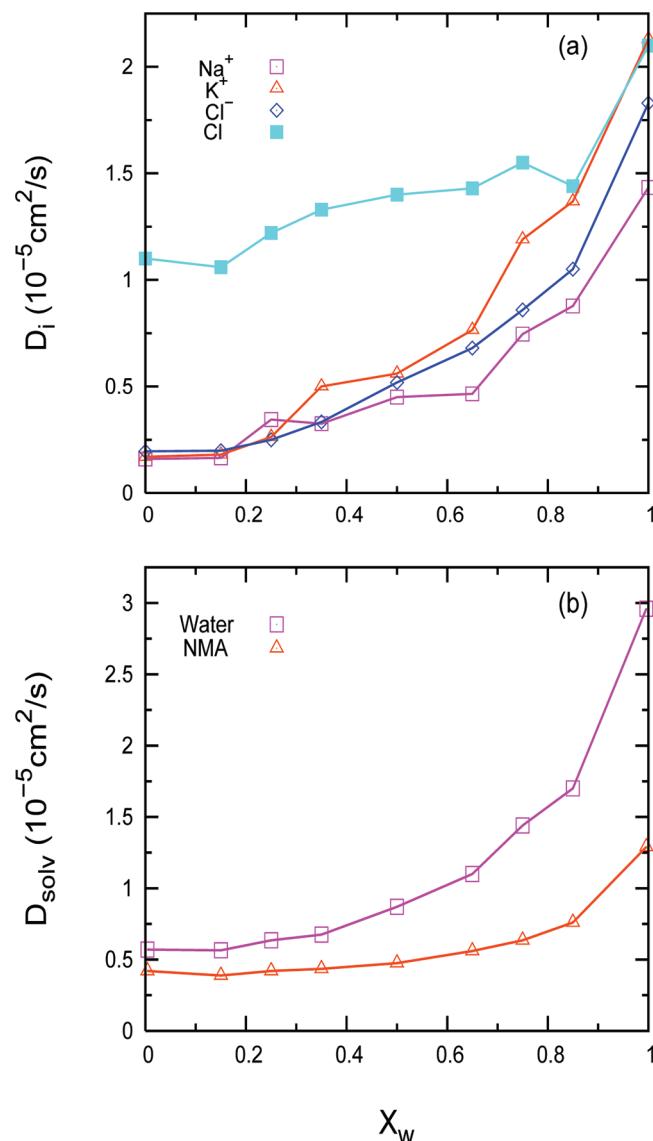


Figure 11. Self-diffusion coefficient values (a) for Na^+ , K^+ , Cl^- , and Cl and (b) for the water and NMA molecules in NMA–water mixtures of varying mole fraction of water.

to water–water hydrogen bonds, and in all cases the strength of the hydrogen bond decreases with dilution.

The orientational motion of solvent molecules is analyzed by calculating the orientational time correlation function, $C_l^\alpha(t)$, defined by

$$C_l^\alpha(t) = \frac{\langle P_l[\mathbf{e}^\alpha(t) \cdot \mathbf{e}^\alpha(0)] \rangle}{\langle P_l[\mathbf{e}^\alpha(0) \cdot \mathbf{e}^\alpha(0)] \rangle} \quad (5)$$

where P_l is the Legendre polynomial of rank l and \mathbf{e}^α is the unit vector which points along the α -axis in the molecular frame. In this work, we have calculated the time dependence of $C_l^\alpha(t)$ for $l = 1$ and 2 and for the three different \mathbf{e}^α , molecular dipole vector μ , N–H vector of NMA, and the O–H vector of water. The orientational correlation time τ_l^α , defined as the time integral of the orientational correlation function

$$\tau_l^\alpha = \int_0^\infty dt C_l^\alpha(t) \quad (6)$$

was obtained by explicit integration of the data of $C_l^\alpha(t)$ from simulations up to 25 ps for NMA, whereas for water we have taken the value up to 10 ps with the time interval of 0.01 ps. The results are shown in Figure 11. Experimentally, the rotational diffusion of

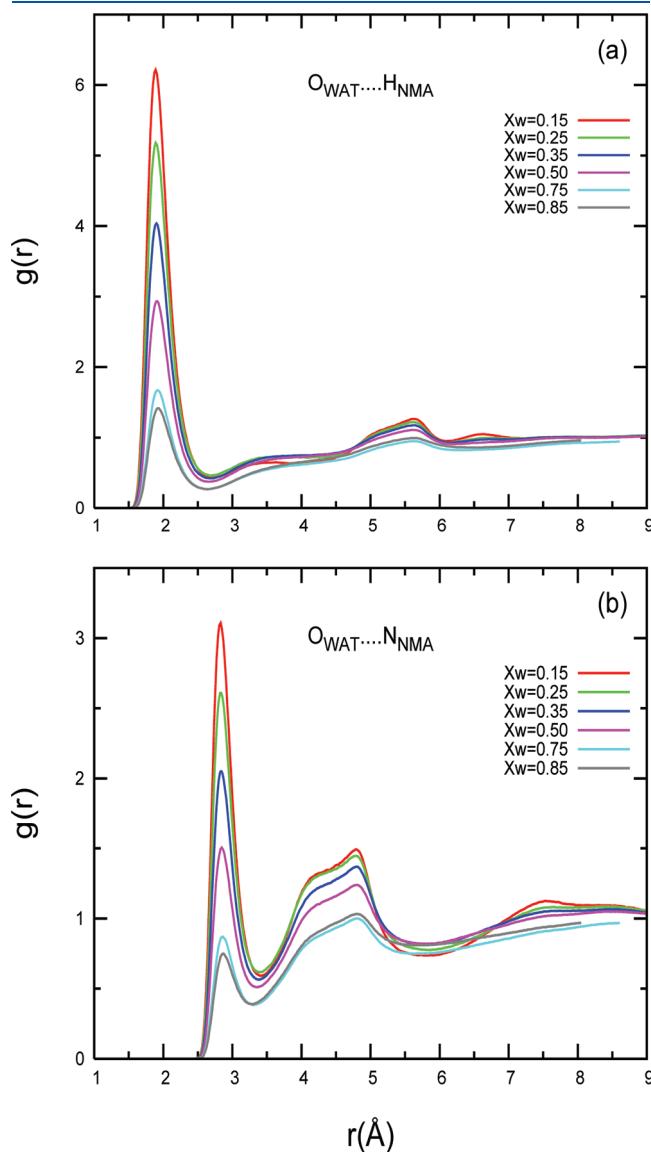


Figure 12. Oxygen (water)–hydrogen (NMA) and oxygen (water)–nitrogen (NMA) radial distribution functions for varying composition of the NMA–water mixtures.

NMA was measured by using femtosecond optical-heterodyne-detected Raman-induced Kerr effect spectroscopy. Such studies have been carried out to explore the temperature effects on rotational diffusion in neat NMA.^{74,89–91} The rotational diffusion

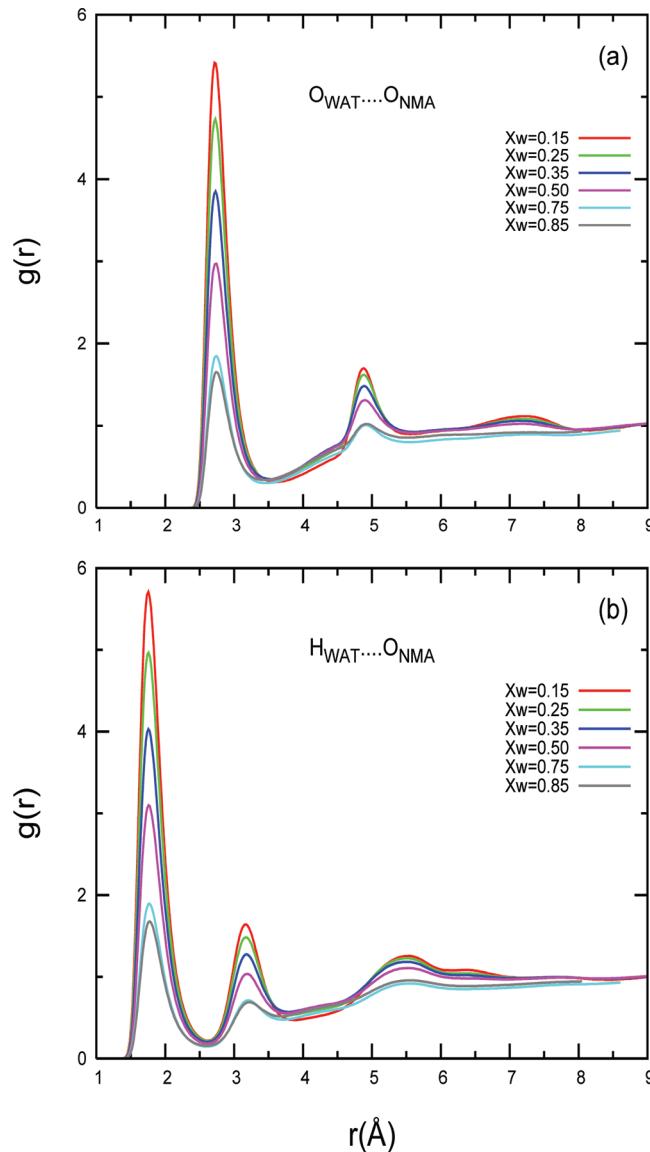


Figure 13. Oxygen (water)–oxygen (NMA) and hydrogen (water)–oxygen (NMA) radial distribution functions for varying composition of the NMA–water mixtures.

Table 3. Average Number of *Intra* and *Inter* Species Hydrogen Bonds in Aqueous NMA Solutions^a

X_w	NMA–NMA (per NMA)	$-N-H \cdots O_w$ (per NMA)	$>C=O \cdots H_w$ (per NMA)	$-N-H \cdots O_w$ (per water)	$>C=O \cdots H_w$ (per water)	water–water (per water)
0.15	1.60 (-30.52)	0.16 (-21.80)	0.27 (-21.29)	0.93	1.52	0.72 (-20.83)
0.25	1.40 (-30.27)	0.26 (-21.38)	0.43 (-21.21)	0.77	1.30	1.16 (-20.58)
0.35	1.26 (-30.20)	0.32 (-21.09)	0.55 (-21.05)	0.60	1.03	1.67 (-20.05)
0.50	1.05 (-29.97)	0.42 (-20.72)	0.75 (-20.89)	0.41	0.74	2.24 (-19.53)
0.65	0.79 (-29.55)	0.54 (-20.31)	0.98 (-20.68)	0.29	0.53	2.66 (-19.23)
0.75	0.78 (-29.60)	0.54 (-20.19)	1.03 (-20.55)	0.18	0.35	3.03 (-18.97)
0.85	0.50 (-29.08)	0.66 (-19.77)	1.31 (-20.28)	0.12	0.23	3.27 (-18.80)

^a The quantities in brackets show the energies of the corresponding hydrogen bonds in kJ/mol.

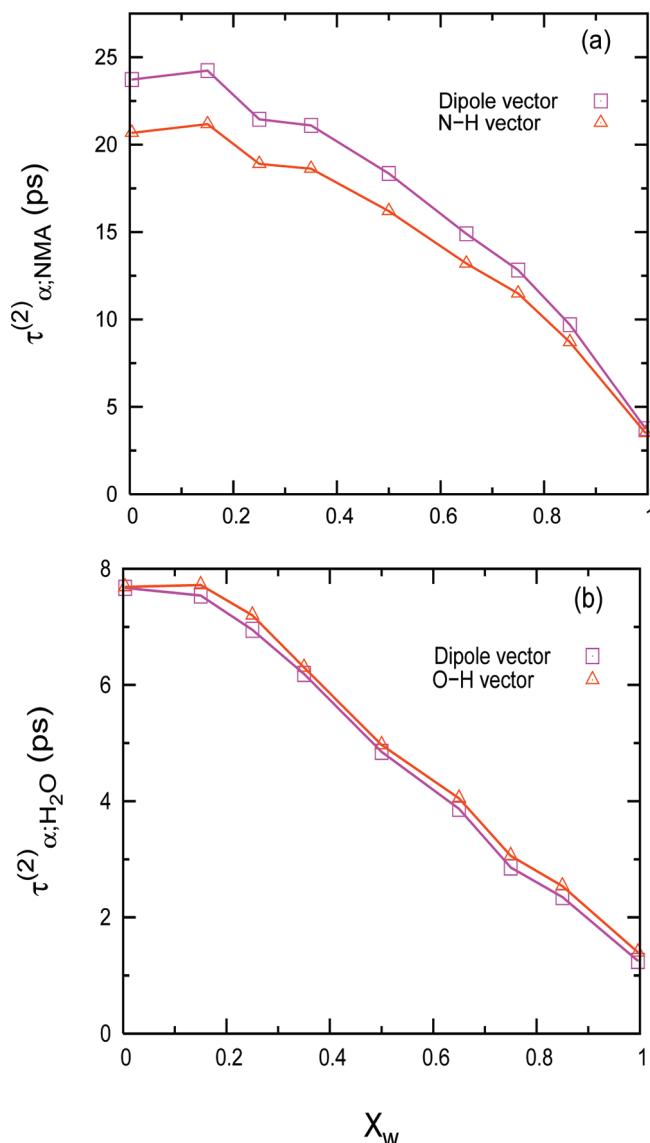


Figure 14. Second rank orientational relaxation times for (a) dipole and N–H vector of NMA and (b) dipole and O–H vector of water in NMA–water mixtures of varying mole fraction of water.

of NMA at varying water content is discussed particularly in ref 74. Experimentally, the orientational relaxation of the N–H and O–H vector can be measured by ^1H – ^{15}N and ^{17}O – ^1H dipolar relaxation NMR experiments. However, we are not aware of any such experimental measurement on the aqueous NMA system at varying composition. Recently, the femtosecond spectroscopic study by Bakker et al.⁷⁵ measured the orientational dynamics for the O–H group of water in aqueous NMA solution with varying concentration. In Figure 14 (a), we present the orientational relaxation times of the dipole and N–H vector of NMA, whereas the dipole and O–H vector of the water molecule are presented in Figure 14 (b), for $l = 2$. It is found that orientational relaxation times for both the solvents change in a nonlinear manner with composition. The initial increase of the orientational relaxation times indicates the stronger *inter* species hydrogen bond as water is added to the NMA but the subsequent loss of *intra* molecular hydrogen bonds at higher concentration the faster the dynamics of the solvent molecules.

4. CONCLUSIONS

In this paper, we have presented the molecular level study of the effects of addition of water on the structure and dynamics of ionic and neutral solutes present in a peptide bond environment. Calculations are done at many different compositions ranging from pure NMA to pure water. We used a combination of isobaric–isothermal and microcanonical molecular dynamics methods because the coupling with thermal and pressure baths can alter the true dynamics of a system.

It is found that ionic solutes prefer water molecules in the first hydration shell irrespective of their charge and size, whereas the neutral solute prefers NMA and is solvated by its methyl groups. We have calculated self-diffusion coefficient values for all the solutes with varying compositions. It is found that the neutral solutes diffuse faster in comparison with ionic solutes when water is added to the NMA which is attributed to the stronger solvation shell for ions compared to neutral solute. To investigate the role of solvent molecules in the solute diffusion picture, the translational and rotational dynamics of water and NMA are also calculated. It is found that the self-diffusion coefficient of solvent molecules decreases initially and then increases with varying water content in the solutions. In all the compositions, the water molecule diffuses faster than NMA which is expected because of smaller size. The qualitative behavior of the composition dependence of diffusion coefficients is strikingly similar to that found for all four solutes considered here. On the other hand, the orientational relaxation times of water and NMA increase initially and then decrease when water is added to the NMA solution. The overall slower dynamics of the solutes and solvent molecules indicate the important role that is played by the different *intra* and *inter* species hydrogen bonds present in aqueous NMA solutions. Here, we have calculated the number and the energies of all different kinds of hydrogen bonds that exist between water and NMA molecules. It is observed that the maximum number of *intra* molecular hydrogen bond per NMA molecule is two, which decreases with dilution, whereas the *inter* molecular hydrogen bonds between water and NMA increase on addition of water. The stability of the hydrogen bond decreases in both cases with dilution.

The initial increase of the orientational relaxation times of the solvent molecules indicates the formation of stronger *inter* molecular hydrogen bonds between the water and NMA molecules when water is added to the NMA solution, whereas the subsequent loss of *intra* molecular hydrogen bonds is faster for the dynamics of the solvent molecules at higher water concentrations.

For the first time, the authors have presented the results of different types of solute diffusion in aqueous NMA solutions along with the translational and rotational diffusion of the associated solvent molecules. We hope that the present work will encourage further experimental studies in this area. Also, the present work can be extended in many different directions. For example, it would be interesting to investigate similar dynamical studies of the solutes and solvent molecules for a concentrated salt solution of NMA where the strength of the hydrogen bonds can also be tuned by changing the concentration of the NMA salt solution. We hope to address this work in the near future.

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■ ACKNOWLEDGMENT

The authors are grateful to the CSIR for the financial support of this work through Grant No 01 (2352)/09 EMR-II and also to the Indian Institute of Technology Bhubaneswar for much assistance to execute the Project.

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