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Hofmeister Ion Interactions with Model Amide Compounds

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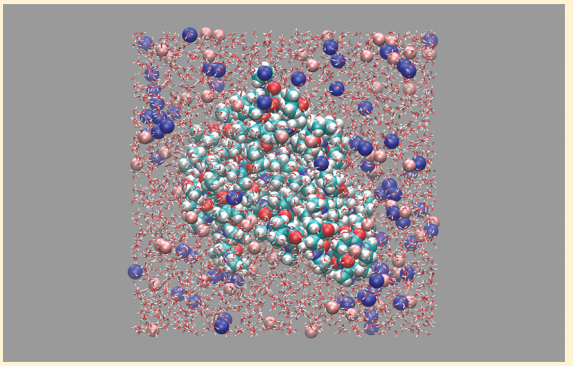
ABSTRACT: Dissolved electrolytes interact with peptides and proteins in aqueous solution. Herein, we study small amide compounds in aqueous electrolyte solutions and link their salting-in and salting-out propensities to molecular-level structural details obtained with molecular simulations. Aqueous solutions of NaF, NaCl, NaBr, NaI, $NaNO_3$, and $NaClO_4$ with *N*-isopropylacrylamide (NiPAM) and *N*-methylacetamide (NMA) have been investigated. Our results show that NiPAM is salted-in by NaI, mediated through iodide interactions with nonpolar groups, while being salted-out by the other salts. Hydrogen-bonding interactions of anions with the amide group of NiPAM could not be identified, while in the systems with NMA all Hofmeister anions formed stable hydrogen bonds with the amide group. These results indicate that the immediate chemical environment of the backbone amide groups should be considered in studies of protein destabilization by dissolved electrolytes. We furthermore report that all salts but NaI provoke a hydrophobic collapse transition of poly(*N*-isopropylacrylamide) in water at 300 K, in qualitative agreement with experimentally measured salt effects on the lower critical solution temperature of this system.



INTRODUCTION

Protein stability can be affected by various chemical agents, such as urea and certain salts.[1] While substantial insights have been gained over the years on interactions of urea with peptides and proteins, the detailed interactions of cations and anions with polar and nonpolar moieties are less well characterized. Polymers with a lower critical solution temperature (LCST) have been used as model systems for studying the influence of different salts on the stability of biological macromolecules.[2−6] These polymers contain hydrophilic groups, typically an amide that hydrogen bonds with water, and hydrophobic groups. At low temperatures, the hydrophilic groups form hydrogen bonds with water, favoring the solvation of the macromolecule. With increasing temperature, the hydrophobic interactions can no longer be balanced by the hydrophilic interactions with water, which leads to collapse of the chains and phase separation from solution. Dissolved electrolytes have a pronounced influence on this collapse transition, and it has been suggested that this effect is due to the ion-specific interactions with both amide and hydrophobic groups on the macromolecule.[1,7] Recent experiments with sodium salts that span the Hofmeister series for anions confirmed that the LCST of poly(*N*-isopropylacrylamide) (PNiPAM) or poly(*N*,*N*-diethylacetamide) is ion specific.[5,8,9] Interestingly, the effect of salts on the LCST of these macromolecular systems is similar to the influence of salts on the stability of proteins,[1,5,10−18] which usually follows a Hofmeister series.[19−21]

Experimentally, it has been observed that the LCST of PNiPAM is affected by anions to a different extent, following the order[5] $SCN^- < I^- < NO_3^- \approx Br^- < ClO_4^- < Cl^- < F^- < H_2PO_4^- < S_2O_3^{2-} < SO_4^{2-} < CO_3^{2-}$. Big chaotropic anions (SCN^- and I^-) that bind water molecules weakly have little effect on the LCST, while the stronger water-binding kosmotropic anions, located at the opposite end of this series, cause a significant shift of the LCST to lower temperatures already at low salt concentrations. Zhang, Cremer, and co-workers[5,6,8] have proposed two interplaying mechanisms, which cause the so-called "salting-out" effect. First, kosmotropic anions polarize water molecules, which are involved in the hydrogen bonding to the amide groups. This weakens the hydrogen bonding of water with the macromolecule, thereby salting it out. Second, the more salt is added into the solution, the more costly it is to hydrate hydrophobic groups of the polymer. This effect is similar to salting-out of benzene, where the presence of strongly hydrated ions leads to an increase of the work of cavity creation resulting in a decrease of the benzene solubility in water.[22] In contrast to kosmotropic anions, Zhang et al.[5,6,8] suggested that large chaotropic anions bind directly to the amide groups on the backbone, causing the "salting-in" effect. Molecular simulations of aqueous salt solutions containing *N*-methylacetamide (NMA) have, however, provided a different picture, in which cations exhibit affinity for the carbonyl oxygen, while large anions (Br^- and I^-) interact with the nonpolar methyl groups, but none of the halide anions show appreciable affinity for the amide hydrogen.[23] This picture has been corroborated by molecular dynamics simulations of PNiPAM in alkali halide solutions.[24] It however remains difficult to assess the qualitative differences in molecular-level details of ion specificity emerging from the above analyses of thermodynamic measurements and molecular simulations. This is in part

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due to the fact that ion-macromolecule "affinities" observed in simulations are usually characterized on the basis of analyses of the electrolyte structure, which, however, is not an experimental observable. Analyses of concentration dependent experimental LCST data, on the other hand, have mostly been based on interpretation of thermodynamic models.

What is needed now and what our work addresses is the establishment of a link between the proposed interaction mechanisms and the experimentally observed salting-in and salting-out of PNiPAM in aqueous salt solutions. A question that needs to be addressed is how electrolyte structure vicinal to the macromolecule (observed in simulations) can quantitatively be related to changes of the LCST observed in experiments. This question is addressed in this Article by studying the preferential solvation of *N*-isopropylacrylamide (NiPAM) molecules in different salt solutions ($NaNO_3$, $NaClO_4$, NaI, NaBr, NaCl, and NaF) with molecular dynamics (MD) simulations. The preferential solvation conveys information on water-versus-salt (or salt-versus-water) affinities for NiPAM, which cannot be inferred on the basis of analyses of ion-NiPAM radial distribution functions (RDF) only. It will be shown that the interaction of iodide with nonpolar groups of NiPAM results in salting-in of the nonpolar groups, while, despite an observed interaction of sodium with the carbonyl oxygen, the larger affinity of the carbonyl oxygen for water (in 1 *m* salt solution) leads to a salting-out of the carbonyl group by sodium. This analysis provides a molecular-level explanation for the hydrophobic collapse of PNiPAM observed in our simulations and in experiments.[5,8]

A second scope of this work has been to investigate if interactions of Hofmeister anions with the amide group depend on the chemical environment of this group within the molecule. To address this question, we compared NiPAM and NMA. It will be shown that, with the same force field for the amide groups of NiPAM and NMA, stable hydrogen bonds can be formed between all Hofmeister anions and the amide hydrogen in NMA, while in NiPAM the corresponding hydrogen bonds are unstable. Despite the fact that the observed formation of anion hydrogen bonds with the NMA amide group depends quite sensitively on the force field model, the comparison with NiPAM clearly indicates that the chemical environment of the amide group must be considered when studying its interaction with dissolved electrolytes.

METHOD AND SIMULATION DETAILS

The simulations have been performed using the Gromacs 4.0.7 package.[25] In the simulations of PNiPAM in pure water, the simulation box consisted of 4939 water molecules and one PNiPAM chain of 80 monomers. To model conditions at 1 *m* salt, 83 salt molecules were added to the box. The SPC/E[26] model has been used to represent water molecules. Nonbonded interactions were described with a nonpolarizable force field of the form:

$$V_{\mathrm{nb}}(r_{ij}) = 4\varepsilon_{ij}\left(\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right) + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \qquad (1)$$

The electrostatic interactions have been calculated using Particle-Mesh Ewald method.[27] For Lennard-Jones interactions, a cutoff of 1.4 nm has been used. The time step of the simulation was 1 fs; the neighbor list has been updated every 5 fs.

PNiPAM has been simulated using OPLS-AA[28] force field parameters, which proved to reproduce the phase transition of PNiPAM in a good agreement with experiment.[29] Intramolecular nonbonded interactions have been calculated for atoms separated by more than three bonds. The simulations were performed with a stochastic dynamics thermostat at a constant temperature (300 K) for all salt solutions, and in range between 280 and 360 K for PNiPAM in pure water. The pressure has been maintained at 1 atm by a Parrinello−Rahman barostat.[30,31]

The ion force field parameters from the work of Dang et al.[32−35] have been used in our work for the simulation of NaF, NaCl, NaBr, and NaI salts. These force fields proved to reproduce well the association constant[36] and ion mobility[35] in SPC/E water. The force fields developed in the work of Krienke et al.[37] have been used for the simulation of $NaClO_4$ and $NaNO_3$. These force fields were obtained by quantum mechanical calculations and reproduced the structure of the solution well.[37] The ion parameters are summarized in Table 1. Lorentz−Berthelot combination rules were used to describe interactions between unlike pairs.

Table 1. Nonbonded Interaction Parameters for Salt Ions

atom	ε_{ii} (kJ mol^{-1})	σ_{ii} (nm)	q_i (e)
	NaF, NaCl, NaBr, NaI[36]		
Na	0.5220	0.2876	+1.0000
F	0.6998	0.3143	−1.0000
Cl	0.5220	0.3785	−1.0000
Br	0.5220	0.3896	−1.0000
I	0.5220	0.4168	−1.0000
	$NaNO_3$ and $NaClO_4$[37]		
Na	0.2730	0.3575	+1.0000
N	0.8368	0.3900	+0.8604
O_N	0.6485	0.3154	−0.6201
Cl	0.9490	0.3950	+1.8820
O_{Cl}	0.8780	0.2960	−0.7205

RESULTS AND DISCUSSION

Validation of the Model. To reproduce the experimentally observed[29] transition of PNiPAM from an expanded state at low temperature to a collapsed state at higher temperatures, we have performed 13 simulations in a temperature range from 280 to 360 K. The PNiPAM radius of gyration has been monitored as a function of temperature. To this end, we performed 100 ns simulations; the last 50 ns was used for the calculation of the gyration radius. In Figure 1, one can see that the hydrophobic collapse transition occurs at a temperature of about 308 K in our simulations, which compares to 305 K in experiment.[29]

It is known from experiments that the LCST of PNiPAM is affected by the presence of salts in solution.[5,6,8,9] The presence of salt results in a decrease of the lower critical solution temperature as the salt concentration is increased.[5] The magnitude of this effect follows a Hofmeister series for the anions. We simulated a PNiPAM chain of 80 monomers in 1 *m* solutions of NaF, NaCl, NaBr, NaI, $NaClO_4$, and $NaNO_3$ at 300 K. We did not attempt to compute the shift of the LCST due to the presence of Hofmeister anions at different concentrations, but rather selected a temperature (300 K) where PNiPAM is in its expanded, fully solvated state in pure water and is known to collapse in the presence of 1 *m* salt. As in case of the salt-free PNiPAM solution, 100 ns simulations have been performed, and the last 50 ns was used for

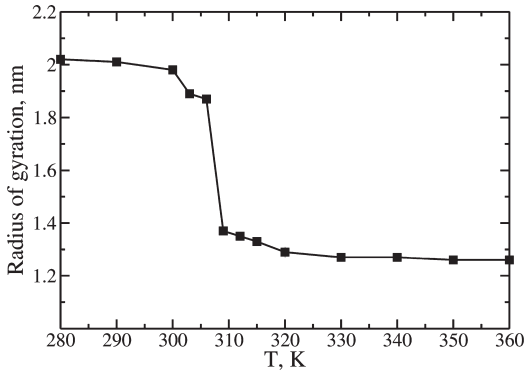

Figure 1. Radius of gyration of the PNiPAM chain in water as a function of temperature.

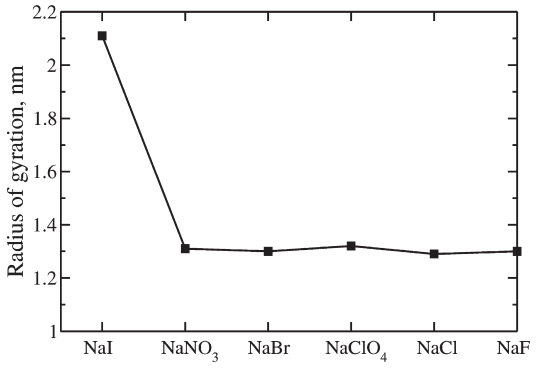

Figure 2. Radius of gyration of the PNiPAM chain in different 1 *m* salt solutions at 300 K.

analyses. Figure 2 presents the PNiPAM radius of gyration versus salt type. As reported in the work of Zhang et al.,[5] PNiPAM remains expanded in 1 *m* solution of NaI at 300 K, while being collapsed in all other solutions. The force field used in our simulations reproduces this experimental observation, at least qualitatively.

Interactions of Hofmeister Anions with Small Amide Compounds. The observed interactions of salt ions with chemical moieties of the PNiPAM chain are affected by the chain conformation and electrolyte concentration. In an attempt to decouple these effects from direct chemical interations between ions and atoms on the backbone and the side groups, we calculated potentials of mean force (PMF) for several anion−NiPAM pairs (considering different atoms on the NiPAM molecule) in pure water. These potentials provide information on solvent-mediated attraction/repulsion between the solvated anion and NiPAM atom groups. For reasons of comparison, we also calculated PMFs with respect to similar atoms on the NMA molecule, which is sometimes used as a proxy for the amide group on the backbones of proteins. Figure 3 shows the chemical structure of PNiPAM monomeric unit and the NMA molecule. The circles indicate the interaction sites with respect to which the PMFs with anions have been calculated: that is, the amide hydrogen, the isopropyl CH_3 of NiPAM, and the methyl group connected to the carbonyl carbon of NMA. In the NiPAM case, the molecule considered had the backbone in Figure 3 replaced by an ethyl group. The OPLS-AA force field parameters are identical for the peptide group of both molecules; the same holds for the two

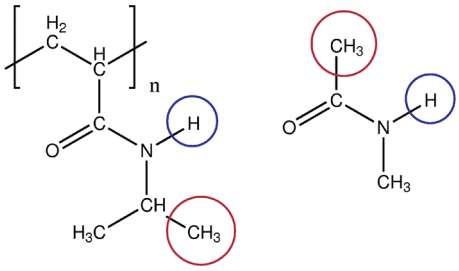

Figure 3. Chemical structure of the PNiPAM monomeric unit and the NMA molecule.

selected methyl groups. Because we here wanted to compare chemically similar moieties on NiPAM and NMA, we have not considered PMFs with the NiPAM ethyl group or the NMA methyl group connected to the amide nitrogen. We used distance constraints between the selected groups of NiPAM or NMA and the anion in a simulation box with 2171 SPC/E water molecules, a single NiPAM (or NMA) molecule, and one explicit sodium ion at constant NpT conditions (300 K, 1 atm.). The force needed to constrain the anion−atom distance was calculated at 40 different distances for each NiPAM/NMA/salt combination and averaged over the last 5 ns in a 10 ns simulation for each distance. The corresponding PMFs are presented in Figure 4, where the PMFs for NiPAM are shown in panels (a) and (b) and the PMFs for NMA are shown in panels (c) and (d).

As one can see in Figure 4a, only I^- shows an appreciable attractive interaction with the NiPAM CH_3 group. Although some oscillations are visible in the PMF curves of the remaining anions, their interactions with CH_3 are all effectively repulsive. The strongest repulsion is observed for F^-, followed by Cl^-, Br^-, ClO_4^-, and NO_3^-, the order of which depends on the distance with respect to the methyl group. The microscopic picture is very similar for the amide group of NiPAM, as can be observed in Figure 4b: I^- shows appreciable affinity for the amide group, while the chaotropic ions Br^-, NO_3^-, and ClO_4^- show no affinity and interact repulsively. Note, however, that the PMF for I^- shows two broad minima around 0.4 and 0.6 nm with neither of these two minima corresponding to a I^-−amide hydrogen-bonding interaction. The observed affinity for I^- in Figure 4b is indirectly mediated through interactions of iodide with nonpolar parts of the NiPAM molecule. Zhang et al.[5] have shown that the shift of the PNiPAM/salt/water LCST, which we here take as a measure of the salting-out efficiency of the salt, follows the order $SCN^- < I^- < NO_3^- \approx Br^- < ClO_4^- < Cl^- < F^-$. Our data suggest that NaI only marginally affects the PNiPAM LCST due to thermodynamically favorable interactions of I^- with the nonpolar parts of NiPAM. Additionally, we observed that Na^+ interacts favorably with the carbonyl oxygen as will be shown later.

Figure 4c shows the PMFs between the anions and the CH_3 groups of NMA. The same order of different anions is observed in comparison with the data for NiPAM in Figure 4a. In the NMA system, minima are however observed in the PMFs at anion−CH_3 contact distances, also for the strongly hydrated fluoride ion. Note, however, that the free energy of the contact minimum for F^- and Cl^- is positive as compared to bulk (at large distance), indicating that contact interactions of F^- and Cl^- with the methyl group of NMA are unfavorable. A distinct difference between NiPAM and NMA is however observed for anions at the amide group. Figure 4d shows the PMFs of anions with the amide group of NMA. Clearly, all anions show affinity for the

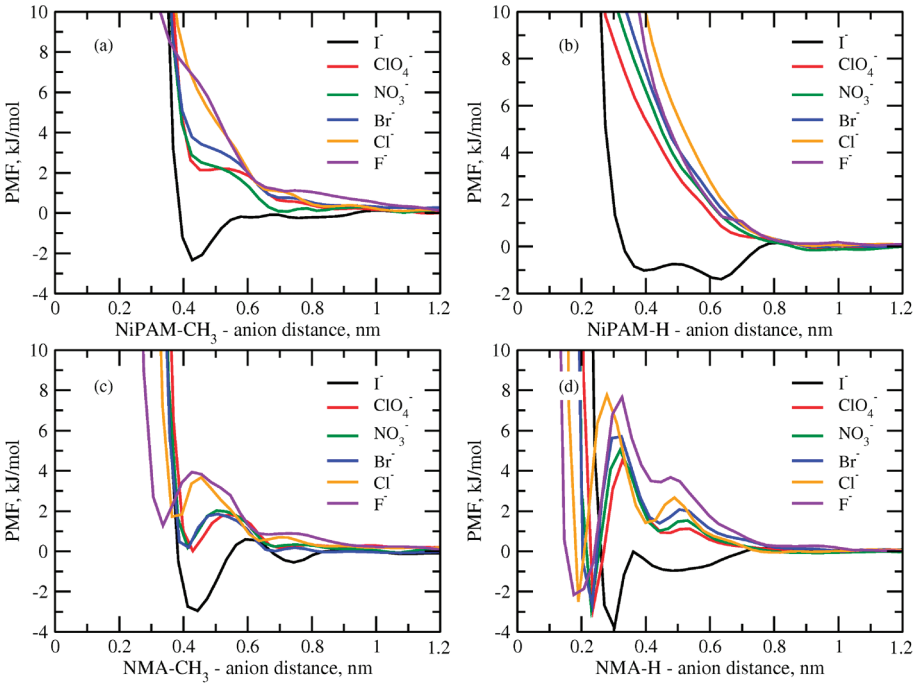

Figure 4. Potentials of mean force of Hofmeister anions with the NiPAM CH_3 group (a), with the NiPAM amide hydrogen (b), with the NMA CH_3 group (c), and with the NMA amide hydrogen (d).

amide group in NMA, in contrast with NiPAM, Figure 4b, where direct anion−amide interactions could not be identified. The contact minima at small distances observed in Figure 4d correspond to hydrogen-bonded configurations of the anions with the amide hydrogen of NMA. Interestingly, the PMFs show significant barriers and secondary minima at larger distances, corresponding to anion−amide pairs separated by a water molecule. Except for the weakly hydrated I^- ion, where also at these larger distances the interaction is favorable, the water-mediated interaction with the amide group is unfavorable for all other anions. The data in Figure 4d thus lead to a picture where direct anion hydrogen-bonding interaction with NMA amide groups is thermodynamically favorable, while at (larger) distances where the hydration shells must be considered the interaction between the anion and the amide group is unfavorable. It is therefore not immediately clear if the anions contribute to salting-in or salting-out of the amide group in NMA. The comparison between NiPAM and NMA in Figure 4 suggests that the chemical environment of the backbone amide groups in proteins plays an important role in determining their affinity for Hofmeister anions.

Changes in experimentally observed LCSTs induced by the various Hofmeister salts cannot directly be correlated with salt-solute RDFs or with the PMFs presented in Figure 4. To make this correlation, the relative affinities of the various chemical moieties for salt and for water need to be compared. In a binary solution mixture with water (denoted W), an infinite dilute solute (denoted S) is salted-in by cosolvent or salt (denoted C) when $G_{SW} - G_{SC} < 0$.[38] In this expression, the quantity G_{ij} (here G_{SW} or G_{SC}) is the Kirkwood−Buff integral (KBI) defined as

$$G_{ij} = \int_0^R [g_{ij}(r) - 1] 4\pi r^2 \, dr \qquad (2)$$

where $g_{ij}(r)$ is the RDF and the integration limit R is taken large enough to ensure that $g(r) - 1 = 0$ for all distances $r \geq R$. $\rho_C G_{SC}$ (with ρ_C the molar concentration of C in the solution) can be interpreted as the change in the number of C molecules in a spherical region of radius R in the solution before and after placing the solute at the origin of that region. A similar interpretation applies to $\rho_W G_{SW}$. With these definitions, one sees that a solute is salted-in if it is preferentially solvated by the salt (relative to water), that is, $G_{SW} - G_{SC} < 0$. Salting-out occurs in the opposite scenario. We have calculated $G_{SW} - G_{SC}$ (using R = 1 nm), identifying S with the chemical groups of NiPAM and NMA considered in Figure 4 and identifying C with the different anions. This choice neglects the contribution of the cation to the solute-salt KBI, which for a 1:1 electrolyte in water can be written as $G_{SC} = [G_{S-} + G_{S+}]/2$. We first investigate the anion contribution using the data from Figure 4, and then move on to include the cation contribution in our analysis. The solute-anion RDFs, $g_{SC}(r) = \exp[-V_{pmf}(r)/k_BT]$, were obtained from the PMFs, $V_{pmf}(r)$, presented in Figure 4, while the solute-water RDFs were obtained directly from the simulated trajectories.

Figure 5 shows the preferential solvation $G_{SW} - G_{SC}$ of NiPAM and NMA, based on calculations using the anion-methyl PMFs (a) and the anion-amide hydrogen PMFs (b). The I^- ion contributes to salting-in of both NiPAM and NMA, while all other anions contribute to salting-out of NiPAM/NMA. This observation is consistent with the experimentally observed shifts of the LCST of PNiPAM/salt solutions; while the LCST slightly increases in solutions with NaI (or NaSCN) at low salt concentrations, it decreases in all other salt solutions.[5] Noteworthy, a similar type of salting-in mechanism as the one discussed here has recently been reported for ionic liquids[39] and amino acids[40] in aqueous solutions containing ClO_4^- ions. The data in Figure 5 further show that the salting-out propensities of all anions but iodide are significantly reduced for NMA in comparison to NiPAM, which is due to anion−amide hydrogen bonding interactions with NMA and a stronger anion affinity for NMA methyl groups.

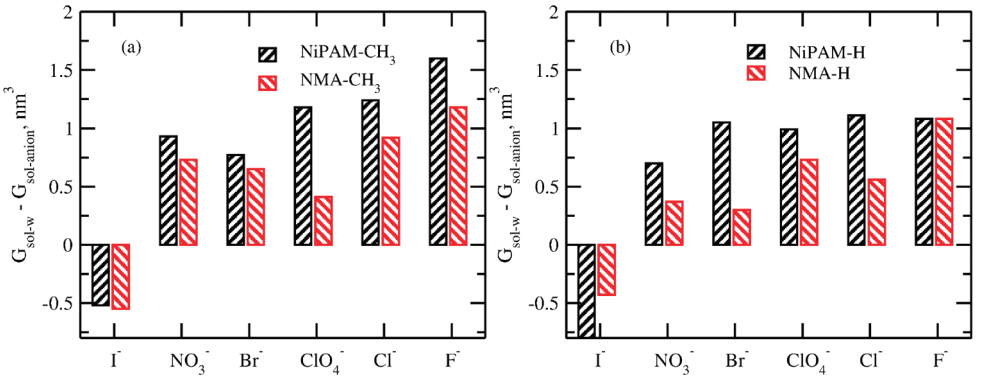

Figure 5. Preferential solvation $G_{SW} - G_{SC}$ of NiPAM and NMA for different Hofmeister anions. (a) Calculations based on anion−CH_3 PMFs. (b) Calculations based on anion−amide hydrogen PMFs.

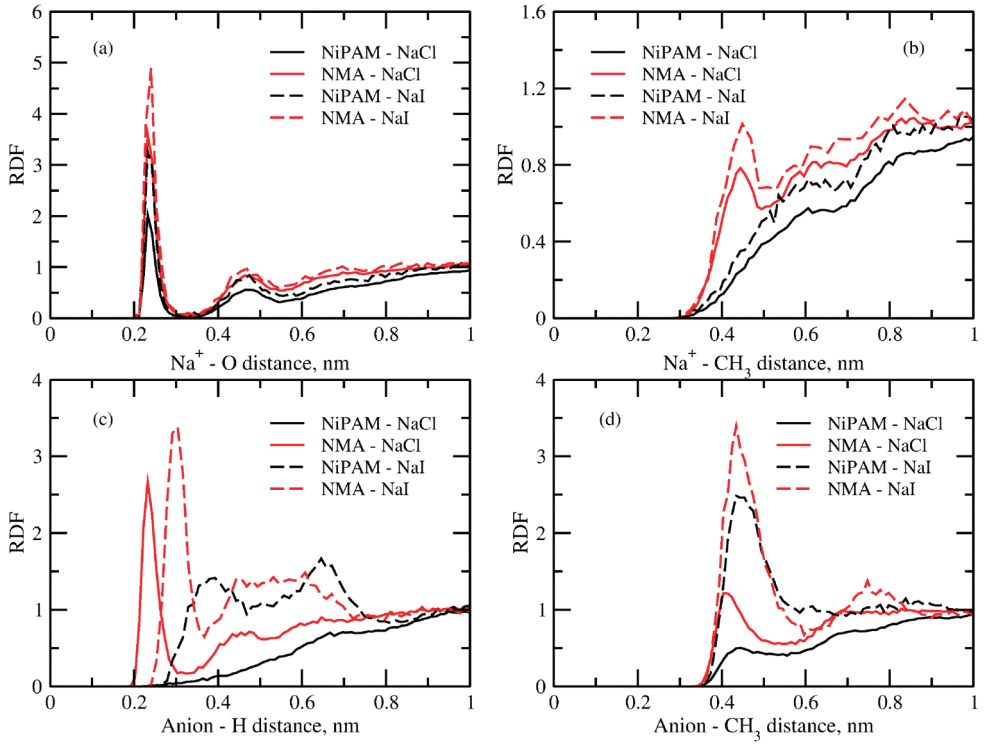

Figure 6. Radial distribution functions in 1 *m* NaCl and NaI salt solutions of NiPAM and NMA (300 K) for (a) Na^+−O(amide), (b) Na^+−CH_3, (c) Cl^-/I^-−H(amide), and (d) Cl^-/I^-−CH_3.

Small Amide Compounds in Concentrated Salt Solutions. To have a closer look at ion specific interactions with NiPAM and NMA in concentrated salt solutions, we simulated a mixture of 8 NiPAM molecules, as well as a mixture of 8 NMA molecules, in 1 *m* solutions of NaCl and NaI at 300 K. Figure 6 shows the radial distribution functions for Na^+ with the oxygen of the amide group, as well as for Na^+ with CH_3 groups of NiPAM and NMA, Cl^-/I^- with CH_3, and Cl^-/I^- with the hydrogen atom of the amide group. For the cation as well as the anion, the affinity with NMA is stronger. In part, this is due to the stronger hydrophobic nature of NiPAM, which causes stronger aggregation in the NiPAM solution and a corresponding screening of the interaction with the salt. Figure 6a shows that the cation interacts with the oxygen of the amide group. Inspection of Figure 6b shows that the interaction between Na^+ and the methyl group is unfavorable. The chloride and iodide anions in turn bind favorably to the amide hydrogen for NMA, while showing weaker affinity for the amide hydrogen of NiPAM (Figure 6c), in agreement with the calculations at single monomer level and low salt concentration in Figure 4. It can also be seen from Figure 6b and d that the anion affinities for the hydrophobic methyl group exceed that of the cation, for both NMA and NiPAM. The observed Na^+ and Cl^-/I^- interactions with NMA agree in part with the results of Heyda et al.,[23] who simulated the same system with different (polarizable and nonpolarizable) force fields. A noticeable difference between the simulations presented here and the work of Heyda et al. involves the interaction of the anion with the amide group. While in the present work (Figures 4 and 6) Hofmeister anions are seen to interact with the amide group of NMA, no such interactions have been observed by Heyda et al. in systems

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with Cl^- and Br^- anions. This discrepancy is due to differences between the force field models used in the simulations. In view of these model dependencies, we cannot unambiguously interpret the interactions of anions with backbone amide groups in proteins based on the present simulations.

Figure 7 shows the preferential solvation $G_{SW} - G_{SC}$ of NMA and NiPAM, based on calculations using the carbonyl oxygen-ion

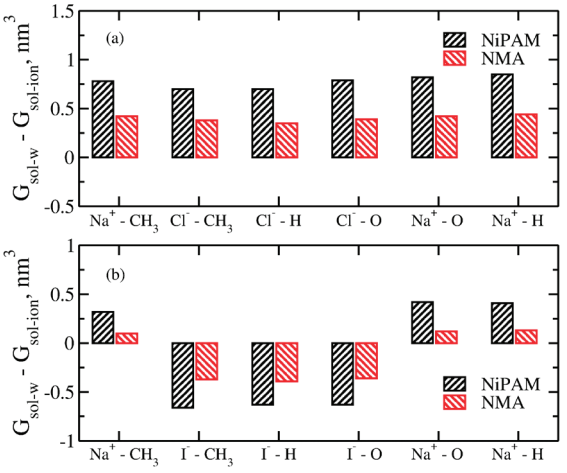

Figure 7. Preferential solvation $G_{SW} - G_{SC}$ of NiPAM and NMA in 1 *m* NaCl (a) and 1 *m* NaI (b) solutions at 300 K.

Table 2. Preferential Solvation ($G_{SW} - G_{SC}$) (units nm^3) of NMA and NiPAM in 1 *m* NaCl and NaI Solution at 300 K

	NaCl	NaI
NMA	0.36	−0.12
NiPAM	0.85	−0.15

RDFs, and the amide hydrogen-ion RDFs in the 1 *m* NaCl and NaI solutions. Note that these calculations, using different RDFs (ion and water structure with respect to methyl groups or amide atoms), provide the same information on the preferential solvation of the NMA or NiPAM molecules. Small differences are however observed (e.g., comparing Na^+-CH_3 and Na^+-O), which is due to our choice of integration limit R = 1 nm, used to compute the KBIs. Figure 7a shows that, both the chloride ion and the sodium ion contribute to salting-out of NMA and NiPAM in NaCl solution. Despite observed interactions of Na^+ with the carbonyl oxygen and Cl^- with the amide hydrogen of NMA in Figure 6, these groups are preferentially hydrated, resulting in salting-out by NaCl. In NaI solution, the cation and anion play opposing roles as shown in Figure 7b. While the sodium cation again tends to salt-out NMA and NiPAM molecules, the iodide anion overcompensates the role of the sodium ion, leading to a net salting-in of both molecules. The observed difference between the I^- and Na^+ KBIs for the system with NaI indicates that locally (within R = 1 nm) electroneutrality is not maintained. This observation supports a molecular-level picture[8] in which iodide binding interactions with PNiPAM increase the charge on the macromolecule and thereby inhibit hydrophobic collapse. Cho et al.[8] assumed that the amide dipoles serve as putative binding sites for large chaotropic anions. Our simulations however do not provide evidence for anion interactions with NiPAM amide dipoles. Table 2 summarizes the preferential solvation of NMA and NiPAM, accounting for both the cation and the anion contributions and using RDFs calculated with respect to the NMA and NiPAM centers of mass.

Ion Specific Interactions with PNiPAM. We finally consider the affinity of the ions for polar and nonpolar groups on the PNiPAM chain in 1 *m* salt solution. To this end, we calculated the RDFs between the ions and the hydrophobic/hydrophilic groups of PNiPAM (Figure 8). The order of RDFs in Figure 8a and b

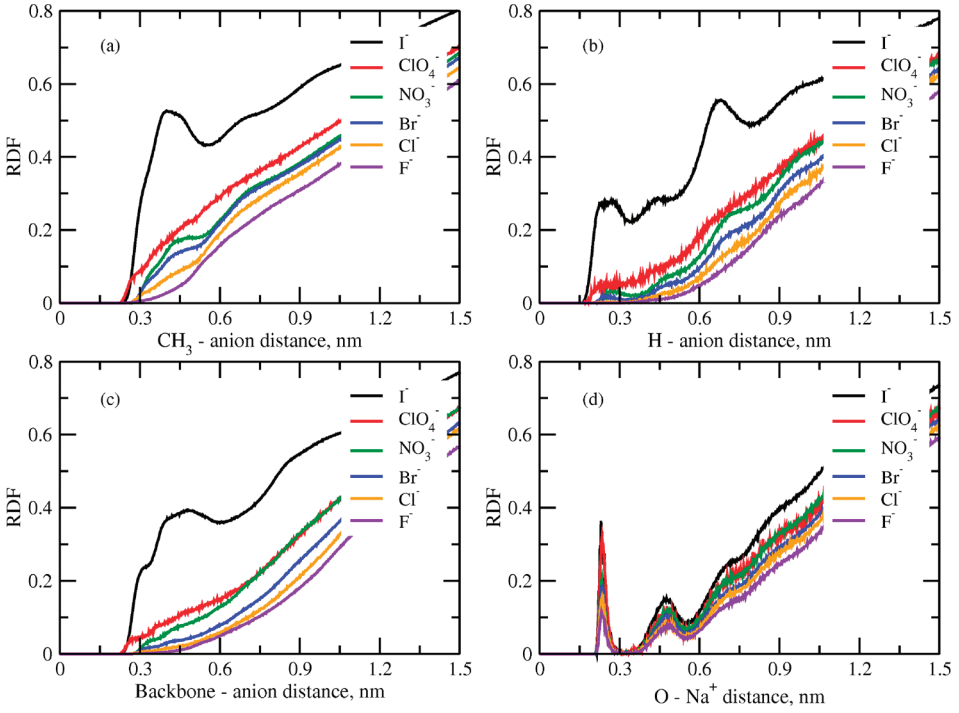

Figure 8. Radial distribution functions between anions and PNiPAM CH_3 groups (a), anions and the PNiPAM amide hydrogen (b), anions and the PNiPAM backbone carbon atoms (c), and Na^+ and the PNiPAM amide oxygen (d) from simulations of PNiPAM in 1 *m* salt solution at 300 K.

follows the series $I^- > ClO_4^- > NO_3^- > Br^- > Cl^- > F^-$. Only I^- interacts with the hydrophobic groups of the PNiPAM chain. Moreover, there is no significant difference between the isopropyl CH_3 groups and the backbone carbon atoms, as can be concluded by comparing the data in Figure 8a and c. The interaction of Na^+ with the amide oxygen is furthermore affected by the nature of the anion (Figure 8d). For example, in presence of I^-, sodium interacts stronger with the amide oxygen. The strength of this interaction decreases with decreasing anion size. The salting-in of the hydrophobic parts of PNiPAM by I^- results in the amide groups being exposed to the solvent, causing a more pronounced interaction between Na^+ and carbonyl oxygens.

CONCLUSIONS

Molecular simulations have been performed of a PNiPAM chain in pure water, as well as in six different 1 *m* sodium salt solutions (NaF, NaCl, NaBr, NaI, $NaClO_4$, $NaNO_3$). The hydrophobic collapse transition of PNiPAM in pure water was observed in our simulations at approximately 308 K, in good agreement with the experimental transition temperature of 305 K.[29] Moreover, at 300 K, expanded coil conformations were observed in the presence of NaI, while collapsed conformations were observed in solutions with $NaClO_4$, $NaNO_3$, NaBr, NaCl, and NaF, in agreement with experimental data.[5] Analyses of the ion affinities for hydrophobic groups and for the hydrophilic amide groups of PNiPAM indicate that Na^+ interacts with the amide group at the carbonyl oxygen, while I^- interacts predominantly with hydrophobic parts of the PNiPAM chain. Analyses of the preferential solvation of these groups by ions or water suggest that the iodide affinity for nonpolar groups is responsible for salting-in of PNiPAM by NaI.

Ion specific interactions with nonpolar and polar moieties of NiPAM molecules in water were further compared to the corresponding interactions with *N*-methylacetamide (NMA) molecules. These simulations showed that the affinity of anions for the amide group depends on its chemical environment. While none of the anions show affinity for the amide group in NiPAM, all monovalent Hofmeister anions form stable hydrogen bonds with the amide hydrogen in NMA. This result indicates that the chemical environment of the peptide group in proteins should be considered in studies of protein destabilization by dissolved electrolytes. The simulations further indicate that the observed interactions of Hofmeister anions with the amide group depend strongly on force field models.

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