# Hydration of Cations: A Key to Understanding of Specific Cation Effects on Aggregation Behaviors of PEO-PPO-PEO Triblock Copolymers

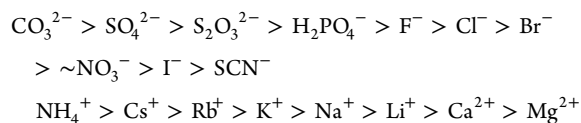Jacob C. Lutter, Tsung-yu Wu, and Yanjie Zhang*

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ABSTRACT: This work reports results from the interactions of a series of monovalent and divalent cations with a triblock copolymer, poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (PEO-PPO-PEO). Phase transition temperatures of the polymer in the presence of chloride salts with six monovalent and eight divalent cations were measured using an automated melting point apparatus. The polymer undergoes a two-step phase transition, consisting of micellization of the polymer followed by aggregation of the micelles, in the presence of all the salts studied herein. The results suggest that hydration of cations plays a key role in determining the interactions between the cations and the polymer. The modulation of the phase transition temperature of the polymer by cations can be explained as a balance between three interactions: direct binding of cations to the oxygen in the polymer chains, cations sharing one water molecule with the polymer in their hydration layer, and cations interacting with the polymer via two water molecules. Monovalent cations Na^+, K^+, Rb^+, and Cs^+ do not bind to the polymer, while Li^+ and NH_4^+ and all the divalent cations investigated including Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Cd^{2+} bind to the polymer. The effects of the cations correlate well with their hydration thermodynamic properties. Mechanisms for cation−polymer interactions are discussed.
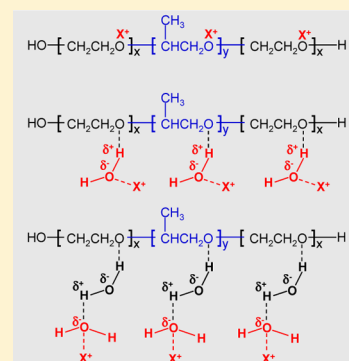
INTRODUCTION

Specific ion effects on the physicochemical properties of aqueous processes such as polymer and protein aggregation,[1−8] protein folding,[9−11] and enzyme activity[12−15] follow an empirical trend that is called the Hofmeister series.[16−21] This series was first discovered over 125 years ago by a Czech protein scientist, Franz Hofmeister, who tested the effects of a variety of inorganic salts on the solubility and conformational stability of proteins.[16,17] Typical orders for the ability of anions and cations to salt proteins out of solution are as follows:[19−21]

$$CO_3^{2−} > SO_4^{2−} > S_2O_3^{2−} > H_2PO_4^− > F^− > Cl^− > Br^−$$
$$> \sim NO_3^− > I^− > SCN^−$$
$$NH_4^+ > Cs^+ > Rb^+ > K^+ > Na^+ > Li^+ > Ca^{2+} > Mg^{2+}$$

Although the Hofmeister effects are general phenomena in many different systems, the molecular level mechanisms of the Hofmeister series are not well understood. Explanations on the molecular origin of the Hofmeister series started to emerge in the past 10 years.[1,19,22−31] Recent studies suggest that multiple mechanisms are involved in a variety of systems.[32] Direct ion−biomacromolecule interactions are believed to be the predominant force responsible for the effects of the Hofmeister series.[1−3,33−37] NMR studies and molecular dynamic simulations have shown that weakly hydrated anions such as $SCN^−$ and $I^−$ bind to the amide nitrogen on the backbone and adjacent α-carbon, while strongly hydrated anions such as $SO_4^{2−}$ are repelled from the backbone and the hydrophobic side chains of an elastin-like peptide.[38] Record et al. proposed

that the Hofmeister effects are related to the ability of ions to partition between the nonpolar surface of the protein and bulk solution.[28−30] In addition, the relative polarization of anions has been found to contribute to the effects of the Hofmeister series.[24,39−41] In some cases, the Hofmeister series is reversed or partially reversed when ion concentration, surface charge, or surface polarity are altered.[6,20,42−45] An article in *C&E News*, "Hofmeister Still Mystifies", highlighted the current status of research on the mechanisms of the Hofmeister series.[32]

The effects of anions on uncharged systems are stronger than cations. Therefore, the studies of the effects of cations are more difficult than similar studies of anions. Cations and anions are different in several ways. Cations are usually smaller in size and more strongly hydrated as compared to anions of similar mass.[46] The hydration of anions is more local than cations; thus, water molecules in the hydration layer of the ions can approach closer to anions than cations.[47] Cations are repelled from hydrophobic surfaces to a larger extent than anions.[33,47] A few recent papers from Cremer and co-workers reported thermodynamic and spectroscopic investigations of cation effects on the aggregation of peptides, interactions with negatively charged hydrophilic surfaces, and their binding to amide groups.[35,36,48] Cremer et al. found weak binding of cations to amide groups.[48] Interestingly, molecular dynamic simulations showed that there was significant association of

monovalent cations such as Li^+, Na^+, and K^+ with carboxylate groups or protein anionic surface charges.[49−54] Moreover, the specific roles of cations in protein stability, enzymatic catalysis, and aqueous solubility of amino acids have been reported.[55−57]

To further explore the interactions of cations with macromolecules, we study the effects of a series of 14 cations on the phase behaviors of a triblock copolymer, poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (PEO-PPO-PEO). PEO-PPO-PEO block copolymers have a hydrophobic PPO block in the middle and two hydrophilic PEO blocks at the ends. These polymers undergo a two-step phase transition as they are heated in aqueous solutions.[58−60] PEO-PPO-PEO block copolymers represent uncharged macromolecules with no carboxylate moieties. The particular polymer we used in this study is L44. L44 is a liquid at room temperature and has a PPO block with molecular weight on the order of 1200 and 40 wt % of PEO block. Previously, we investigated the specific anion effects on the phase transition of L44 and proposed the underlying mechanisms for how anions interact with the polymer and further modulate its phase behaviors.[4] Our studies showed that the polymer underwent a two-step phase transition in the presence of poorly hydrated anions. The first step is the micellization, where the hydrophobic PPO blocks interact with each other to form the core of the micelles. The second step is the aggregation of the micelles induced by the dehydration of the PEO blocks. The effects of poorly hydrated anions were correlated to the changes in the interfacial tension at the polymer/aqueous interfaces and anion binding to the hydrophobic portion of the polymer. On the other hand, L44 exhibits a single-step aggregation in the presence of well hydrated anions. The effects of strongly hydrated anions were correlated to polarization of hydration water around the hydrophilic moieties. In our current study, we choose chloride as a common anion for all 14 cations employed. Chloride anion interacts with the polymer solely through changing the interfacial tension at the polymer/aqueous interfaces as shown in Figure 1. We find that the hydration of cations is a
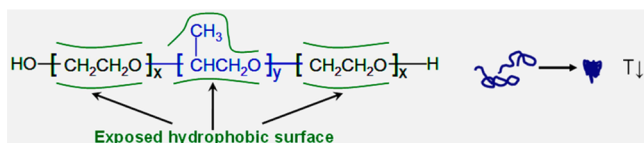

Figure 1. Schematic illustration of the effect of chloride anion on the phase transition of PEO-PPO-PEO. The reaction shown on the right represents the aggregation of the polymer. The interfacial tension at the PPO/water and PEO/water increases in the presence of Cl^-. As a consequence, the phase transition temperature for both steps decreases.

key factor in determining how cations affect the phase transition temperature of the polymer. Cations interact with the polymer in three ways: directly binding to the oxygen in the polymer, sharing one water molecule with the polymer in the hydration layer, or interacting with the polymer via two water molecules.

EXPERIMENTAL SECTION

All of the chloride salts employed in this study, LiCl, NaCl, KCl, RbCl, CsCl, NH_4Cl, $MgCl_2$, $CaCl_2$, $SrCl_2$, $BaCl_2$, $CoCl_2$, $NiCl_2$, $CuCl_2$, and $CdCl_2$, were ordered from Fisher Scientific Inc. Pluronic L44, average molecular weight of 2200 D, was provided by BASF Corporation (Edison, NJ). Low-conductivity H_2O with a minimum resistivity of 18 MΩ·cm produced from a NANOpure Ultrapure Water System (Barnstead, Dubuque, IA) was used to prepare all the polymer and salt solutions. Stock solutions of L44 at 20 mg/mL in water were prepared at room temperature. Aliquots of these solutions were mixed with water or inorganic salt solutions to the desired concentrations. The final polymer concentration for all measurements was 10 mg/mL. The concentrations of inorganic salts ranged from 0 to 2.0 M. Due to low salt solubility, measurements at 2.0 M salt concentration were not carried out for $BaCl_2$, $SrCl_2$, $CoCl_2$, and $NiCl_2$.

The phase transition temperatures of L44 solutions in the presence of chloride salts were measured with an automated melting point apparatus (Optimelt MPA100, Stanford Research System).[4] Briefly, three capillary tubes each filled with 10 μL of sample were placed into the apparatus and heated at a rate of 2 °C/min. To ensure both phase transitions were observed, we studied the temperature range from 35 to 95 °C. Real-time images of the samples were continuously captured by a built-in camera. Digital image processing was used to produce plots of scattering intensity as a function of temperature. Phase transition temperatures were recorded as the initial break points of these curves.[61] Micellization temperatures were recorded as the first phase transition that occurs at lower temperature; cloud point temperatures were recorded as the second phase transition that appears at higher temperature. The phase transition temperature at each salt concentration was the average value of six repeated measurements. Typical standard errors of the measurements are about ±0.05 to ±0.10 °C.

RESULTS AND DISCUSSION

Phase Transition Temperature of PEO-PPO-PEO as a Function of Salt Concentration. Fourteen chloride salts, LiCl, NaCl, KCl, RbCl, CsCl, NH_4Cl, $MgCl_2$, $CaCl_2$, $SrCl_2$, $BaCl_2$, $CoCl_2$, $NiCl_2$, $CuCl_2$, and $CdCl_2$, were employed to investigate the specific cation effects on the phase behaviors of a PEO-PPO-PEO block copolymer, L44. Our previous studies have shown that L44 underwent a two-step phase transition in the presence of NaCl.[4] Switching the cation from a sodium ion to the cations listed above does not alter the two-step feature of the phase transition. The first phase transition that occurs at lower temperature is micelle formation due to the dehydration of PPO blocks. The second phase transition at higher temperature is the aggregation of micelles induced by dehydration of the PEO blocks. Figure 2 shows the plots of the phase transition temperatures of L44 solutions as a function of ion identity and salt concentration for monovalent cations. In both the first and second steps, the phase transition temperature changes linearly with salt concentration for NaCl, KCl, RbCl, and CsCl. On the other hand, LiCl and NH_4Cl show a nonlinear dependence of phase transition temperature on salt concentration. The nonlinear dependence in the second step is more obvious than that in the first step. The relative ability of monovalent cations to decrease the phase transition temperature can be ranked as $Cs^+ > Rb^+ > K^+ > Na^+ > NH_4^+ > Li^+$. The plots for phase transition temperature vs salt concentration exhibit clear curvatures when divalent cations of alkaline earth metals and transition metals are introduced into the solution as shown in Figure 3. For clarity, the data for alkaline earth metal cations and transition metal cations are plotted separately. Among their own series, the abilities of divalent cations to depress the phase transition temperature are
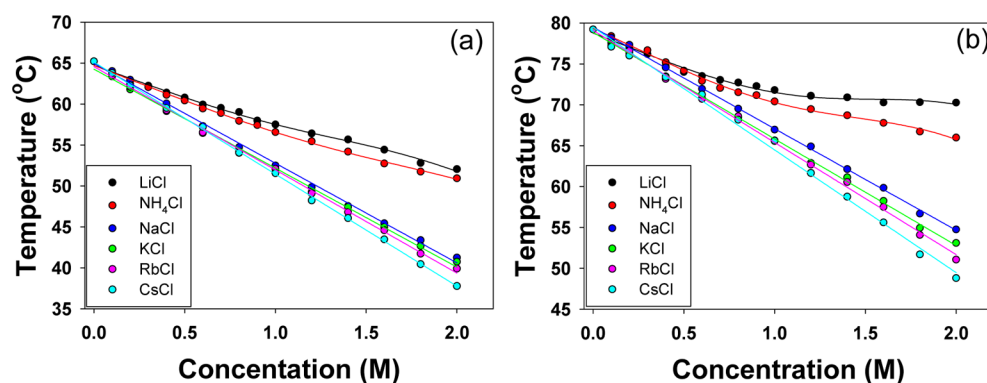
Figure 2. Phase transition temperature of L44 as a function of monovalent cation type and concentration: (a) the first step of the phase transition for L44 plotted vs concentration of monovalent cations; (b) the second step of the phase transition for L44 against concentration of monovalent cations. The lines represent the best fit to the data using eq 1 (NaCl, KCl, RbCl, and CsCl) or eq 2 (LiCl and NH$_4$Cl).
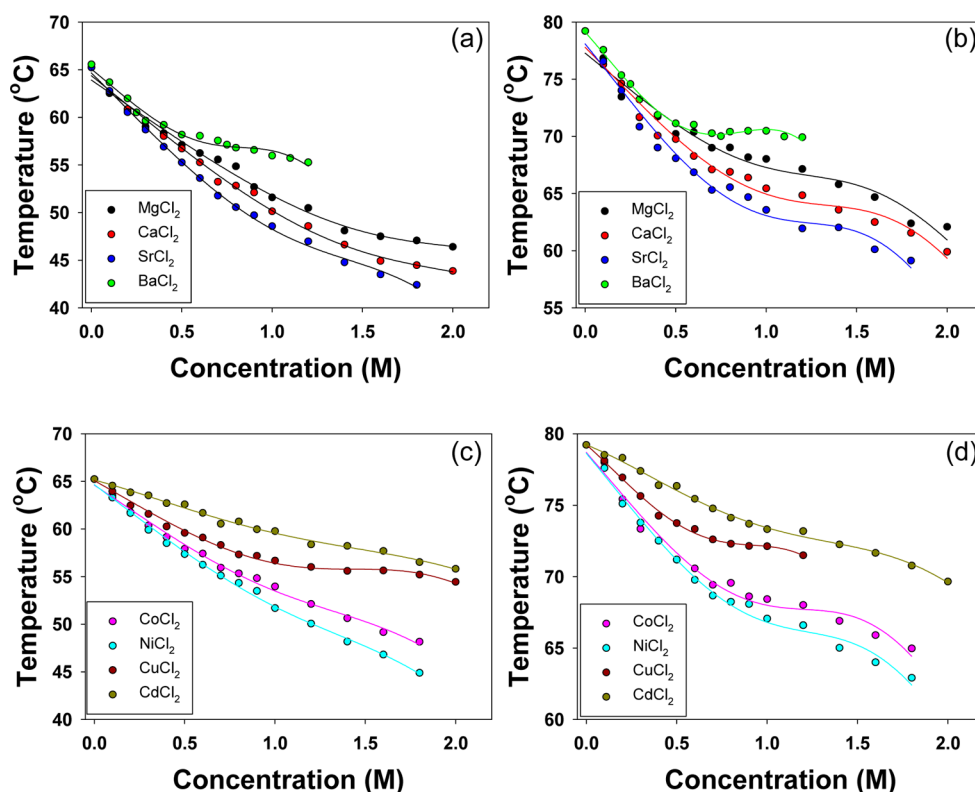

Figure 3. Phase transition temperature of L44 as a function of divalent cation type and concentration: (a) the first step of the phase transition for L44 plotted vs concentration of alkaline earth metal cations; (b) the second step of the phase transition for L44 plotted vs concentration of alkaline earth metal cations; (c) the first step of the phase transition for L44 plotted vs concentration of transition metal cations; (d) the second step of the phase transition for L44 plotted vs concentration of transition metal cations. The lines represent the best fit to the data using eq 2.

ranked as Sr^{2+} > Ca^{2+} > Mg^{2+} > Ba^{2+} and Ni^{2+} > Co^{2+} > Cu^{2+} > Cd^{2+}.

Modeling of the Phase Transition in the Presence of Cations. The effect of the common anion, Cl$^-$, employed in this study can be explained by Cl$^-$'s ability to change the interfacial tension at the hydrophobic/aqueous interfaces as discussed previously.[4] Both steps of the phase transition are linearly dependent on chloride concentration.[4] Clearly, we are not able to isolate cations from a salt solution. Therefore, the effects of salts we observed herein are joint effects of cation and the Cl$^-$ anion. In aqueous solutions, the solvation process for a cation is its transfer from a fixed point in vacuum to a fixed point in solution.[62] A model of a hydrated ion is a bare ion surrounded by a layer of immobilized water molecules. Beyond

this hydration layer, the cation still interacts with its surroundings electrostatically.[62] Cations could interact with the polymer in three ways distinguished by how they share water molecules with the polymer. Cations and the polymer can interact directly, share one water molecule in their first hydration shell, or interact via two water molecules in their first hydration shells as shown in Figure 4. This model is similar to a reaction of two ionic solutes in aqueous solution, which can be written as M$^+$ + X$^-$ ⇔ M$^+$∥X$^-$ ⇔ M$^+$|X$^-$ ⇔ MX.[51,52,63] MX represents the product of the reaction with no water molecule between M$^+$ and X$^-$. M$^+$|X$^-$ and M$^+$∥X$^-$ are intermediate states with one water molecule (contact ion pair) or two water molecules (solvent separated ion pair) bridging M$^+$ and X$^-$.
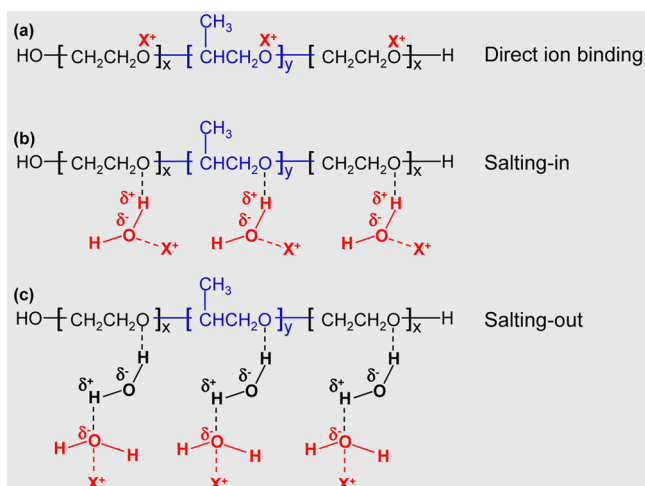
Figure 4. Schematic illustration of the interactions between cations and PEO-PPO-PEO: (a) the direct association of cations to the polar moieties of the polymer (oxygen); (b) cations and the polymer are bridged by one water molecule; (c) cations and the polymer are separated by two water molecules.

First, direct binding of cations to the oxygen in the polymer through electrostatic interactions will increase the polymer solubility and raise the phase transition temperature (Figure 4a). The cations with high charge densities such as Li$^+$ and divalent cations have a tendency to associate with the polymer via electrostatic interactions. If the hydration of a certain cation is relatively weak, it could shed its hydration water and bind to the polar part of the polymer chains (the oxygen atoms). The binding of cations to oxygen should reach saturation at high cation concentrations.[1−4,36] The binding of divalent cations to the polymer could create a bridge between two polymer chains because the two positive charges are able to interact with two oxygen atoms in polymer chains.[64] Second, cations could polarize the water molecules that are directly hydrogen-bonded to the oxygen in the polymer (Figure 4b). When a cation is present in the vicinity of a water molecule that is directly hydrogen-bonded to the polymer, the cation draws electron density to the oxygen and leaves the hydrogen in the water

molecule more positively charged. The cation in turn strengthens the hydrogen binding of the water molecule to the polymer's oxygen. A water molecule in the first hydration layer serves as a bridge between the polymer and the cation. This mechanism makes the dehydration from the polymer more difficult and increases the phase transition temperature. Third, the interactions between the cations and the polymer could be mediated by two water molecules bridging the cation and the oxygen in the polymer (Figure 4c). This mechanism actually weakens the hydrogen bonding between water and the oxygen in the polymer chains. Therefore, the hydration water around the polymer is easier to remove and the phase transition temperature decreases. Two forms of polarization of hydration water around the polymer's oxygen should coexist when a cation is present in the vicinity of the polymer. The effect of water polarization by cations should be a net result of the competition and balance between these two forms of polarization. Moreover, the magnitude of these two forms of polarization of water molecules should be linearly proportional to the cation concentration in the solution.[1,3] The ability of a cation to polarize water molecules should correlate to the hydration thermodynamics of the cation.[46] It should be noted that the model shown in Figure 4 is consistent with the thermodynamic discussion provided below. The model will need to be further validated by spectroscopic and computational studies of the interactions between cations and the polymer.

On the basis of the interactions between cations and the polymer, the changes in phase transition temperatures of the polymer in the presence of cations can be modeled by simple equations. For the linear dependence of the phase transition temperature on salt concentration, namely, NaCl, KCl, RbCl, and CsCl, the data can be fitted into a linear equation:

$$T = T_0 + c[M] \tag{1}$$

where T is the phase transition temperature of the polymer at any salt concentration, T_0 is the phase transition temperature in the absence of salt, and $[M]$ is the molar concentration of salt. The constant c has units of °C/M and represents the rate of the change in phase transition temperature of the polymer. For all other cations that show curvatures of phase transition

Table 1. Fitted Values of B_{max}, K_d, b, and c Abstracted from the Plots of Phase Transition Temperature Measurements as a Function of Salt Concentration^a

	first step					second step				
cation	B_{max} (°C)	K_d (M)	b (M^{-2})	c (°C/M)	residue c (°C/M)	B_{max} (°C)	K_d (M)	b (M^{-2})	c (°C/M)	residue c (°C/M)
Li$^+$	6.7	4.1	−0.79	−9.6	2.6	27.6	4.1	−0.51	−15.3	−2.9
NH$_4^+$	10.5	4.9	−0.46	−10.7	1.5	36.4	3.1	−0.46	−21.4	−9.0
Na$^+$				−12.2	0				−12.4	0
K$^+$				−12.1	0.1				−13.0	−0.6
Rb$^+$				−12.6	−0.4				−13.7	−1.3
Cs$^+$				−13.1	−0.9				−14.0	−1.6
Mg^{2+}	25.5	8.3	−0.43	−16.1	8.3	34.1	3.8	−0.77	−23.6	1.2
Ca^{2+}	35.6	6.2	−0.39	−21.0	3.4	39.8	3.6	−0.69	−27.1	−2.3
Sr^{2+}	38.5	3.7	−0.60	−29.0	−4.6	48.4	3.3	−0.78	−34.3	−9.5
Ba^{2+}	27.4	2.1	−1.69	−28.2	−3.8	44.3	2.1	−1.51	−38.7	−13.9
Co^{2+}	18.9	3.5	−0.69	−18.0	6.4	35.6	3.2	−0.82	−25.6	−0.8
Ni^{2+}	17.3	3.7	−0.69	−18.9	5.5	34.9	3.2	−0.79	−26.1	−1.3
Cu^{2+}	29.4	4.0	−0.62	−18.0	6.4	33.1	2.0	−1.19	−27.7	−2.9
Cd^{2+}	27.8	2.7	−0.37	−15.3	9.1	39.3	2.5	−0.43	−20.9	3.9

^{a}Residue c values relative to that of NaCl are also included.

temperatures as a function of salt concentration, the data are modeled using a linear term plus a Langmuir-type binding term:[6,36]

$$T = T_0 + c[M] + \frac{B_{max}[M]e^{-b[M]^2}}{K_d + [M]e^{-b[M]^2}} \qquad (2)$$

in which T, T_0, c, and $[M]$ bear the same physical meanings as in eq 1. B_{max} represents the maximum phase transition temperature increase due to direct cation binding at the saturation. K_d represents the apparent dissociation constant of the cations from the polymer. A lower K_d corresponds to a tighter binding. The term in the exponential, b, describes the electrostatic interactions between the polymer and the cation. The fit with eq 2, a quadratic form of the Langmuir equation, should be considered as phenomenological to generate the best fitting as was observed with cations interacting with an elastin-like polypeptide.[36] The lines that are drawn through the data in Figures 2 and 3 are fitting lines using eqs 1 and 2. The abstracted fitting parameters are summarized in Table 1. These fitting parameters are used to correlate to the physical properties of cations listed in Table 2. The numerical values of hydration thermodynamics for the different cations indicate that the ΔG_{hydr} is primarily enthalpic at moderate temperatures.

Table 2. Thermodynamic Properties of Hydration and the Ionic Radius of the Cations Employed in This Study[a]

cation	ΔS_{hydr} (J K^{-1} mol^{-1})	ΔH_{hydr} (kJ mol^{-1})	ΔG_{hydr} (kJ mol^{-1})	ionic radius (pm)
Li$^+$	−142	−531	−481	69
NH$_4^+$	−112	−329	−292	148
Na$^+$	−111	−416	−375	102
K$^+$	−74	−334	−304	138
Rb$^+$	−65	−308	−281	149
Cs$^+$	−59	−283	−258	170
Mg^{2+}	−331	−1949	−1838	72
Ca^{2+}	−252	−1602	−1515	100
Sr^{2+}	−242	−1470	−1386	113
Ba^{2+}	−205	−1332	−1258	136
Co^{2+}	−337	−2036	−1922	75
Ni^{2+}	−351	−2119	−1992	69
Cu^{2+}	−320	−2123	−2016	73
Cd^{2+}	−285	−1833	−1763	95

[a]These values are obtained from ref 46.

Effects of Monovalent Cations. As shown in Figure 2, the phase transition of the polymer in the presence of NaCl, KCl, RbCl, and CsCl decreases linearly with salt concentration. This decrease indicates that Na$^+$, K$^+$, Rb$^+$, and Cs$^+$ do not bind to the polymer through direct binding to the oxygen in the polymer chains. In contrast, Li$^+$ and NH$_4^+$ show significant binding to the polymer with disassociation constant (K_d) of ∼4 M. B_{max} values for Li$^+$ and NH$_4^+$ in the second step are larger than those of the first step, meaning that the effect of binding to the two PEO ending blocks is greater than binding to the PPO central block of the polymer. This behavior is consistent with the results reported previously that Li$^+$ interacts with PEO blocks stronger than the PPO blocks in the polymer.[65] The linear constant, c, includes the influence of Cl$^-$ and water polarization effects as discussed above. The c values are very similar to each other among the monovalent cations except for Li$^+$ and NH$_4^+$. Here it is assumed that the sodium ion has equal ability to

polarize water molecules through mechanisms 2 and 3 as shown in Figure 4b,c, so the c value for NaCl is solely from Cl$^-$. In other words, the following discussions on cation effects are based on comparison to NaCl as a standard. If a c value for a certain cation is more negative than NaCl, that particular cation will have a salting-out effect as compared to Na$^+$. As a consequence, the cation interacting with the polymer via two water molecules (Figure 4c) will be more prevalent than the mechanism shown in Figure 4b. The residue c (°C/M) column in Table 1 lists the c values after taking the influence of Cl$^-$ (c value for NaCl) out. Positive residue c values can be interpreted as salting-in by the cation sharing one water molecule with the polymer (Figure 4b), while negative residue c values indicate a salting-out effect by the cation interacting with the polymer via two water molecules (Figure 4c). In the first step of the phase transition that involves dehydration of PPO blocks, Li$^+$ and NH4$^+$ show mild salting-in effects; K$^+$ is about the same as Na$^+$, neither salting-in nor salting-out; Rb$^+$ and Cs$^+$ exhibit slight salting-out effects. In the second step of the phase transition in which the PEO blocks are dehydrated, all of these monovalent cations have salting-out effects.

The constants c for monovalent cations are plotted against the thermodynamic properties of cations including hydration entropy (ΔS_{hydr}), hydration enthalpy (ΔH_{hydr}), and hydration Gibbs free energy (ΔG_{hydr}) as shown in Figure 5. These plots help us indentify the correlations between the changes in phase transition temperature as a function of salt concentration and the hydration thermodynamics of cations. It can be observed that strongly hydrated cations with more negative ΔS_{hydr}, ΔH_{hydr}, and ΔG_{hydr} tend to show less negative c values. The correlation of c values to the hydration of cations is quite good except for Li$^+$ in the second step of the phase transition and NH$_4^+$ in both steps. The deviation of NH$_4^+$ from the trend line may be due to its capability of forming multiple hydrogen bonds with water molecules and the polymer.[36,66] The cations shown in Figure 5 carry one positive charge so larger cations have smaller charge density. Therefore, larger monovalent cations have weaker interactions with water molecules through electrostatic attraction as compared to smaller monovalent cations. In general, hydration Gibbs free energy of ions is inversely proportional to ionic radius of the ions.[62] Therefore, the c values should also correlate to the ionic radius of cations as demonstrated in Figure 5d. Larger cations such as Cs$^+$ are hydrated weakly as compared to smaller cations, so they tend to interact with the polymer via two water molecules. As a consequence, larger cations have a salting-out effect on the polymer, and more negative c values are observed for these cations. The c value indicated by the blue dashed lines in Figure 5 represents the contribution from Cl$^-$. The monovalent cations that are located above the blue dashed lines have salting-in effects on the polymer while those that appear below have salting-out effects.

Effects of Divalent Cations. When divalent cations of alkaline earth metals and transition metals are introduced into the polymer solution, the plots of phase transition temperature as a function of salt concentration show clear curvatures (Figure 3). All of these divalent cations bind to the polymer, and the extent of cation binding can be characterized by the magnitude of B_{max}. Plots of B_{max} with respect to the thermodynamic properties of cation hydration are shown in Figure 6a−c. The plots suggest that strongly hydrated cations such as Ni^{2+} and Co^{2+} show smaller B_{max}, and weakly hydrated cations show larger B_{max}. Also, B_{max} values correlate well to the
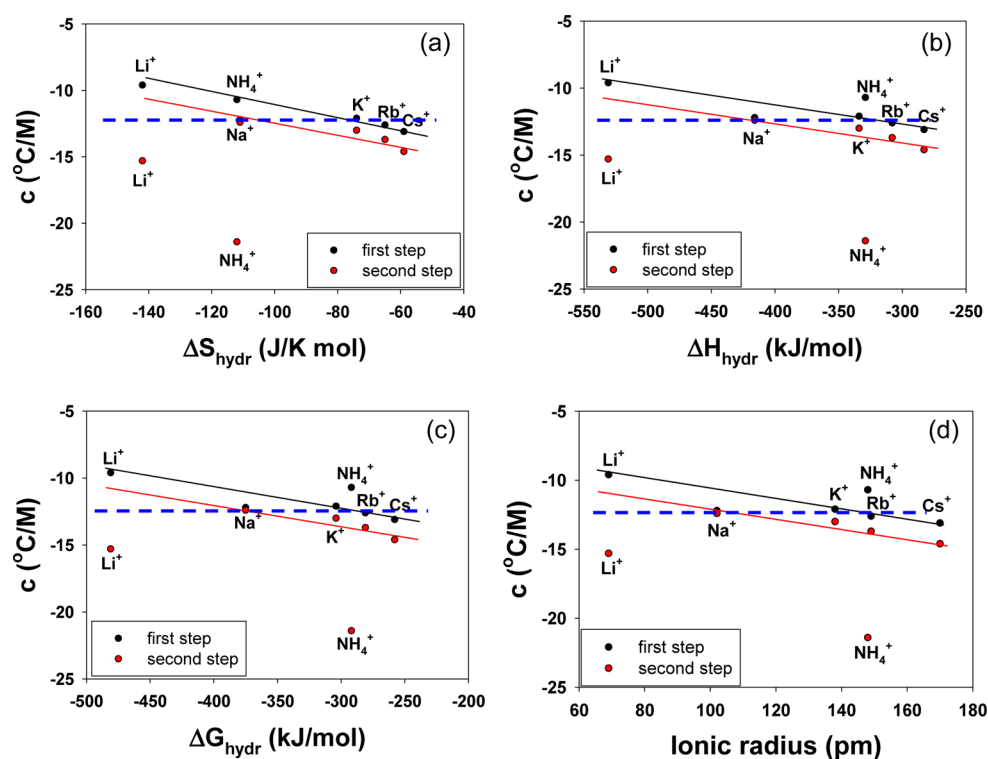
Figure 5. Plots of c values vs properties of monovalent cations: (a) c values vs hydration entropy; (b) c values vs hydration enthalpy; (c) c values vs hydration Gibbs free energy; (d) c values vs ionic radius. The blue dashed lines represent the contribution from Cl^- to the c value.
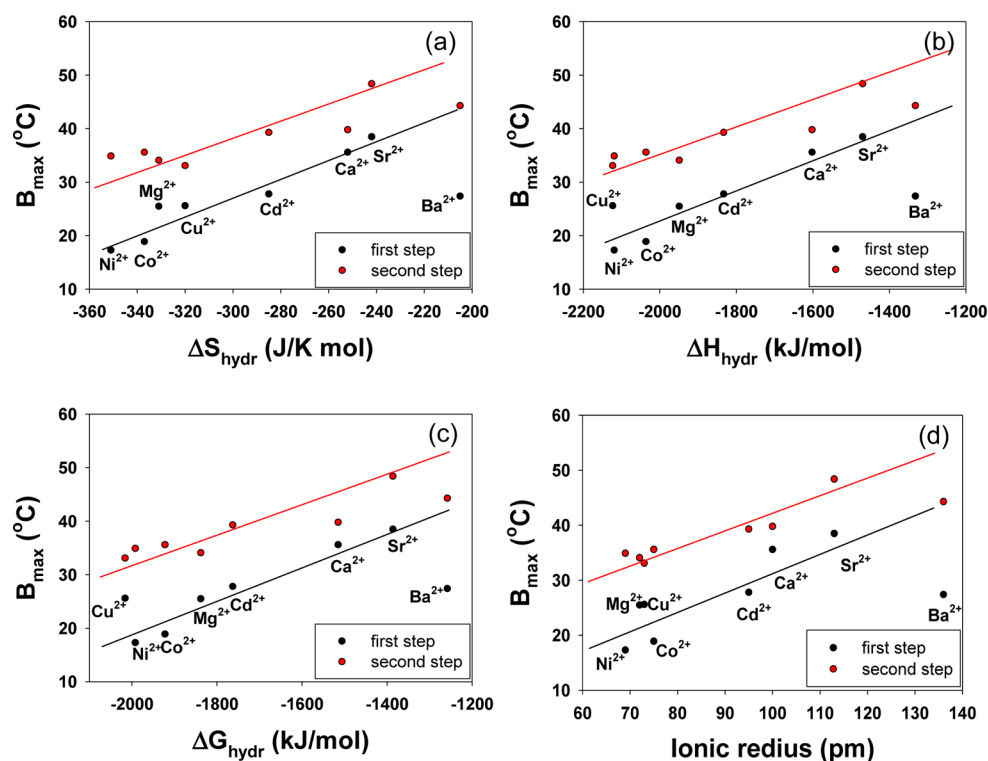

Figure 6. Plots of B_{max} values vs properties of divalent cations: (a) B_{max} values vs hydration entropy; (b) B_{max} values vs hydration enthalpy; (c) B_{max} values vs hydration Gibbs free energy; (d) B_{max} values vs ionic radius.

ionic radius of the cations as shown in Figure 6d. Larger divalent cations are weakly hydrated as compared to smaller divalent cations, so larger cations can shed their hydration water to have stronger binding to the polymer.

The analysis of c values for divalent cations follows the same assumption as for the monovalent cations that we take Na^+ as a neutral cation in the discussion of salting-in or salting-out ability of divalent cations. To calculate the residue c, twice as
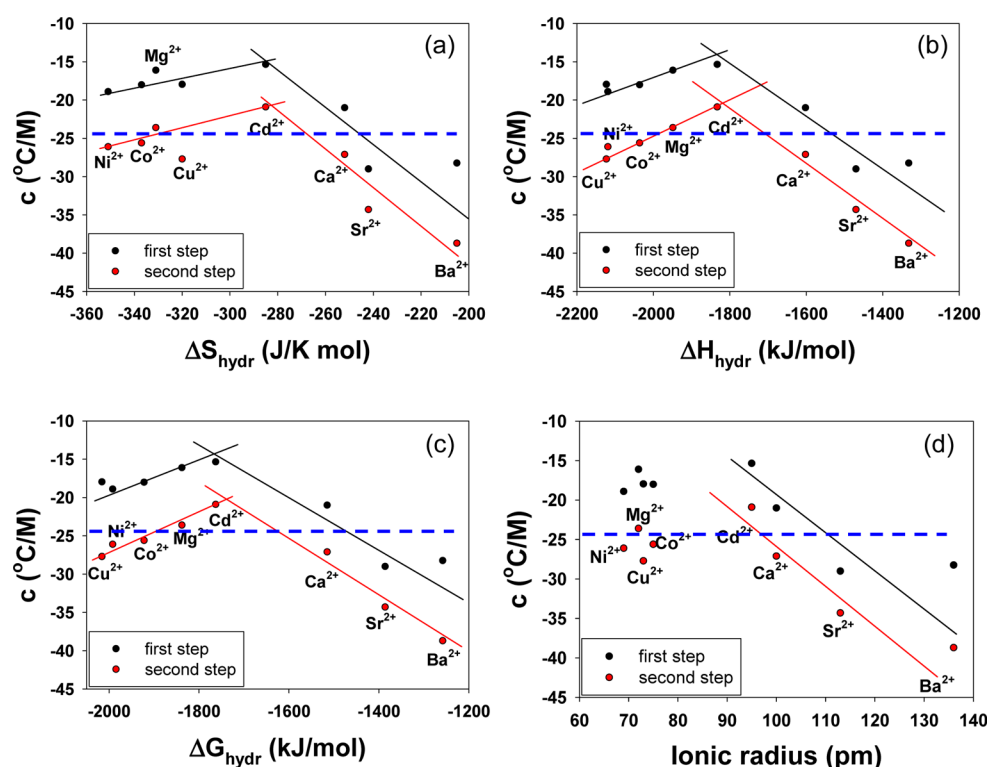
Figure 7. Plots of c values vs properties of divalent cations: (a) c values vs hydration entropy; (b) c values vs hydration enthalpy; (c) c values vs hydration Gibbs free energy; (d) c values vs ionic radius. The blue dashed lines represent the contribution from Cl^- to the c value.
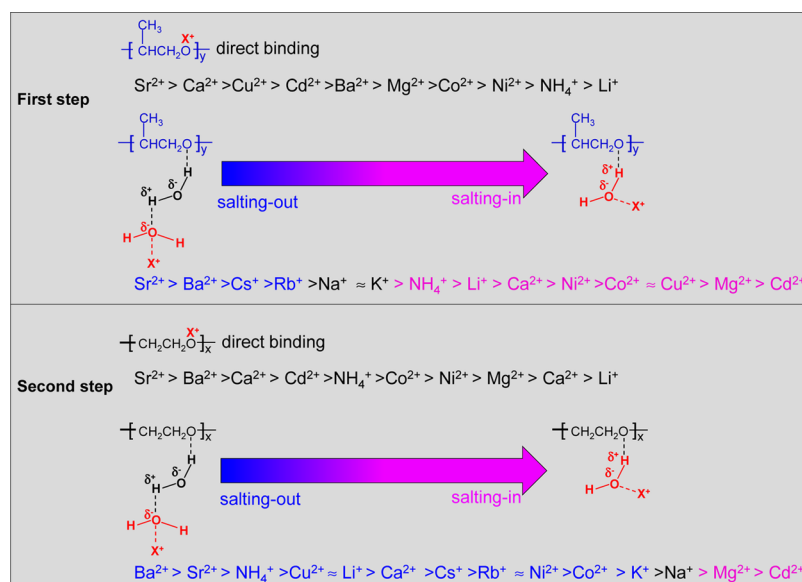

Figure 8. Summary of cation effects on each step of the phase transition of the polymer. The direct cation binding is ranked by B_{max} values for the cations. The salting-out and salting-in ability of cations is ordered by residue c values.

much as the c value for NaCl is subtracted from the total c values for the salts containing divalent cations. In the first step of the phase transition, almost all the divalent cations show positive residue c values except for Sr^{2+} and Ba^{2+}. These positive residue c values indicate that the cations interact with the PPO blocks through sharing one water molecule (salting-in, Figure 4b). On the other hand, Sr^{2+} and Ba^{2+} interact with the PPO blocks via two water molecules (salting-out, Figure 4c). In the second step of the phase transition, only Mg^{2+} and Cd^{2+} exhibit salting-in effects while all other divalent cations show salting-

out effects. When the c values are plotted vs the thermodynamic properties of divalent cations, very interesting correlations emerge as shown in Figure 7a−c. There is a maximum in c value around the position of Cd^{2+}. To the right of Cd^{2+}, c values decrease with the decrease in hydration (less negative in ΔS_{hydr}, ΔH_{hydr}, and ΔG_{hydr}). To the left of Cd^{2+}, in contrast, c values increase with the decrease in hydration. Cd^{2+} has the strongest ability to salt the polymer into solution. Divalent cations with stronger or weaker hydration than Cd^{2+} show decreased salting-in effects as compared to Cd^{2+}. This phenomenon is consistent

with the Law of Matching Water Affinities (LMWA) that was proposed recently by Collins.[67−69] LMWA states that the least soluble salts are formed by ion pairs with similar hydration energies,[67−69] and the law has been applied to explain the interactions between ions and charged protein surfaces.[49,50] It should be pointed out that LMWA behavior, particularly with divalent cations, observed in our current studies is the interaction of cations with a neutral polymer. The blue dashed lines in Figure 7 represent the contribution from Cl^-. The divalent cations that appear above the blue dashed lines are salting-in agents while those that appear below have salting-out effects on the phase transition of the polymer. Mg^{2+} and Cd^{2+} have salting-in effects on both steps of the phase transition, while Sr^{2+} and Ba^{2+} show salting-out effect on both steps. All other divalent cations studied herein salt in the polymer in the first step of the phase transition but salt out the polymer in the second step. In general, the c values are less negative in the first step as compared to the second step of the phase transition. If the same c values are plotted against the ionic radius of divalent cations, this plot shows a good correlation between the c values and the ionic radius for the divalent cations to the right of Cd^{2+} (Figure 7d). For the divalent cations that are to the left of Cd^{2+}, the c values are clustered together because these cations are very similar in size.

Ordering of Cation Effects on the Phase Transition Temperature of PEO-PPO-PEO. On the basis of the discussion above, the effects on cations on the phase behaviors of PEO-PPO-PEO are ranked as shown in Figure 8. In both steps of the phase transition, Na^+, K^+, Rb^+, and Cs^+ do not bind to the polymer, and these four cations are not included in the ranking of direct ion binding. The ability of cations to bind to the oxygen in the polymer is ordered by their B_{max} values. The relative position of some cations varies slightly between the two steps. However, a general trend is observed that cations with weaker hydration (to the left end of the series in Figure 8) show stronger binding than the cations with stronger hydration. The ability of cations to polarize the water molecules that are in the first hydration layer of the polymer is ranked by their net contributions to the c values (residue c values in Table 1) from the most negative to the most positive as in Figure 8. The cations with weaker hydration tend to interact with the polymer via two water molecules to induce a salting-out effect on the polymer. On the other hand, cations with stronger hydration interact with the polymer by sharing the same hydration water to induce a salting-in effect on the polymer. The first and the second steps of the phase transitions share a common trend that polarization of water in the first hydration layer of the polymer is determined by the hydration of cations. It should be noted that, in the first step of the phase transition, only four cations (Sr^{2+}, Ba^{2+}, Cs^+, Rb^+) show salting-out effects and all the other cations have salting-in effects on the polymer. In contrast, in the second step of the phase transition, only Mg^{2+} and Cd^{2+} have salting-in effects and all other cations to the left of Na^+ salt the polymer out of the solution.

CONCLUSIONS

This work investigates the mechanisms of cation effects on the phase behaviors of a PEO-PPO-PEO block copolymer. From the results, it is concluded that the hydration thermodynamics of cations is a key factor in determining how cations modulate the phase transition temperature of PEO-PPO-PEO. The cations' degree of hydration strongly influences how they interact with the polymer. Cations could bind directly to the

polymer, share one water molecule with the polymer in a hydration layer, or interact with the polymer via a bridge of two water molecules. These mechanisms may explain the specific cation effects on other aqueous processes in solution. The relative position of a particular cation may shift in the Hofmeister series or switch from salting-out to salting-in (or vice versa) if the surface properties of a system change. However, the hydration of cations should be a common mechanism to consider when specific cation effects are discussed.

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Zhang, Y. J.; Furyk, S.; Bergbreiter, D. E.; Cremer, P. S. Specific Ion Effects on the Water Solubility of Macromolecules: PNIPAM and the Hofmeister Series. *J. Am. Chem. Soc.* **2005**, *127*, 14505−14510.

(2) Zhang, Y. J.; Furyk, S.; Sagle, L. B.; Cho, Y.; Bergbreiter, D. E.; Cremer, P. S. Effects of Hofmeister Anions on the LCST of PNIPAM as a Function of Molecular Weight. *J. Phys. Chem. C* **2007**, *111*, 8916−8924.

(3) Cho, Y. H.; Zhang, Y. J.; Christensen, T.; Sagle, L. B.; Chilkoti, A.; Cremer, P. S. Effects of Hofmeister Anions on the Phase Transition Temperature of Elastin-Like Polypeptides. *J. Phys. Chem. B* **2008**, *112*, 13765−13771.

(4) Deyerle, B. A.; Zhang, Y. J. Effects of Hofmeister Anions on the Aggregation Behavior of PEO-PPO-PEO Triblock Copolymers. *Langmuir* **2011**, *27*, 9203−9210.

(5) Thormann, E. On Understanding of the Hofmeister Effect: How Addition of Salt Alters the Stability of Temperature Responsive Polymers in Aqueous Solutions. *RSC Adv.* **2012**, *2*, 8297−8305.

(6) Zhang, Y. J.; Cremer, P. S. The Inverse and Direct Hofmeister Series for Lysozyme. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 15249−15253.

(7) Salis, A.; Cugia, F.; Parsons, D. F.; Ninham, B. W.; Monduzzi, M. Hofmeister Series Reversal for Lysozyme by Change in pH and Salt Concentration: Insights from Electrophoretic Mobility Measurements. *Phys. Chem. Chem. Phys.* **2012**, *14*, 4343−4346.

(8) Boström, M.; Parsons, D. F.; Salis, A.; Ninham, B. W.; Monduzzi, M. Possible Origin of the Inverse and Direct Hofmeister Series for Lysozyme at Low and High Salt Concentration. *Langmuir* **2011**, *27*, 9504−9511.

(9) Broering, J. M.; Bommarius, A. S. Evaluation of Hofmeister Effects on the Kinetic Stability of Proteins. *J. Phys. Chem. B* **2005**, *109*, 20612−20619.

(10) von Hansen, Y.; Kalcher, I.; Dzubiella, J. Ion Specificity in α-Helical Folding Kinetics. *J. Phys. Chem. B* **2010**, *114*, 13815−13822.

(11) Crevenna, A. H.; Naredi-Rainer, N.; Lamb, D. C.; Wedlich-Söldner, R. Effects of Hofmeister Ions on the α-Helical Structure of Protein. *Biophys. J.* **2012**, *102*, 907−915.

(12) Pinna, M. C.; Bauduin, P.; Touraud, D.; Monduzzi, M.; Ninham, B. W.; Kunz, W. Hofmeister Effects in Biology: Effect of Choline Addition on the Salt-Induced Super Activity of Horseradish Peroxidase

and Its Implication for Salt Resistance of Plants. *J. Phys. Chem. B* **2005**, *109*, 16511−16514.

(13) Pinna, M. C.; Salis, A.; Monduzzi, M.; Ninham, B. W. Hofmeister Series: The Hydrolytic Activity of Aspergillus Niger Lipase Depends on Specific Anion Effects. *J. Phys. Chem. B* **2005**, *109*, 5406−5408.

(14) Bauduin, P.; Nohmie, F.; Touraud, D.; Neueder, R.; Kunz, W.; Ninham, B. W. Hofmeister Specific-Ion Effects on Enzyme Activity and Buffer pH: Horseradish Peroxidase in Citrate Buffer. *J. Mol. Liq.* **2006**, *123*, 14−19.

(15) Vrbka, L.; Jungwirth, P.; Bauduin, P.; Touraud, D.; Kunz, W. Specific Ion Effects at Protein Surfaces: A Molecular Dynamics Study of Bovine Pancreatic Trypsin Inhibitor and Horseradish Peroxidase in Selected Salt Solutions. *J. Phys. Chem. B* **2006**, *110*, 7036−7043.

(16) Hofmeister, F. Zur Lehre Von Der Wirkung Der Salze. *Arch. Exp. Pathol. Pharmakol.* **1888**, *24*, 247−260.

(17) Kunz, W.; Henle, J.; Ninham, B. W. 'Zur Lehre Von Der Wirkung Der Salze' (About the Science of the Effect of Salts): Franz Hofmeister's Historical Papers. *Curr. Opin. Colloid Interface Sci.* **2004**, *9*, 19−37.

(18) Lo Nostro, P.; Ninham, B. W. Hofmeister Phenomena: An Update on Ion Specificity in Biology. *Chem. Rev.* **2012**, *112*, 2286−2322.

(19) Zhang, Y. J.; Cremer, P. S. Interactions between Macro-molecules and Ions: The Hofmeister Series. *Curr. Opin. Chem. Biol.* **2006**, *10*, 658−663.

(20) Zhang, Y. J.; Cremer, P. S. Chemistry of Hofmeister Anions and Osmolytes. *Annu. Rev. Phys. Chem.* **2010**, *61*, 63−83.

(21) Kunz, W.; Neueder, R. In *Specific Ion Effects*; Kunz, W., Ed.; World Scientific Publishing Co.: 2009.

(22) Omta, A. W.; Kropman, M. F.; Woutersen, S.; Bakker, H. J. Negligible Effect of Ions on the Hydrogen-Bond Structure in Liquid Water. *Science* **2003**, *301*, 347−349.

(23) Batchelor, J. D.; Olteanu, A.; Tripathy, A.; Pielak, G. J. Impact of Protein Denaturants and Stabilizers on Water Structure. *J. Am. Chem. Soc.* **2004**, *126*, 1958−1961.

(24) Jungwirth, P.; Tobias, D. J. Ions at the Air/Water Interface. *J. Phys. Chem. B* **2002**, *106*, 6361−6373.

(25) Lund, M.; Jungwirth, P. Patchy Proteins, Anions, and the Hofmeister Series. *J. Phys.: Condens. Matter* **2008**, *20*, 494218.

(26) Lund, M.; Vacha, R.; Jungwirth, P. Specific Ion Binding to Macromolecules: Effects of Hydrophobicity and Ion Pairing. *Langmuir* **2008**, *24*, 3387−3391.

(27) Lund, M.; Vrbka, L.; Jungwirth, P. Specific Ion Binding to Nonpolar Surface Patches of Proteins. *J. Am. Chem. Soc.* **2008**, *130*, 11582−11583.

(28) Pegram, L. M.; Record, M. T. Hofmeister Salt Effects on Surface Tension Arise from Partitioning of Anions and Cations between Bulk Water and the Air-Water Interface. *J. Phys. Chem. B* **2007**, *111*, 5411−5417.

(29) Pegram, L. M.; Record, M. T. Thermodynamic Origin of Hofmeister Ion Effects. *J. Phys. Chem. B* **2008**, *112*, 9428−9436.

(30) Pegram, L. M.; Record, M. T. Quantifying Accumulation or Exclusion of H⁺, HO⁻, and Hofmeister Salt Ions near Interfaces. *Chem. Phys. Lett.* **2008**, *467*, 1−8.

(31) Smith, J. D.; Saykally, R. J.; Geissler, P. L. The Effect of Dissolved Halide Anions on Hydrogen Bonding in Liquid Water. *J. Am. Chem. Soc.* **2007**, *129*, 13847−13856.

(32) Wilson, E. K. Hofmeister Still Mystifies. *Chem. Eng. News* **2012**, *90* (29), 42−43.

(33) Chen, X.; Yang, T. L.; Kataoka, S.; Cremer, P. S. Specific Ion Effects on Interfacial Water Structure near Macromolecules. *J. Am. Chem. Soc.* **2007**, *129*, 12272−12279.

(34) Chen, X.; Flores, S. C.; Lim, S. M.; Zhang, Y. J.; Yang, T. L.; Kherb, J.; Cremer, P. S. Specific Anion Effects on Water Structure Adjacent to Protein Monolayers. *Langmuir* **2010**, *26*, 16447−16454.

(35) Flores, S. C.; Kherb, J.; Konelick, N.; Chen, X.; Cremer, P. S. The Effects of Hofmeister Cations at Negatively Charged Hydrophilic Surfaces. *J. Phys. Chem. C* **2012**, *116*, 5730−5734.

(36) Kherb, J.; Flores, S. C.; Cremer, P. S. Role of Carboxylate Side Chains in the Cation Hofmeister Series. *J. Phys. Chem. B* **2012**, *116*, 7389−7397.

(37) Beck, T. L. A Local Entropic Signature of Specific Ion Hydration. *J. Phys. Chem. B* **2011**, *115*, 9776−9781.

(38) Rembert, K. B.; Paterová, J.; Heyda, J.; Hilty, C.; Jungwirth, P.; Cremer, P. S. Molecular Mechanisms of Ion-Specific Effects on Proteins. *J. Am. Chem. Soc.* **2012**, *134*, 10039−10046.

(39) Ninham, B. W.; Yaminsky, V. Ion Binding and Ion Specificity: The Hofmeister Effect and Onsager and Lifshitz Theories. *Langmuir* **1997**, *13*, 2097−2108.

(40) Boström, M.; Williams, D. R. M.; Ninham, B. W. Special Ion Effects: Why the Properties of Lysozyme in Salt Solutions Follow a Hofmeister Series. *Biophys. J.* **2003**, *85*, 686−694.

(41) Ghosal, S.; Hemminger, J. C.; Bluhm, H.; Mun, B. S.; Hebenstreit, E. L. D.; Ketteler, G.; Ogletree, D. F.; Requejo, F. G.; Salmeron, M. Electron Spectroscopy of Aqueous Solution Interfaces Reveals Surface Enhancement of Halides. *Science* **2005**, *307*, 563−566.

(42) Finet, S.; Skouri-Panet, F.; Casselyn, M.; Bonnete, F.; Tardieu, A. The Hofmeister Effect as Seen by SAXS in Protein Solutions. *Curr. Opin. Colloid Interface Sci.* **2004**, *9*, 112−116.

(43) Schwierz, N.; Horinek, D.; Netz, R. R. Reversed Anionic Hofmeister Series: The Interplay of Surface Charge and Surface Polarity. *Langmuir* **2010**, *26*, 7370−7379.

(44) López-León, T.; Santander-Ortega, M. J.; Ortega-Vinuesa, J. L.; Bastos-González, D. Hofmeister Effects in Colloidal Systems: Influence of the Surface Nature. *J. Phys. Chem. C* **2008**, *112*, 16060−16069.

(45) Schwierz, N.; Horinek, D.; Netz, R. R. Anionic and Cationic Hofmeister Effects on Hydrophobic and Hydrophilic Surfaces. *Langmuir* **2013**, *29*, 2602−2614.

(46) Marcus, Y. *Ion Properties*; Marcel Dekker, Inc.: New York, 1997.

(47) Yang, L.; Fan, Y.; Gao, Y. Q. Differences of Cations and Anions: Their Hydration, Surface Adsorption, and Impact on Water Dynamics. *J. Phys. Chem. B* **2011**, *115*, 12456−12465.

(48) Okur, H. I.; Kherb, J.; Cremer, P. S. Cations Bind Only Weakly to Amides in Aqueous Solutions. *J. Am. Chem. Soc.* **2013**, *135*, 5062−5067.

(49) Vrbka, L.; Vondrasek, J.; Jagoda-Cwiklik, B.; Vacha, R.; Jungwirth, P. Quantification and Rationalization of the Higher Affinity of Sodium over Potassium to Protein Surfaces. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 15440−15444.

(50) Hess, B.; van der Vegt, N. F. A. Cation Specific Binding with Protein Surface Charges. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 13296−13300.

(51) Annapureddy, H. V. R.; Dang, L. X. Molecular Mechanism of Specific Ion Interactions between Alkali Cations and Acetate Anion in Aqueous Solution: A Molecular Dynamics Study. *J. Phys. Chem. B* **2012**, *116*, 7492−7498.

(52) Nguyen, P. T. M.; Nguyen, V. T.; Annapureddy, H. V. R.; Dang, L. X.; Do, D. D. Thermodynamics and Kinetics of Na⁺/K⁺-Formate Ion Pairs Association in Polarizable Water: A Molecular Dynamics Study. *Chem. Phys. Lett.* **2012**, *554*, 90−95.

(53) Heyda, J.; Vincent, J. C.; Tobias, D. J.; Dzubiella, J.; Jungwirth, P. Ion Specificity at the Peptide Bond: Molecular Dynamics Simulations of *N*-Methylacetamide in Aqueous Salt Solutions. *J. Phys. Chem. B* **2010**, *114*, 1213−1220.

(54) Du, H.; Wickramasinghe, R.; Qian, X. H. Effects of Salt on the Lower Critical Solution Temperature of Poly(*N*-Isopropylacrylamide). *J. Phys. Chem. B* **2010**, *114*, 16594−16604.

(55) Sedlák, E.; Stagg, L.; Wittung-Stafshede, P. Effect of Hofmeister Ions on Protein Thermal Stability: Roles of Ion Hydration and Peptide Groups? *Arch. Biochem. Biophys.* **2008**, *479*, 69−73.

(56) Tomé, L. I. N.; Pinho, S. P.; Jorge, M.; Gomes, J. R. B.; Coutinho, J. A. P. Salting-in with a Salting-out Agent: Explaining the Cation Specific Effects on the Aqueous Solubility of Amino Acids. *J. Phys. Chem. B* **2013**, *117*, 6116−6128.

(57) Štěpánková, V.; Paterová, J.; Damborský, J.; Jungwirth, P.; Chaloupková, R.; Heyda, J. Cation Specific Effects on Enzymatic

Catalysis Drive by Interactions at the Tunnel Mouth. *J. Phys. Chem. B* **2013**, *117*, 6394−6402.

(58) Alexandridis, P.; Hatton, T. A. Poly(Ethylene Oxide)-Poly-(Propylene Oxide)-Poly(Ethylene Oxide) Block-Copolymer Surfactants in Aqueous-Solutions and at Interfaces - Thermodynamics, Structure, Dynamics, and Modeling. *Colloids Surf., A* **1995**, *96*, 1−46.

(59) Alexandridis, P. Poly(Ethylene Oxide) Poly(Propylene Oxide) Block Copolymer Surfactants. *Curr. Opin. Colloid Interface Sci.* **1997**, *2*, 478−489.

(60) Alexandridis, P.; Holzwarth, J. F. Differential Scanning Calorimetry Investigation of the Effect of Salts on Aqueous Solution Properties of an Amphiphilic Block Copolymer (Poloxamer). *Langmuir* **1997**, *13*, 6074−6082.

(61) Schild, H. G.; Tirrell, D. A. Microcalorimetric Detection of Lower Critical Solution Temperatures in Aqueous Polymer-Solutions. *J. Phys. Chem.* **1990**, *94*, 4352−4356.

(62) Marcus, Y. Thermodynamics of Ion Hydration and Its Interpretation in Terms of a Commom Model. *Pure Appl. Chem.* **1987**, *59*, 1093−1101.

(63) Smith, D. E.; Dang, L. X. Computer Simulations of NaCl Association in Polarizable Water. *J. Chem. Phys.* **1994**, *100*, 3757−3766.

(64) Beaudoin, E.; Gourier, C.; Hiorns, R. C.; François, J. Structure and Properties of Hydrophobically End-Capped Poly(Ethylene Oxide) Solutions in the Presence of Monovalent and Divalent Cations. *J. Colloid Interface Sci.* **2002**, *251*, 398−408.

(65) Ganguly, R.; Aswal, V. K. Improved Micellar Hydration and Gelation Characteristics of PEO-PPO-PEO Triblock Copolymer Solutions in the Presence of LiCl. *J. Phys. Chem. B* **2008**, *112*, 7726−7731.

(66) Sada, K.; Tani, T.; Shinkai, S. Organic Ammonium Carboxylates as Supramolecular Building Blocks: The Role of Ionic Hydrogen Bonding. *Synlett* **2006**, *15*, 2364−2374.

(67) Collins, K. D. Ions from the Hofmeister Series and Osmolytes: Effects on Proteins in Solution and in the Crystallization Process. *Methods* **2004**, *34*, 300−311.

(68) Collins, K. D.; Neilson, G. W.; Enderby, J. E. Ions in Water: Characterizing the Forces That Control Chemical Processes and Biological Structure. *Biophys. Chem.* **2007**, *128*, 95−104.

(69) Collins, K. D. Sticky Ions in Biological Systems. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 5553−5557.