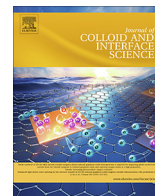




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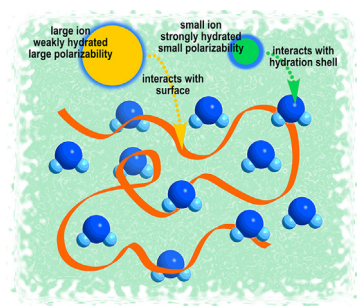
## The Hofmeister series: Specific ion effects in aqueous polymer solutions

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## GRAPHICAL ABSTRACT



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## ABSTRACT

Specific ion effects in aqueous polymer solutions have been under active investigation over the past few decades. The current state-of-the-art research is primarily focused on the understanding of the mechanisms through which ions interact with macromolecules and affect their solution stability. Hence, we herein first present the current opinion on the sources of ion-specific effects and review the relevant studies. This includes a summary of the molecular mechanisms through which ions can interact with polymers, quantification of the affinity of ions for the polymer surface, a thermodynamic description of the effects of salts on polymer stability, as well as a discussion on the different forces that contribute to ion–polymer interplay. Finally, we also highlight future research issues that call for further scrutiny. These include fundamental questions on the mechanisms of ion-specific effects and their correlation with polymer properties as well as a discussion on the specific ion effects in more complex systems such as mixed electrolyte solutions.

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## 1. Background

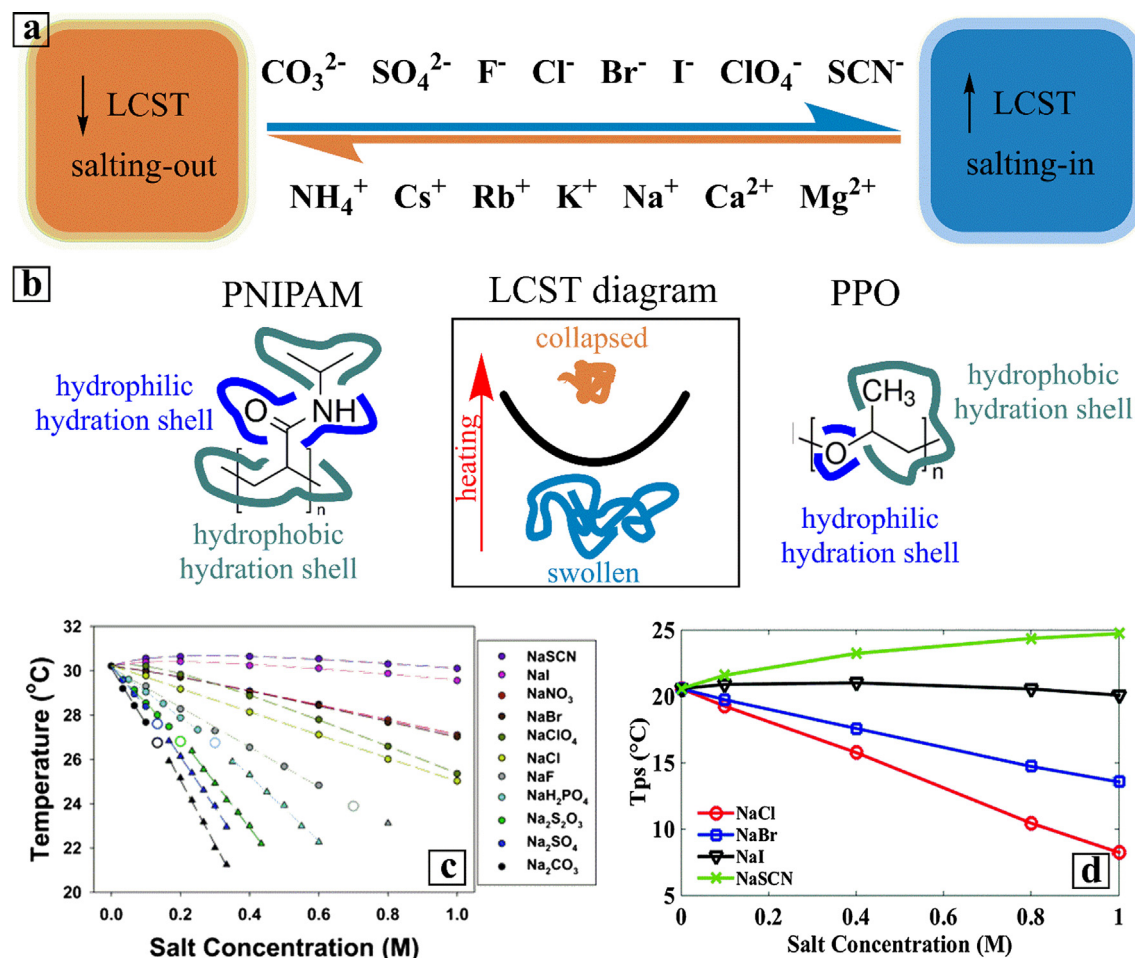
It has been more than a century since the Czech protein scientist Franz Hofmeister reported that ions, even those bearing the same charge, differently affect the solubility of egg-white protein in water [1,2]. He proposed separate anion and cation rankings, commonly known as the Hofmeister series, in the order of their ability to precipitate the investigated protein. Similarly, the unique effects of different ions on the stability of proteins in solution have been recognized as the Hofmeister effects. However, it was soon realized that the existence of Hofmeister, or more correctly “specific ion” effects, is not limited to aqueous protein solutions. Decades of active research have led to the belief that specific ion effects are ubiquitous. Various physicochemical phenomena, in both aqueous [3] and non-aqueous [4] media, such as enzymatic activity [5–7], bacterial growth [8–10], bubble coalescence [11–14], membrane permeability [15,16], molecular self-assembly [17–19], and colloidal stability [20–24] exhibit ion-specificity. Among these various systems, the ion-specific effects on the stability (solubility) of thermo-responsive polymers in water have been extensively investigated [25–33], which is the subject of our interest herein. Thermo-responsive polymers, which belong to the large family of smart, or stimuli-responsive, materials undergo a marked transition in water-miscibility and structural conformation upon temperature change [34–36]. The solution stability of such polymers is typically represented by a lower critical solution temperature (LCST) phase diagram. Below the phase transition (collapse) temperature, the polymer chain adopts a hydrated and swollen conformation and is considered as being hydrophilic. When heated to the collapse temperature, which is concentration dependent, the polymer chain will shrink and dehydrate to become a hydrophobic collapsed globule.

The specific effects of different ions on the stability of thermo-responsive polymers have often been quantified in terms of the shift in the collapse temperature as a function of salt type and concentration. According to the original (direct/normal) Hofmeister series (Fig. 1a), the ions located on the right side [e.g.,  $\text{SCN}^-$ ] can enhance the polymer stability and increase the phase separation temperature, an effect known as the salting-in effect. On the other hand, as the sequences become more left-shifted, the ions [e.g.,  $\text{F}^-$ ] exhibit a stronger destabilizing effect on the polymer in the solution (i.e., they decrease the collapse temperature) and produce a salting-out effect. Anions reportedly render a more pronounced effect than that exhibited by cations. Thus, the difference between the effects of various anions on the polymer stability in the presence of a fixed cation is more pronounced than the effects of various cations in the presence of a common anion. This difference has been attributed to the relatively larger size, higher polarizability, and different hydration characteristics of anions compared to those of cations [37–42]. Hence, most reported studies have focused on investigating the effects of different salts with a common cation, typically  $\text{Na}^+$  as the borderline ion. Therefore, herein, we primarily

discuss the anionic Hofmeister series; nevertheless, one must be aware that even for a fixed cation, the specific salt effects on the polymer stability are a cumulative result of both the anion and cation.

Even though the ion-specificity itself is accepted as an established principle, research on its mechanisms in macromolecular solutions is still under progression. In the earliest attempts, the Hofmeister-related phenomena were interpreted merely based on the specific interactions between the ions and water molecules and their subsequent influence on the water hydrogen-bonding network. By that time, it had already been confirmed that ions in water could no longer be considered as point charges because the ionic radii, shape, and type (cation or anion) could strongly affect the dynamics and energetics of the water molecules in their hydration shell [43–48]. The ion-specific hydration was therefore addressed by grouping the ions into kosmotropes and chaotropes according to their water affinity [49–54]. The term kosmotropic describes the behavior of ions of small size and high charge density, which tightly bind adjacent water molecules and immobilize them. In contrast, the term chaotropic represents the effect of large bulky ions of low surface charge density, which bind water less strongly than water binds itself in the bulk solution, thus “freeing up” the water molecules. Accordingly, the charge density of ions determines their water affinity, while the water affinity controls their behavior. The distinctions between the bulk solution behavior of kosmotropes and chaotropes have been highlighted in several works investigating physicochemical parameters such as the Jones-Dole viscosity coefficient [46], electrophoretic mobility [55,56], first and second shell hydration numbers [56–59], energetics of hydration [59–62], activity coefficient [63,64], and ion pairing [65,66].

Even though they employ different approaches, all these studies imply a thicker and tighter hydration shell for the kosmotropes and a thinner and looser hydration shell for the chaotropes. It has been shown that these hydration parameters mostly comply with the Hofmeister series. Therefore, the hydration strength, or the water affinity, was also considered as a satisfactory explanation for the specific ion effects in macromolecular solutions. However, later studies have revealed that such a rudimentary description fails to include all the facets of the ion-specificity when another solute (i.e., an interfacial region), is present. Depending on the interfacial properties (e.g., surface charge, polarity, softness, and inhomogeneity), anomalies and reversals in the Hofmeister series have been observed in multiple systems, indicating a close interplay between the ions and interface. Accordingly, besides the specificity in their hydration behavior, ions show specific interactions with surfaces that can give rise to their interfacial accumulation or depletion [67–75]. In an effort to assess the interplay between ions and surfaces, air–water and uncharged hydrophobic solute–water interfaces were investigated as model systems. For these uniform non-polar surfaces, it has been suggested that the weakly hydrated anions (chaotropes) preferentially accumulate at the surface, while



**Fig. 1.** (a) Hofmeister series: ions on the right side produce a salting-in (stabilizing) effect on the polymer, whereas the ions on the left side lead to a salting-out (destabilizing) effect.  $\text{Cl}^-$  and  $\text{Na}^+$  ions are typically considered as the borderline between the strongly and weakly hydrated anions and cations, respectively. (b) Schematic illustration of the hydration behavior of two model thermo-responsive polymers, poly(*N*-isopropylacrylamide) (PNIPAM) and poly(propylene oxide) (PPO). (c) Effect of the different sodium salts on the phase separation temperature of PNIPAM. (Reprinted with permission from [89]. Copyright (2019) American Chemical Society.) (d) Effect of the different sodium salts on the phase separation temperature of PPO. (Reproduced from [90] with permission from the PCCP Owner Societies).

the strongly hydrated anions (kosmotropes) are effectively depleted from the interfacial region. Notably, the trend for cations was reported to be more anomalous and less ion-specific. Such surface-related ion-specificity has been mainly attributed to the size- and shape-dependent polarizability of the ions and the contribution from the ion-surface dispersion forces, which were entirely overlooked by the classic electrostatic theories [76,77]. Later studies on model charged and uncharged hydrophilic and hydrophobic surfaces have affirmed that ion-specific contributions from the electrostatic, dispersion, and hydration forces could lead to a net attractive or repulsive interaction between the ions and surfaces and could thus corroborate both direct and reversed sequences [78–83].

Salt-polymer solutions comprise a complex crowded mixture of water molecules, polymer chains, and ions, where each component effectively interacts with the other components. Hence, it is naive to expect such a system to be solely governed by the hydration capacity of the ions in the bulk solution. Instead, we must necessarily consider the cross-effects and interplay between all the existing components, i.e., ion-water (ion hydration), ion-polymer (surface-related interactions), ion-ion (ion pairing), polymer-water (polymer hydration), polymer-polymer (intra- and inter-chain forces), and water-water (hydrogen bonding) interactions. Each of these interactions can contribute (directly or indirectly) to the polymer stability in solution and are susceptible to the

amount and type of ions present. In addition, one must consider the complex nature of polymer hydration. Thermo-responsive polymers generally comprise both polar and apolar regions, each of which possesses unique hydration characteristics that are differently affected by ions (Fig. 1b) [84–88]. The polar parts on the polymer backbone typically form hydrogen bonds with water molecules that introduce a favorable enthalpic term to the free energy of mixing. On the other hand, the nonpolar regions are surrounded by a tight network of water molecules due to the entropically unfavorable hydrophobic effect. The balance of these two opposing effects determines the stability of the polymer in water at different temperatures: below the phase separation temperature, the favorable enthalpic term is dominant and the polymer remains hydrated. On crossing the collapse temperature, the unfavorable entropic term enforces polymer phase separation, whereby the water molecules are released from the hydrophobic hydration shell and attain a higher entropy.

Thus, ion interaction with the polymer surface and its hydration shell is greatly correlated with the chemical structure and surface properties of the polymer, suggesting that the specific ion effects are indeed “polymer-specific”. A particular salt can therefore exert different effects on different polymers. This behavior can be observed more clearly in Fig. 1 (panels c and d), which compares the effects of several sodium salts on poly(*N*-isopropylacrylamide) (PNIPAM) and poly(propylene oxide) PPO.

The ion-specific effects of salts can be grouped into four categories according to the salt concentration-dependence of the phase separation temperature: (i) the salting-out effect with a linear dependence on the salt concentration, e.g., the effect of NaF on PNIPAM and PPO; (ii) the salting-out effect with a non-linear concentration-dependence, e.g., the effect of NaBr on PNIPAM (notably, NaBr has a linear salting-out effect on PPO); (iii) the non-linear salting-in effect with a maximum (turnover) at relatively low salt concentrations, e.g., the effect of NaI on PNIPAM and PPO; and (iv) the nonlinear salting-in effect with no turnover until relatively high salt concentrations are present, e.g., the effect of NaSCN on PPO (notably, NaSCN has a rather weak salting-in effect on PNIPAM with a turnover at  $\sim 400$  mM). Moreover, the effect of a particular salt differs in strength (difference between the phase transition temperatures in the salt-free and saline solutions) for different polymers. For example, 1 M NaCl gives rise to  $\sim 5$  °C drop in the phase separation temperature of PNIPAM but displays a significantly larger effect ( $\sim 12$  °C decrement) on PPO. Such differences can also be seen in other thermo-responsive polymers such as poly(ethylene oxide) [91,92], poly(*N*-vinylcaprolactam) [93,94], poly(*N*-vinylacetamide) [95], poly(2-oxazoline) [96], poly(*N,N*-diethylacrylamide) [97], polyesters [98], and poly(vinylpyrrolidone) [99]. As we will discuss later, even for a particular polymer, variations in molecular weight, solution concentration, and chain conformation influence the magnitude of the specific ion effects (Section 3.3).

This work aims to address the abovementioned issues in two ways. Our first objective is to recapitulate the essential mechanisms that can describe the ion-specific effects in polymer solutions. We begin with the triple mechanisms suggested by Cremer et al., which examine the specific ion effects on polymers from a molecular perspective. We next discuss the solute partitioning model proposed by Pegram and Record, which provides a solution for quantifying the accumulation (depletion) of different ions at (from) model nonpolar, polar, and macromolecular surfaces. Subsequently, we introduce the recently proposed thermodynamic description of the specific ion effects by Dzubiella and Heyda. Further, to understand the possible mechanisms and interactions that can drive the ions to the surfaces, the law of matching water affinities (LMWA) by Collins and the theory of dispersion interactions by Ninham et al. are outlined. We proceed to discuss some notable works on the contributions of the surface properties and hydration forces to ion-specific effects. Our second objective is to highlight some of the missing pieces of the “Hofmeister puzzle”, which in our opinion need further investigation. This includes uncertainties surrounding the behavior of weakly hydrated salts, correlation of salt effects with the polymer properties, and specific ion effects in complex crowded systems.

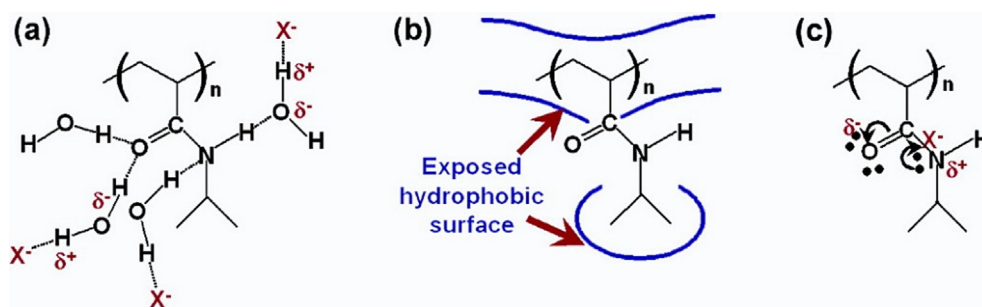
## 2. Overview of the mechanisms

### 2.1. Triple effects: polarization, surface tension, and direct binding

Cremer et al. have published a series of papers going back to 2004, in which they investigated the specific ion effects on PNIPAM [89,100–103], lysozyme [104], elastin-like polypeptides [105,106], fatty amine monolayers [107], negatively charged hydrophilic surfaces [108], proteins [109–111], water hydrogen bonding, and interfacial structure [79]. In their most recognized work [89], they discussed three primary molecular mechanisms, in which the anions can affect the stability of PNIPAM as well as other thermo-responsive macromolecules (Fig. 2).

According to the first suggested mechanism (panel a), the strongly hydrated anions interact with the PNIPAM hydration shell by polarizing the water molecules that are hydrogen-bonded, as a proton donor or a proton acceptor, to the amide groups on the polymer backbone. Hence, dehydration of the hydrophilic amide groups is facilitated and a linear salting-out effect and polymer destabilization occur. The authors have argued that the ability of the anions to polarize the water molecules, i.e., the salting-out power or slope of  $\Delta T(c)$ , directly correlates to their entropies of hydration. Thus, the polarization/salting-out effect becomes larger with increasing the strength of anion hydration. These arguments infer that the polarization effect is not only limited to the amide groups but can also be considered as a general mechanism through which the strongly hydrated anions can destabilize the hydration of the hydrophilic/polar groups of the polymers. With regards to the second mechanism (panel b), the authors suggested that anions could also interfere with the hydrophobic hydration of the polymer by increasing the surface tension of the cavity surrounding the nonpolar surfaces of the polymer; i.e., the aliphatic backbone and isopropyl side chains for PNIPAM. As a result, hydrophobic hydration becomes more entropically costly, thereby promoting shrinkage of the hydrophobic surface. This gives rise to polymer destabilization and a linear salting-out effect. As claimed in the initial work, all the investigated anions, regardless of their hydration capacity, could negatively affect the hydrophobic hydration and subsequently exhibit a destabilizing effect on PNIPAM. Nonetheless, their later publication [102] and another relevant report [112] have partly discussed that depending on the polymer surface chemistry, some weakly hydrated anions could also decrease the surface tension at the hydrophobic polymeric surface and hence, cause polymer stabilization and a salting-in effect.

It is apparent that the first two mechanisms elucidate how anions can interact, albeit differently, with the hydration shell of the polymer. Instead, the third suggested mechanism addresses the interplay between the anions and polymer surface rather than



**Fig. 2.** Anion interactions with the hydration shell and surface of poly(*N*-isopropylacrylamide) (PNIPAM). (Reprinted with permission from [89]. Copyright (2019) American Chemical Society.) (a) Polarization effect through which strongly hydrated anions interact with the hydrophilic hydration shell (water molecules hydrogen-bonded to the amide groups) giving rise to a linear salting-out effect. (b) Surface tension effect through which the strongly and weakly hydrated anions can interfere with the hydrophobic hydration and produce a linear salting-out effect by enhancing the surface tension at the nonpolar polymeric surfaces. (c) Direct binding of the weakly hydrated anions to the partially positively charged sites on the polymer backbone, which produces a non-linear salting-in effect.



direct interaction with the polymer hydration shell. Accordingly, the weakly hydrated anions can directly bind to specific moieties on the polymer backbone and produce a non-linear salting-in effect (panel c). The binding mechanism has been more closely examined in several works [97,106,113], which consider how and where on the polymer the anions could bind. While the authors underlined the amide moiety as the binding site in the initial work, it can be inferred from their later works that not only the amide moiety but also any atom bearing a partial positive charge due to a relatively large dipole moment could be a potential binding site. This non-linear salting-in effect often reaches a maximum (turn-over) after which a linear salting-out behavior is observed (Fig. 1c; e.g., NaSCN). The authors have speculated that the observed maxima and turnover behavior originate from saturation of the available binding sites over the polymer backbone, while the subsequent salting-out effect has been linked to the destabilizing surface tension effect.

To quantitatively evaluate the effects of salts on the phase separation temperature of PNIPAM (Fig. 1c), the authors suggested the empirical equation:

$$T - T_0 = c[M] + \frac{B_{\max} K_A [M]}{1 + K_A [M]} \quad (1)$$

where  $T$  is the phase separation temperature of PNIPAM in the saline solution,  $T_0$  is the phase separation temperature in the salt-free solution, and  $[M]$  is the molar concentration of the salt. Parameter  $c$  is the slope of the linear trend (Fig. 1c and Table 1; e.g.,  $F^-$ ), which represents the strength of the first and second mechanisms and therefore demonstrates the salting-out power. The last term in the equation, which is reminiscent of the Langmuir isotherm binding model, is responsible for the nonlinear salting-in effect (Fig. 1c and Table 1; e.g.,  $SCN^-$ ). Accordingly,  $K_A$  is the binding constant that indicates the affinity of the anion for the binding sites, while  $B_{\max}$  is the maximum increment in the phase separation temperature at the saturation point.

Four distinct ion-specific behaviors have been inferred with respect to the observed trends for the fitting parameters (Table 1). For divalent anions with a notable hydration capacity, e.g.,  $SO_4^{2-}$ , a linear salting-out effect characterized by zero  $K_A$  and  $B_{\max}$  and a large value for  $c$ , was reported. Importantly, a two-step phase transition was observed at relatively high salt concentrations, while an initial slope for low concentrations and two different slopes (first and second steps) corresponding to a high salt concentration regime were obtained (Fig. 1c and Table 1; e.g.,  $SO_4^{2-}$ ). As claimed by the authors [102], the slope at relatively low salt concentrations and the first step of high salt concentration (the stronger

salting-out) fairly correlate to the entropy of hydration of anions, referred to as the polarization effect. On the other hand, the slope of the second step at relatively high salt concentrations (the weaker salting-out) complies with the effect of anions on the surface tension of water; this was considered to represent the surface tension effect. For strongly hydrated monovalent anions, e.g.,  $F^-$ , a linear salting-out effect (slope is concentration-independent) corresponding to zero  $K_A$  and  $B_{\max}$  values was observed. Here, constant  $c$  represents the polarization effect and scales with the entropy of hydration of the anion. For weakly hydrated borderline anions, e.g.,  $Br^-$ , a non-linear salting-out effect was demonstrated. In this case, the  $K_A$  and  $B_{\max}$  values are non-zero and generally increase as the anions become weaker in hydration. The  $c$ -value representing the salting-out effect is relatively smaller than those of anions with a linear salting-out effect and is possibly related to the surface tension increment data. Finally, weakly hydrated anions with a non-linear salting-in effect, e.g.,  $SCN^-$ , could be identified by relatively large  $K_A$  and  $B_{\max}$  values together with rather small  $c$ -values that correlate to the surface tension effect.

The framework suggested by Cremer et al. is worthy since it interprets the ion-specific effects from a molecular interaction point of view. More importantly, the ion effects are discussed with respect to the stability and hydration of the polymer; hence, these triple mechanisms have been often used to describe the effect of salts on polymers phase separation temperature. There are indeed certain aspects of this work that need further attention. First, it should be noted that the observed shifts in the phase separation temperature must be considered as the cumulative effect of the anions with the sodium counterion. Accordingly, it is more correct to discuss the obtained fitting parameters with respect to the salts instead of just the anions. Second, the suggested empirical equation requires fitting to the experimental data for each polymer; hence, it cannot be used as a predictive model. It can, however, highlight the differences between the salting-in and salting-out effects based on the sign and magnitude of the obtained fitting parameters. The other note on Eq. (1) pertains to the meaningfulness of the extracted parameters, considering the number of fitting parameters and limited range of data points. However, the functional form of Eq. (1) can be considered valid as it has been confirmed by thermodynamic modeling, which will be discussed later (Section 2.3). Finally, the suggested mechanisms need further examination in terms of how the suggested ion-polymer interaction mechanisms (i) are affected by the polymer properties (e.g. chemical composition) and (ii) can alter the polymer stability in water (e.g. bound anions enhance the phase separation temperature).

**Table 1**

$B_{\max}$ ,  $K_A$ , and  $c$  parameters obtained from fitting the empirical equation to the experimental lower critical solution temperature (LCST) data of poly(N-isopropylacrylamide) (PNIPAM) in the saline solutions; anion surface tension increments ( $\sigma$ ) and entropy of hydration ( $\Delta S_{\text{hydr}}$ ) values are also included. (Adapted with permission from [89]. Copyright (2019) American Chemical Society.)

Anion	$\sigma$ (mN L/mol)	$\Delta S_{\text{hydr}}$ (J/K mol)	$B_{\max}$ (°C)	$K_A$ (M <sup>-1</sup> )	$c$ (°C/mol)		
					Initial	First step	Second step
$CO_3^{2-}$	2.6	-245	-	-	-25.1	-29.0	-9.7
$SO_4^{2-}$	2.7	-200	-	-	-18.3	-23.1	-10.0
$S_2O_3^{2-}$	2.9	-180	-	-	-16.3	-20.3	-10.9
$H_2PO_4^-$	2.3	-166	-	-	-11.5	-14.7	-8.3
$F^-$	2.0	-137	-	-	-9.0	-	-
$Cl^-$	1.6	-75	-	-	-5.3	-	-
$Br^-$	1.3	-59	0.7	2.7	-3.7	-	-
$NO_3^-$	1.1	-76	0.6	2.9	-3.5	-	-
$I^-$	1.0	-36	1.1	4.3	-1.5	-	-
$ClO_4^-$	1.4	-57	1.8	5.1	-6.4	-	-
$SCN^-$	0.5	-66	1.6	4.3	-1.4	-	-

\*In the empirical equation by Cremer et al.,  $c$  parameter represents the slope of the linear trend of  $\Delta T(c)$ ,  $K_A$  is the binding constant, and  $B_{\max}$  indicates the maximum increment in the phase separation temperature at the saturation point.

## 2.2. Solute partitioning model (SPM): surface accumulation/exclusion

Pegram and Record have evaluated the effect of salts, as well as nonelectrolyte osmolytes and denaturants such as urea, on the air–water surface tension [114,115] and stability of biopolymers in water [116–122]. Their studies have chiefly focused on quantitative assessment of the accumulation/exclusion of ions with respect to model surfaces using the Solute Partitioning Model (SPM). The suggested model examines the interplay between ions and model surfaces in terms of the partition coefficient of the ions and surface hydration term. Similar to the two-state model used for assessing protein folding [123–125], the authors also considered two possible thermodynamic states for any aqueous interface subjected to the salts. Regarding the stability of macromolecules in aqueous solution, these two states are considered as the swollen coil and collapsed globule states. Notably, for protein systems (discussed by the authors), these states are typically referred to as the unfolded and native states, respectively. The standard free energy change of transition between these two states is recognized as  $\Delta G^\circ$  and can be calculated from the experimental equilibrium constant  $K$  [126–129]. The effect of salts on the conformational transition is then quantified using the “ $m$ -value” defined as the first-order derivative of the standard free energy change of the transition (at constant temperature) with respect to the salt concentration:

$$m - \text{value} = \frac{d\Delta G^\circ}{dm_{\text{salt}}} = -RT \frac{d\ln K}{dm_{\text{salt}}} \quad (2)$$

As mentioned above, the  $m$ -value from the SPM can characterize the effect of salts not only on the conformational transition of macromolecules but also on any aqueous process accompanied with a change in the surface area exposed to water. Accordingly, in their initial work the authors compared the surface tension of water and several saline solutions and obtained the anion and cation partition coefficient values with respect to the air–water interface as a non-polar and uniform model surface [114]. For such a system, the change in the water surface tension in the presence of ions can then be interpreted as the exchange of water molecules between the bulk solution and air–water interface. In this case, the  $m$ -value of each salt is correlated to its molar surface tension increment and can be calculated from the slope of the linear

regression in Fig. 3a. The authors later investigated the effect of salts on the solubility of model nonpolar solutes such as benzene (Fig. 3b) [116,117], where  $K$  was considered as the solubility of the compound and the  $m$ -value represented the “Setschenow coefficient” (ratio of the solubility in saline and salt-free solutions) [130–133].

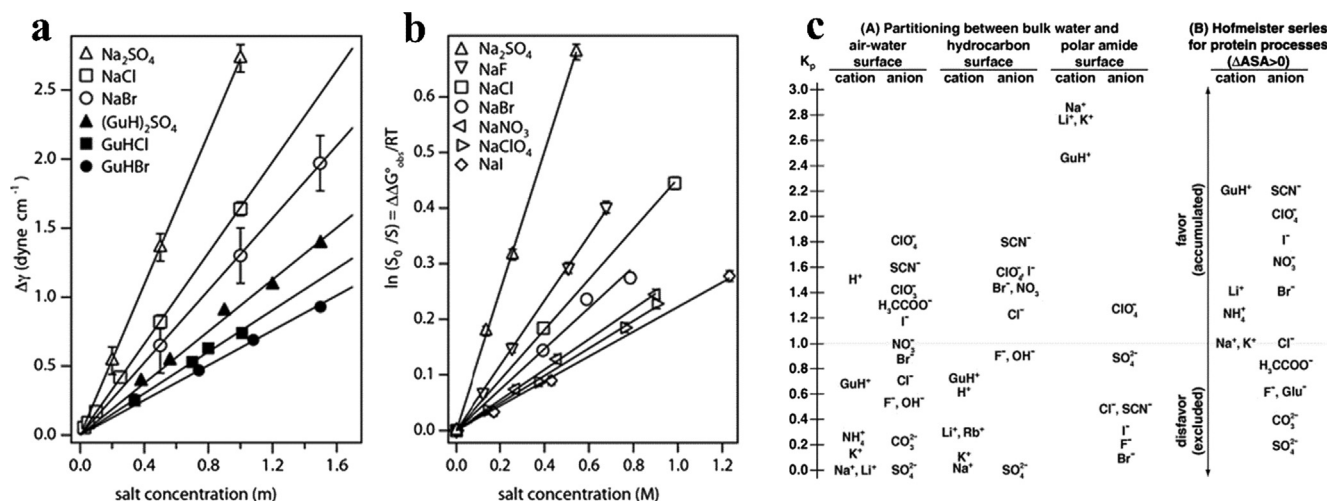
Regarding the effect of salts on macromolecular (called biopolymer in the original work but we discuss it with respect to both natural and synthetic polymers herein) systems, the  $m$ -value can be interpreted in terms of the chemical potential derivatives of the macromolecular solute with respect to the salt concentration. Accordingly, the interaction of ions with the macromolecule modifies the activity coefficient of the macromolecule ( $f_m$ ) in solution. The authors argued that the activity coefficient derivative ( $d\ln f_m/dm_{\text{salt}}$ ) approximates the reduced chemical potential derivatives:

$$m - \text{value} = -RT \frac{d\ln K}{dm_{\text{salt}}} = RT \Delta \frac{d\ln f_m}{dm_{\text{salt}}} = \Delta \frac{d\mu_m}{dm_{\text{salt}}} = \Delta \mu \quad (3)$$

Accordingly, the  $m$ -values for different salts can be experimentally determined either from the solubility measurements or osmometry [118,119]. According to the SPM, the obtained  $m$ -value for a particular salt is related to the change in the accessible surface area ( $\Delta ASA$ ) of the macromolecule through the proportionality constant ( $\alpha$ ), which includes specific terms for the average surface hydration and ion partitioning. The former term is considered as the number of water molecules per surface area (b), while the latter term is taken into account using  $K_p$  as a measure of the local competition, between water and ions, for the host surface:

$$\begin{aligned} \frac{m - \text{value}}{RT} &= \frac{\Delta \mu}{RT} = \alpha \Delta ASA \\ &= \frac{-(v_+ K_{p,+} + v_- K_{p,-} - v)b(1 + \varepsilon_{\pm})}{55.5} \Delta ASA \end{aligned} \quad (4)$$

where  $\varepsilon$  is the self-nonideality correction term for the salt, which is the derivative of the activity coefficient of the salt with respect to its concentration. The number of ions per salt formula is represented by  $v$  and separate partition coefficients for the cation and anion are considered. An important assumption was that the contributions by the cation and anion to the  $m$ -value of the salt are additive and thus, the partition coefficient value of a given ion is independent of its counterion in a given salt. The interaction potential ( $\alpha$ )



accordingly quantifies both the strength and direction of the short-range interactions between the salt and macromolecular surface, which has been reported to be almost independent of the  $\Delta\text{ASA}$  and salt concentration ( $\leq 1$  M).

To use the above equation, the  $m$ -values for different salts are experimentally obtained for the aqueous process under investigation. Next, an estimated value for the  $\Delta\text{ASA}$  due to transition from the swollen to the globular state is obtained. For a salt where both the anion and cation are then fully excluded from the surface ( $K_p$  values approach zero), the lower bound value of surface hydration ( $b$ ) is estimated. Finally, the  $K_p$  values for the series of anions can be found from their corresponding salts with a fully excluded cation pair. This calculates the single partitioning coefficients of different anions and cations at non-polar, polar, and protein model surfaces (Fig. 3c). For a chemically heterogeneous surface (e.g., proteins), the average hydration and solute partition coefficient of different functional groups (e.g., polar amide and nonpolar aliphatic and aromatic regions) that compose the surface are used, again by assuming additivity of the effects. The obtained  $K_p$  value, which is defined as the ratio of the ionic concentration between the model surface and bulk solution, can quantitatively describe the surface accumulation/exclusion of the ions. On this basis, a  $K_p$  value  $> 1$  indicates relatively strong surface affinity and accumulation, while  $K_p < 1$  demonstrates predominant surface exclusion.

Fig. 3c reveals that the anion affinity for the air–water interfacial region complies with that observed in the original Hofmeister series. Accordingly, poorly hydrated anions preferentially accumulate at the air–water interface; e.g., the local concentration of  $\text{SCN}^-$  is predicted to exceed its bulk concentrations 1.6-fold. The strongly hydrated anions (e.g.,  $\text{SO}_4^{2-}$  with a  $K_p \sim 0.5$ ) are however effectively repelled from the air–water interface. On the other hand, almost all the cations are excluded from the air–water interface characterized by  $K_p$  values close to zero. Moreover, the trends for the cations seem to be more irregular (anomalous series), while the  $K_p$  values for different cations are not significantly different (weak ion-specificity). Considering the effect of salts on the solubility of model nonpolar solutes, a similar trend was inferred, suggesting that weakly hydrated anions also exhibit a strong affinity for hydrocarbon molecular surfaces. Notably, the sequence for cations is again less regular but generally demonstrates surface exclusion. Accordingly, it can be deduced that the surface tension increments observed from adding different salts are consistent with the effects of these salts on the processes that primarily expose or bury the hydrocarbon surface. With respect to the polar amide surfaces, most of the anions are excluded from the surface, while cations are more readily adsorbed. Considering the combination of these effects on a model protein surface, the authors concluded that the ordering of anions with respect to macromolecular processes is determined by whether the anions are accumulated or excluded from the nonpolar regions. Accordingly, weakly hydrated anions that produce a salting-in effect exhibit a significant surface affinity, while those with a salting-out effect demonstrate surface exclusion. For cations, even though the trend in surface affinity is anomalous,  $K_p$  values  $\sim 1$  (and slightly larger) can be inferred. This indicates that the cations are not fully excluded from the macromolecular surface. Hence, the effect of salts on the polymer stability cannot be solely attributed to the anions but is also affected by the cations.

The SPM by Pegram and Record is valuable considering its ability to quantitatively interpret and predict the surface accumulation/exclusion of ions. The two critical aspects of SPM that need consideration are the (i) additivity assumption and (ii) linearity of the free energy changes. As stated by the authors, the main premise of their analysis is that the contributions to the solute and salt effects are all independent and additive. However, deviations from the additivity assumption have been found in several systems as

we will discuss later (Section 3.4). On the other hand, most of the weakly hydrated salts produce non-linear thermodynamic changes to the phase separation temperature. The  $m$ -value will therefore depend on the salt concentration, and the second order derivatives of the free energy change must be implemented into the model; this will be discussed further in Section 2.3 below.

### 2.3. Thermodynamic description of specific ion effects

Dzubiella et al. published a series of modeling and simulation studies in which they evaluated specific ion effects on polymer and protein stability from a thermodynamic point of view [134–139]. The phase separation (collapse) of a macromolecule herein is again envisaged as a conformational transition between the extended/swollen coil and collapsed globular states. Nevertheless, instead of investigating the linear behavior of the free energy changes (as in the SPM), the thermodynamic model accounts for the non-linear thermodynamic changes of the phase separation temperature. The authors hence suggested that even though the thermodynamic model is similar to the SPM in principle, it better describes the non-monotonic (nonlinear) effect of weakly hydrated anions on the phase separation temperature. On that premise, the authors derived the following equation based on the second-order expansion of the two-state free energy in the  $(c,T)$  parameter space:

$$\Delta T(c) \simeq -\frac{mc + \frac{1}{2}m'c^2}{\Delta S_0 + \Delta S'_0 c} \quad (5)$$

where  $m$  is termed the “ion-specific coefficient” and quantifies the salt concentration-dependence of the free energy function for the two-state model. The authors discussed that at sufficiently low salt concentrations, where linear behavior of the free energy change is typically observed, the value of  $m$  can be considered to be equal to that attained from the SPM. In the denominator,  $\Delta S_0$  represents the entropy of the polymer phase separation in the salt-free solution, which is a constant fitting parameter for each polymer. The derivative terms ( $m'$  and  $\Delta S'_0$ ), also referred to as the second-order corrections, account for the salt concentration-dependence of  $m$  and  $\Delta S_0$ , respectively, and are responsible for the nonlinear changes in the phase separation temperature. By fitting the thermodynamic model to the reported experimental data for PNIPAM (Cremer et al.), the authors calculated the thermodynamic parameters for each salt. They also theoretically estimated the  $\Delta\text{ASA}$  for the coil-to-globule transition of PNIPAM and subsequently calculated the  $m$ -values from the SPM to underline the difference between the linear and nonlinear approaches. Additionally, the thermodynamic parameters were compared to those obtained from the empirical equation by Cremer et al.. Since both the equations have the same functional form, a comparison between the fitting parameters of the two models is plausible; however, the thermodynamic parameters are indeed physically meaningful.

Based on the obtained thermodynamic data, the authors proposed two different mechanisms for specific ion effects in polymer solutions (notably, the fitted parameters herein are discussed with respect to the salts, not the anions): (i) when  $\Delta T(c)$  is monotonically linear, as seen for the strongly hydrated salts (e.g., NaF), the second-order correction terms  $m'$  and  $\Delta S'_0$  are equal to zero and thus, the salt effect can be solely described by the thermodynamic  $m$  parameter. The authors interpreted this linear free energy change behavior in terms of the “excluded-volume mechanism”, suggesting that strongly hydrated salts are effectively repelled from the polymeric surface and subsequently produce an ion-depleted volume around the surface. Accordingly, the ions can be considered as simple hard spheres with specific excluded volumes that are independent of the temperature and ion concentration.

Thus, transfer of the monomer from the interior globule to the solvent is accompanied by an increment in the salt-inaccessible volume, which can then produce a linear salting-out effect. (ii) when  $\Delta T(c)$  exhibits appreciable curvature, as for the weakly hydrated salts, a non-monotonic behavior due to second-order corrections to the free energy change and (or) transition entropy is obtained. This originates from direct interaction between the salt and polymeric surface. Accordingly, the turnover behavior observed for most of the weakly hydrated salts originates from preferential adsorption to the coil over the globular state at low salt concentrations and preferential adsorption onto the globule over the coil state at high salt concentrations.

The authors speculated on the origin of the strong curvature in the effect of weakly hydrated anions, such as perchlorate, based on their previous work (Fig. 4) [135]. Notably, the second-order corrections for most of the weakly hydrated salts (e.g., NaBr, NaNO<sub>3</sub>, NaI, and NaSCN) are approximately of the same order of magnitude, while for NaClO<sub>4</sub> with a considerable curvature in the effect, these values (specifically  $m'$ ) were found to be significantly larger. This work used MD simulation studies to investigate the collapse and swelling behavior of a generic thermo-responsive polymer with varying interaction strengths between the polymer units and cosolute (NaClO<sub>4</sub> in this case). Based on this systematic investigation, it was ratiocinated that polymer swelling is most significant if both the monomer–monomer and monomer–cosolute interactions are weakly attractive. Thus, in the most swollen state, the cosolute density inside the coil is remarkably bulk-like and homogeneous. On the other hand, it was argued that highly attractive monomer–cosolute interactions could induce a collapsed state. Nevertheless, unlike the collapsed conformation induced by purely repulsive cosolvents (as observed in the presence of a linear salting-out effect), the collapsed conformation exhibits a considerably enhanced cosolute density within the polymer globule. Accordingly, although similar at first glance, the two collapsed states may result from entirely different mechanisms with distinct structural and thermodynamic properties. From the molecular perspective, the authors speculated that a highly attractive cosolute such as NaClO<sub>4</sub> accumulates within the polymer coil and might produce a “cross-linking-like effect” that can promote a globular and collapsed state.

The thermodynamic model herein complements the previously discussed works. First, it accounts for non-linear changes in the phase separation temperature, which were not implemented in the SPM. Second, while Eq. (5) affirms the functional form of the empirical equation by Cremer et al., it is composed of thermo-

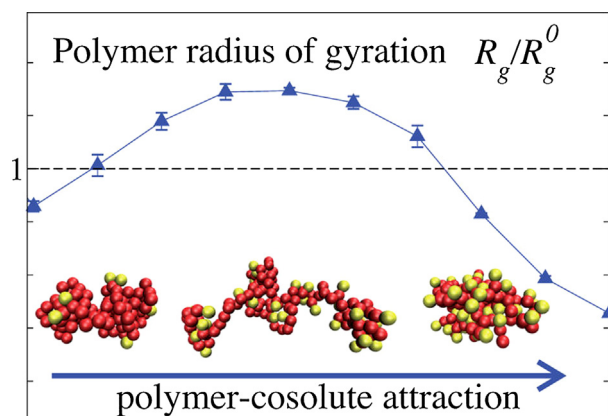
dynamic parameters that are more physically meaningful. Accordingly, conclusions obtained from this model together with the molecular mechanisms suggested by Cremer et al. could provide further information on how salts, specifically weakly hydrated entities, affect the hydration and stability of the polymers.

#### 2.4. Law of matching water affinities (LMWA) and matching of effective ion size (MEIS)

So far, the suggested mechanisms for ion-specificity hint at the effective exclusion of strongly hydrated salts from the polymeric surface, while those of a weak hydration nature are believed to accumulate at the interface. We will next introduce some theories and hypotheses that have addressed the sources of ion-specificity and driving forces behind the tendency or reluctance of the ions to interact with the polymeric surface. These works do not particularly discuss polymer systems but can still be useful to interpret and predict ion-specific interactions with polymeric surfaces.

The LMWA was proposed by Collins to justify the direct/indirect Hofmeister sequences observed for the binding affinities between ion–counterion and ion–charged groups [3,140–144]. Even though this mechanism seems more relevant for the Coulombic binding of ions to proteins and synthetic polyelectrolytes, we partly discuss it herein since it could be relevant in the prediction of the binding affinity of ions to partially charged atoms on neutral polymer chains (third mechanism by Cremer et al.) and polyelectrolytes. According to the LMWA, ions and (also charged moieties on macromolecules are generally considered as being kosmotropic (small and strongly hydrated) or chaotropic (large and weakly hydrated), based on their hydration strength and the effect on the water molecules in their hydration shell. Thus, the tendency of different anions and cations to bind and form ion pairs is assessed according to the “like seeks like” rule; i.e., kosmotropes favorably pair with kosmotropes and chaotropes prefer chaotropes. The volcano plot, which illustrates the enthalpy of dissolution of salts (a measure of how favorable ion pairing is) with respect to the difference between the enthalpy of hydration of individual ions (a measure of chaotropicity/kosmotropicity), compares the stability of different ion pairs. In the first case, kosmotrope–chaotrope salts (pairs), e.g., LiI and CsF, favorably dissociate into the hydrated entities, due to the stronger kosmotrope–water interaction in solution compared to the kosmotrope–chaotrope interaction in the crystal state. By contrast, two kosmotropes, e.g., LiF, are more stable in the paired state because the kosmotrope–kosmotrope interaction is stronger than the kosmotrope–water interaction. Thus, the dissociation of kosmotrope–kosmotrope salts is enthalpically costly. Analogously, for the chaotrope–chaotrope salts, e.g., CsI, the paired state is more stable due to the relatively stronger water–water interaction over the water–chaotrope interaction.

Based on this empirical hypothesis, Kunz proposed a qualitative explanation of the Hofmeister series for the binding of counterions to the charged surfactant headgroups and protein residues [145–149]. Similar to the LMWA, a chaotropic (soft) counterion has a greater binding affinity toward chaotropic charged groups. Accordingly, when weakly charged moieties are present on the polymer backbone, a direct Hofmeister series is expected, suggesting a tendency of weakly hydrated ions to bind to the polymer surface. As mentioned above, this is relevant for the third mechanism proposed by Cremer et al. where weakly hydrated anions possibly bind to the partially charged atoms on the polymer backbone. However, it still does not provide a theoretical explanation. In contrast, kosmotropic (hard) counterions favor binding to the kosmotropic charged headgroups. Hence, when strongly charged moieties are present on the polymer backbone, a reversed Hofmeister series is predicted and the kosmotropic ions bind to the polymeric surface more readily. Evidently, the LMWA can



**Fig. 4.** Schematic illustration of the polymer coil size as a function of polymer–cosolute attraction. Highly attractive cosolutes may give rise to a collapsed state while the cosolute is highly accumulated at the polymer surface. (Reprinted with permission from [135]. Copyright (2019) American Chemical Society.)



solely describe, but not theoretically explain, the experimentally observed series for the affinity of counterions for different charged groups. It is also based on the hydration behavior of ions at infinite dilution; however, it does not justify how this can be valid for finite concentrations. In addition, as seen from the partition coefficients obtained from the SPM, weakly hydrated anions exhibit a relatively strong affinity even toward uncharged polymeric (aliphatic and aromatic hydrocarbon) and non-polymeric (e.g., air–water interface) surfaces. The LMWA cannot, however, address such behaviors since it only considers the electrostatic binding and ion hydration contributions.

Mazzini and Craig addressed these issues in a recent work where they examined the volcano plots in non-aqueous solvents [150]. Unlike the LMWA, in which the volcano plot is interpreted with respect to ion–solvent (water) interaction [represented by solvation (hydration) energy], the authors herein consider the characteristics of the ions (e.g. size, charge density, and polarizability) as the fundamental reason behind the volcano plots. Except for the trend for anions in aprotic solvents, the volcano plots in non-aqueous protic and aprotic solvents exhibit the same trend as that observed in water both at infinite dilution and real concentrations. Considering this, the authors suggested that the volcano plots arise from the ion size instead of the ion–solvent interaction; hence, they proposed that the matching of effective ion size (MEIS) is a more useful and general way of addressing ion-specificity. The importance of ion size brings up critical interpretations on the fundamental origins of ion-specificity and its correlation with solvent/surface properties, which will be discussed in Section 2.5 below.

## 2.5. Ion-specific dispersion interactions

Ninham et al. adopted a more fundamental approach to address the fact that electrostatic and hydration contributions cannot solely describe the ion-specific effects at the interfaces, e.g., the affinity of weakly hydrated anions toward the uncharged hydrophobic surfaces. As previously discussed, the existence of non-electrostatic interactions can be inferred even from the specific hydration of ions at infinite dilution. Considering monovalent anions as an example, while the ionic charge is identical for all the entities, both the ionic radius and shape (e.g., nonspherical anisotropy of polyatomic ions such as  $\text{SCN}^-$ ) could be entirely different. As a result, the hydration characteristics, such as the entropy of hydration and hydration shell numbers, significantly differ between different ions. As another example, one can compare the hydration behavior of anions and cations. Considering  $\text{K}^+$  and  $\text{F}^-$  ions as monovalent ions of similar size and shape, one would expect comparable hydration characteristics according to the electrostatic theories. Nevertheless, the former is characterized as a chaotrope, while the latter is a kosmotrope. This indicates that besides geometrical contributions, the source of the chemical interactions could also vary between different ions. Thus, one can expect non-electrostatic contributions to the ion–surface interaction.

On this basis, Ninham et al. proposed dispersion interaction as an always-existing source of ion-specificity [151–169]. Accordingly, besides the possible Coulombic interactions, the ions experience an additional dispersion potential at any aqueous interface that can be quantified using the Lifshitz theory for Van der Waals forces. A straightforward description of this theory can be obtained by modeling the energy potential of a colloidal particle in an electrolyte solution [68]. To include the contribution of the dispersion forces, the authors added an additional mean field term ( $U_x^{\text{dispersion}}$ ) to the mean field Poisson–Boltzmann equation:

$$\rho_x = \rho_0 e^{-(ze\psi_x + U_x^{\text{dispersion}})/kT} \quad (6)$$

The dispersion potential term includes the contributions from the image forces, many body dipole–dipole forces, dipole–induced dipole forces, and induced dipole–induced dipole forces, which all strongly depend on the nature (both chemical and geometrical) of the participating entities. The dispersion potential herein is given as:

$$U_{\pm}(x) = \frac{1}{x^3} \int_0^{\infty} \frac{\alpha(i\omega)}{\varepsilon_w(i\omega)} \left( \frac{\varepsilon_w(i\omega) - \varepsilon_s(i\omega)}{\varepsilon_w(i\omega) + \varepsilon_s(i\omega)} \right) d\omega \quad (7)$$

where  $\alpha$  represents the polarizability of the ions and  $\varepsilon$  refers to the dielectric constants of water and the target surface. In the equation, the integral is a sum over the frequencies and thus, the frequency-dependence of the dielectric function of the substrate with respect to water determines the sign (attraction or repulsion) of the dispersion potential. It is accordingly affirmed that any ion at any interface experiences an additional dispersion potential, which can either enhance or attenuate the electrostatic potential. This, in turn, reveals the difference between the LMWA and the dispersion theory. While the former is concerned with the electrostatic binding of ions to discrete charged sites, the latter theory describes the sum of the electrostatic and dispersion interactions of ions with a uniformly charged surface with a dielectric function (Fig. 5).

The authors have also suggested a more simplified equation where the dispersion potential is estimated from the static polarizability of the ions and a single adsorption frequency estimated from the ionization potentials and electron affinities of the ions:

$$U_x^{\text{dispersion}} = \frac{\alpha^*(0)h\omega(n_w^2 - n_s^2)}{16\pi x^3} \quad (8)$$

where  $n$  represents the refractive indices for water and the polymeric surface,  $h\omega/2\pi$  is the ionization potential of the ion, and  $\alpha^*(0)$  is the static polarizability of the ion. Accordingly, the difference between the refractive indices of water (solvent) and the polymeric surface determines the sign of the dispersion potential, i.e. if the refractive index of the substrate is relatively larger, the dispersion potential will then be positive and vice versa. On the other hand, the strength of the dispersion force (for a fixed ion) increases as the difference between the refractive indices becomes more significant. Equally important, an increment in the ion polarizability evidently leads to a stronger dispersion potential, demonstrating why large polarizable ions in the Hofmeister series exhibit a relatively stronger affinity for polymeric surfaces.

Using the same framework and considering the dynamic polarizability terms, Parsons and Ninham also embedded the role of the hydration forces into the energy potential acting on the ions [170–172]. Accordingly and based on the LMWA, they speculated that any water molecule is relatively free to move in and out of the hydration shell of a chaotropic ion. This signifies that a chaotropic ion can be modeled independently of its hydration layer. On the other hand, the lifetime of the water molecules in the hydration

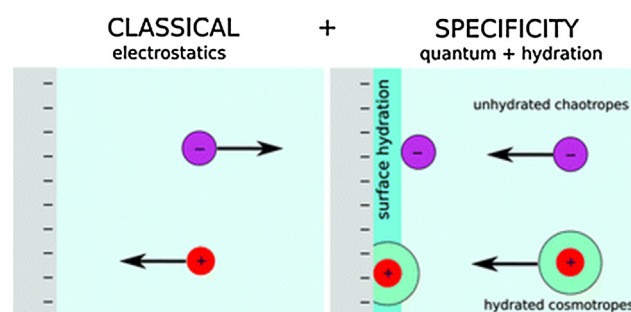


Fig. 5. Dispersion, electrostatic, and hydration forces acting on ions near a charged surface. (Reproduced from [76] with permission from the PCCP Owner Societies.)

shell of kosmotropes is relatively long, indicating that the hydration shell moves together with the ion. The authors implemented this idea by adding a hydration layer to the modeled kosmotropes, by calculating the effective hydrated radius (by including the first hydration shell into the radius) and polarizability (by including the product of the water polarizability and hydration shell number) of the ion. Such a variation in the ionic size and polarizability is accompanied by two opposing effects on the dispersion potential, i.e., the increased ionic size weakens the dispersion potential, while the larger polarizability strengthens it. In contrast, the chaotropes were modeled without any effectively enhanced ionic size or polarizability. Using the same idea, the surface hydration was implemented by considering a permanent hydration layer for the hydrophilic surfaces. The authors then proposed (based on the LMWA) that strongly hydrated kosmotropic ions may penetrate the hydration layer of the hydrophilic surface. On the other hand, a chaotropic ion is excluded from the surface hydration layer, which then produces a repulsive entropic contribution. The steric effect was addressed by assuming a hard sphere ionic radius, which prevents the ion from approaching the surface more closely than this distance (the effect of surface hydration was included in the same way). Accordingly, the addition of the dispersion potential and steric hydration effect to the total free energy of the system results in two effects: a direct contribution to the ion–surface interaction potential and an indirect contribution due to the adsorption of ions to the surface, thereby modifying the ion concentration profiles. This can change both the electrostatic and entropic contributions to the ion–surface interaction potential.

The theory of dispersion forces together with recent findings on ion-specific effects in non-aqueous systems provide valuable knowledge on the origins of ion-specific trends as well as the roles of the solvent and surface properties. Mazzini and Craig performed studies in non-aqueous solvents aiming for a universal understanding of the sources of ion-specific effects. The authors first investigated the standard partial molar volumes and standard electrostrictive volumes of anions and cations in aqueous and non-aqueous solvents [173]. Accordingly, they concluded that the ordering of specific ion effects for the standard molar volumes and electrostriction of electrolytes at infinite dilution, where no surface is involved and the effect of the concentration is negligible, is independent of the solvent. To confirm this, the authors investigated ion-specificity in different solvents using size exclusion chromatography [174]. Washabaugh and Collins previously demonstrated that small strongly hydrated ions render a shorter retention time compared to that afforded by “sticky” large polarizable ions that interact with the stationary phase (direct series in water). Regarding non-aqueous systems, Mazzini and Craig inferred direct, anomalous, and reversed series. The authors have argued that the difference is not due to the protic or aprotic nature of the solvents but is a result of the solvent polarizability. Accordingly, in solvents with low polarizability (water and methanol), large polarizable ions strongly interact with the stationary phase (direct Hofmeister series), whereas in solvents with high static polarizability (dimethyl sulfoxide and propylene carbonate) the large polarizable ions favorably interact with the solvent and present a weaker tendency to the surface (reversed Hofmeister series). Solvents with static polarizability values that fall between the low and high values present an intermediate situation, where ion-specificity is weak and the series are anomalous. Similar behavior was inferred for a polymeric surface, where the ion-specific effects on the conformation in a polyelectrolyte film in aqueous and non-aqueous solutions were examined.

Based on these studies, Mazzini and Craig concluded that ion-specific trends arise from the ions, independent of the solvent and surface. The solvent and surface, on the other hand, could be considered as perturbations that can not only affect the magnitude

of the ion-specific effects but also reverse the series. This is in accordance with the model suggested by Ninham et al. Accordingly (Eq. (8)), for a fixed solvent and surface, the ordering of the ion-specific effects is determined by variations in the ion polarizability (or roughly by the ion size as suggested by Mazzini and Craig). On the other hand, for a given ion, variations in the surface and solvent properties can affect the magnitude and sign of the interaction potential. The critical point here is to include solvent polarizability (in addition to dielectric properties) as a contributing parameter.

## 2.6. Hydration forces and surface properties

As discussed in the previous section, specific ion effects at the polymeric surfaces result from a delicate balance between the electrostatic, entropic, dispersion, and hydration forces. Accordingly, while one can argue that the ordering of ion-specific effects originates from the intrinsic characteristics of ions, it is known that variations in the solvent and surface properties can perturb these effects. We will herein briefly recap a few works that discuss how surface hydration and properties can affect the ion-specific effects in accordance with the model suggested by Ninham et al. Although these studies are not directly discussed in relation to the specific ion effects in polymer solutions, they can still be employed to predict the affinity of ions for polymeric surfaces.

As the first pertinent work, Sivan et al. investigated the role of surface hydration as an effective parameter that influences the surface affinity of ions [175–178]. These studies primarily focused on performing atomic force microscopy (AFM) colloidal probe measurements between negatively charged silica surfaces in the presence of different counterions, e.g., alkali cations. In addition to the long-range double layer forces, they also detected short-ranged (<4 nm) hydration forces, which were found to be ion-specific. These repulsive forces were attributed to the preferential adsorption of the counterions to the silica surface. At low pH values, the large chaotropic counterions (i.e.,  $\text{Cs}^+$ ) adsorb more readily to the silica surface (direct Hofmeister series). In contrast, at high pH values, the small kosmotropic counterions (i.e.,  $\text{Li}^+$ ) presented a more substantial surface accumulation (reversed Hofmeister series). The authors discussed this reversal in the adsorption sequences based on the relative hydration strength of the ions and silica surface. According to the LMWA, chaotropic ions exhibiting weaker interaction with water than water–water bonding were considered as “hydrophobe” ions. On the other hand, kosmotropic ions having stronger interaction with water than water–water bonding were referred to as “hydrophile” ions. Similarly, two different hydration states were suggested for the surface: (i) at low pH values, the silanol groups on the silica surface are protonated and form relatively weak hydrogen bonds with water compared to the water–water hydrogen bonds in solution. Under these conditions, the authors argued that the free energy of the system could be minimized by expelling the chaotropic ion from the solution, where it disrupts the water–water hydrogen bond network to the “hydrophobic” surface and breaks the weaker silanol–water bonds. Accordingly, a direct Hofmeister series is obtained. (ii) at high pH values, however, the silanol groups on the silica surface are deprotonated and display stronger hydrogen bonds with water compared to those in the bulk solution. Hence, the chaotropic ion is effectively repelled from the “hydrophilic” surface and remains in the solution where the free energy cost is lower compared to disruption of the strong surface–water bonds. On the other hand, the hydrophilic kosmotropic ions are favorably attracted to the strongly hydrated surface, so a reversed Hofmeister series is expected. The authors therefore hypothesized that large ions inevitably accumulate near the hydrophobic surfaces, while small ions favor hydrophilic surfaces [178].

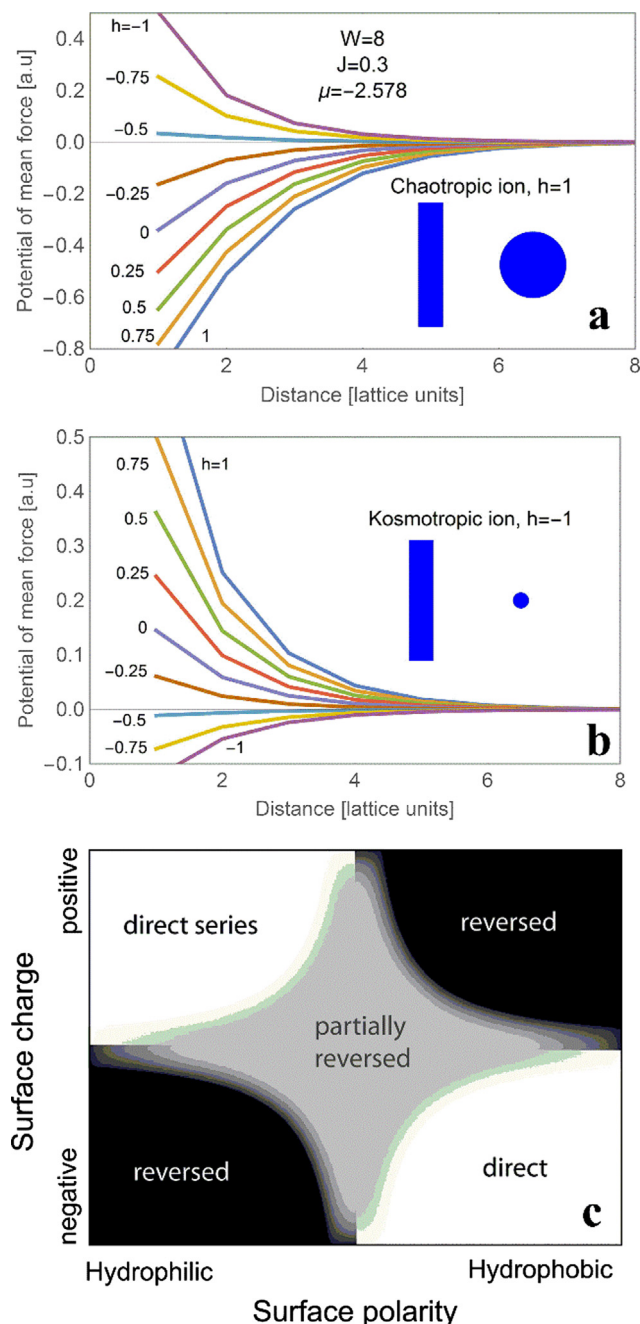
To further examine this idea, the potential of the mean force between the model ions and surfaces of varying polarities (hydrophobicity) were calculated using two-dimensional lattice gas modeling (Fig. 6a, b) [178]. The polarity of the ions and surfaces in this work was quantified by the hydrophobicity index ( $h$ ), which is in the range of  $-1$  (most hydrophilic) to  $+1$  (most hydrophobic). Thus, the model kosmotropic ion was represented by  $h = -1$ , the chaotropic ion was characterized by  $h = 1$ , and the medium (water) presented the value  $h = -5$ . As illustrated in Fig. 6a, the chaotropic ion is repelled from the fully ( $h = -1$ ) and slightly less ( $h = -0.75$ ) hydrophilic surfaces. Nevertheless, the ion exhibits preferential

adsorption to all the hydrophobic surfaces and the attraction progressively grows with the increase in the hydrophobicity level of the surface. The affinity of the model kosmotropic ion, however, indicates an opposite trend (Fig. 6b), i.e., adsorption to the hydrophilic surfaces ( $h = -0.75$  and  $-1$ ) but exclusion from the relatively hydrophobic surfaces ( $h > -0.5$ ). Another interesting conclusion from these calculations is the effect of the “hydrophobicity contrast” between the surface and medium. Fig. 6 illustrates that when the surface has the same average hydrophobicity index as the medium (in this case  $h = -0.5$ ), the net force acting on the kosmotropic or chaotropic ions is approximately zero. This suggests that the ion-specificity at the interfaces is not only governed by the characteristics of ions but also is affected by variations in the surface properties, in agreement with the theory of dispersion forces where the difference in the refractive indices of the surface and medium was discussed.

In another relevant work, Bastos-Gonzalez et al. highlighted the role of ion hydration and the surface properties [179–186]. They conducted a series of systematic experiments on colloidal and polymer latex particles through which the colloidal stability, kinetics of aggregation, surface charge, and surface forces were assessed in the presence of different salts. The authors claimed that ranking of the surface affinity of the ions could follow a direct, reversed, or partially reversed Hofmeister series, depending on the polarity and surface charge of the host surface. Notably, the authors also studied  $\text{IO}_3^-$  as a large and polarizable ion that is expected to exhibit a significant affinity for hydrophobic surfaces. Nevertheless, the anion is effectively repelled from nonpolar surfaces but adsorbs to hydrophilic surfaces, an effect which has been attributed to the unusually strong hydration strength of the ion [179]. It was accordingly suggested that the surface affinity of ions is not only determined by their size and polarizability but also by their hydration strength.

The authors further highlighted the significance of the hydration forces by comparing the ion-specific behavior of two bulky organic ions, namely tetraphenylarsonium cation ( $\text{Ph}_4\text{As}^+$ ) cation and tetraphenylborate anion ( $\text{Ph}_4\text{B}^-$ ) anion. Even though both ions are of similar size and chemical structure, they have different hydration strengths due to the difference between the interaction of anions and cations with water. The authors investigated the effects of both ions on PNIPAM using MD simulation and experimental studies [180]. Based on the calculated potential of the mean force and pair distribution functions, the authors suggested that the anion displays a more favorable interaction with the polymer and exhibits preferential accumulation at the hydrophobic areas. On the other hand, electrophoretic measurements on the cationic and anionic PNIPAM microgels revealed that as counterions (with respect to the charged PNIPAM microgels), both ions could produce a surface charge inversion; however, the anion exhibited a more significant effect.

The findings of all the works addressing the role of surface hydration and properties were summarized by Schwierz et al. into a phase diagram [187–191]. These authors carried out molecular dynamic simulations combined with modeling studies to investigate the ion-surface interactions with model surfaces containing non-polar methyl ( $\text{CH}_3$ ) and polar hydroxide ( $\text{OH}$ ), carboxyl ( $\text{COOH}$ ), and carboxylate ( $\text{COO}^-$ ) groups. Using a two-step modeling approach, they first quantified the single-ion surface interaction potentials for different ions at these model surfaces. In the second step, the calculated interaction potentials were imported into the Poisson–Boltzmann theory to determine the density profiles of the ions at the surfaces. Accordingly, the authors proposed a “universal” phase diagram for the Hofmeister series of ions as a function of the surface charge and polarity (Fig. 6c), which can predict the direct, reversed, and partially reversed sequences.



**Fig. 6.** (a), (b) Potential of the mean force between the chaotropic/kosmotropic ions and surfaces of varying hydrophobicity indices. (Reprinted from [178], Copyright (2019), with permission from Elsevier). (c) Schematic description of the Hofmeister phase diagram for surfaces of different polarities and charges. (Reprinted with permission from [187], Copyright (2019) American Chemical Society.)



### 3. Missing points and future prospects

The previous sections are an overview of the essential mechanisms that can be used to describe the specific effects of salts in aqueous polymer solutions. One can accordingly infer that all the proposed mechanisms concur with the accumulation of weakly hydrated salts at the polymeric surface and the exclusion of strongly hydrated salts. The underlying difference between these studies is indeed the origin of the surface accumulation/exclusion of the ions, where some authors have postulated on the binding of the ions to specific charged moieties on the polymer backbone, i.e., the charged functional groups in polyelectrolytes or the partially charged atoms in neutral polymers. In addition to the electrostatic contribution, it has been argued that a dispersion potential is always present between ions and any surface, which is strongly affected by the nature of the entities. Finally, it has been argued that the hydration characteristics of both the ion and surface could influence the surface affinity of the ion. This overall interpretation of the specific ion effects has been fairly accepted for two primary reasons: first, it can generally distinguish between the salting-in and salting-out effects by introducing surface partitioning as a quantitative criterion. Second, it provides a correlation between the Hofmeister series and various physiochemical characteristics of the ions, e.g., the salting-out series are in accordance with the entropies of hydration, while the salting-in sequence somewhat follows the partitioning coefficients at the polymeric surfaces. Despite the general recognition of the current opinion, we believe that some critical aspects of the specific ion effects in polymer solutions have not yet been addressed comprehensively. These will be discussed in the subsequent sections.

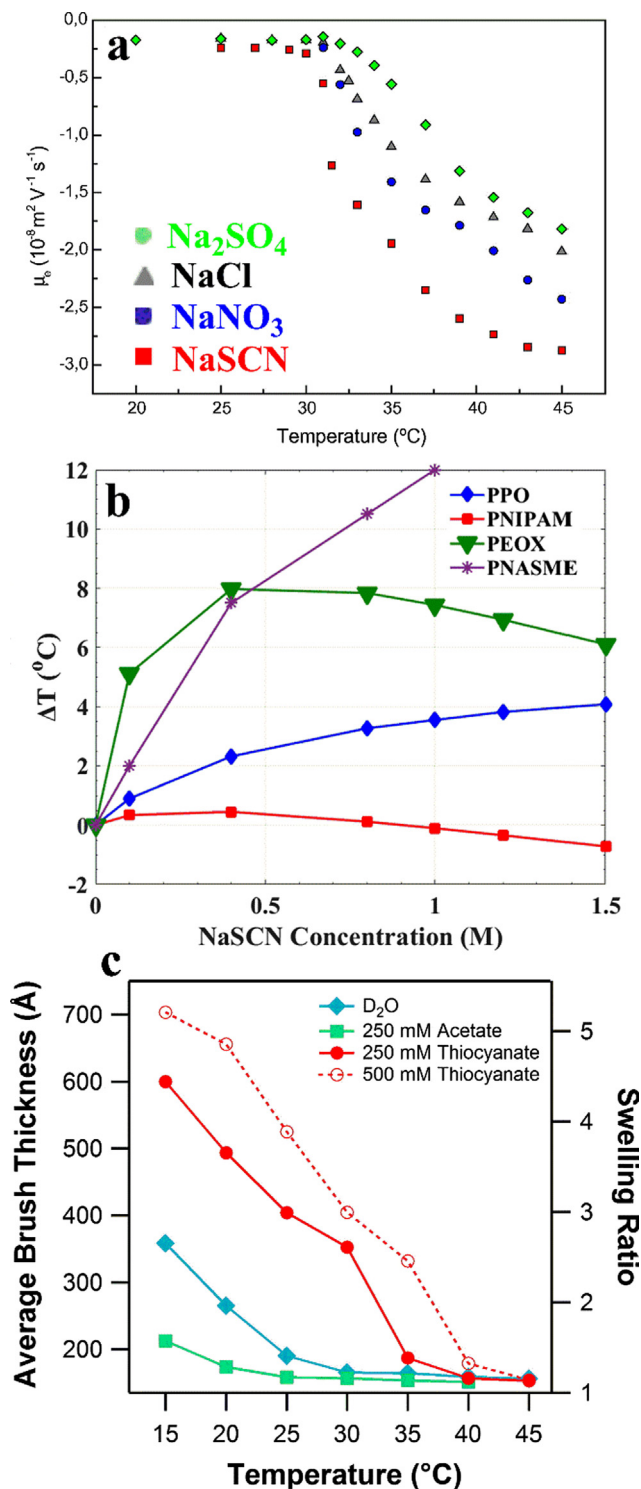
#### 3.1. Accumulation at the polymer surface: what are the sources of stabilization?

While the idea of weakly hydrated salts being accumulated at the polymeric surfaces sounds adequately robust, the source(s) of the salting-in effect and polymer stabilization must be identified. The first plausible mechanism comprises electrostatic stabilization. Considering the ions bound to the polymer backbone, one would expect similarities between such partially charged chains and a generic polyelectrolyte. Several studies on the stability of colloidal [192–196] and macromolecular [197–199] systems in saline solutions, which present a surface charge modulation effect due to the surface adsorption of the ions, have been reported in the literature.

For example, Bastos-Gonzalez et al. conducted electrophoretic measurements on polymeric latex particles in different saline solutions. In one of their studies, they assessed the surface charge of the anionic and cationic PNIPAM microgel particles in the presence of 10 mM sodium salts (Fig. 7a) [183].

Regarding the anionic entity, it was demonstrated that the microgel surface charge becomes more negative in the presence of NaSCN and  $\text{NaNO}_3$  solutions, suggesting affinity of the anions for the PNIPAM surface. On the other hand, the surface charge values measured in the presence of NaCl and  $\text{Na}_2\text{SO}_4$  solutions were comparable, affirming the surface exclusion of both anions. The authors have accordingly suggested that the adsorption of weakly hydrated anions can modify the charge of the polymeric surface. A similar adsorption sequence was deduced for the cationic particles; nevertheless, adsorption of the  $\text{SCN}^-$  ions to the particles produced a surface charge inversion. This surface charge reversal was also demonstrated by  $\text{NO}_3^-$ , to a smaller extent, where the partial accumulation of the counter ions almost neutralized the positive surface charge of the particles. The surface charge in the presence of NaCl and  $\text{Na}_2\text{SO}_4$  solutions was again found to be almost equal.

In another relevant work, Schwierz et al. conducted MD simulation and modeling studies through which the effect of ions on the



**Fig. 7.** (a) Electrophoretic mobility of anionic poly(*N*-isopropylacrylamide) (PNIPAM) particles as a function of temperature in salt solutions. (Adapted from [183], Copyright (2019), with permission from Elsevier). (b) Comparison of the effect of NaSCN on the phase separation temperature of poly(propylene oxide) (PPO) [90], PNIPAM [89], poly(2-ethyl-2-oxazoline) (PEOX) [200], and poly(*N*-acryloylsarcosine methyl ester) (PNASME) [201]. (c) Swelling of an ethylene glycol-based polymer brush layer in the presence of NaSCN. (Reprinted from [202], Copyright (2019), with permission from Elsevier).

interaction and surface charge of model hydrophilic and hydrophobic neutral and charged surfaces was examined [187–191]. Accordingly, they suggested that the effective surface charge (obtained from the extended Poisson–Boltzmann model) of the host sub-



strate is affected by the presence of surface-active ions. Their theoretical findings were further supported by AFM force measurements between the colloidal surfaces, which indicated ion-specific variations in the electrostatic repulsive force and the calculated surface charge.

If we acknowledge that accumulation of ions can modify the surface charge of the polymer chains, one can speculate about intra- and inter-chain electrostatic repulsions, where the former may cause swelling of the individual polymer coil and the latter hinders inter-chain aggregation. Nevertheless, the extent and mechanism by which the induced surface charge can contribute toward the polymer stability in terms of increasing the collapse temperature must be determined. Perhaps the most critical consideration regarding the electrostatic forces is the salt concentration in the solution. One must notice that at sufficiently high salt concentrations, even strong polyelectrolytes (with a fixed number of permanently ionized groups) enter a strong screening limit. Under this condition, the stabilizing electrostatic effects become negligible and the polymer behaves similarly to a neutral chain [203,204]. On that premise, even if the bound ions can induce a partial charge on the polymer chains, the electrostatic contribution should be minor in a high salt concentration regime. However, weakly hydrated salts such as NaSCN present a strong salting-in effect on the phase separation temperature of some polymers, even at relatively high salt concentrations (Fig. 7b). Considering PPO as an example, a considerably strong and growing salting-in effect is observed even in the presence of 1.5 M NaSCN, a concentration in which the Debye length is only 0.25 nm, and the electrostatic repulsions should be effectively suppressed. It is therefore reasonable to speculate that the salting-in effect, at least at relatively high salt concentrations, cannot originate solely from electrostatic repulsions.

As an alternative mechanism, Cohen et al. discussed the osmotic pressure contribution toward the stabilization and swelling of neutral polymers and hydrogels in the presence of weakly hydrated salts [205–207]. The authors demonstrated that the osmotic pressure of poly(acrylamide) in the solution is increased in the presence of weakly hydrated salts, due to a reduced free energy of mixing. Accordingly, they suggested that the zones of excess salt around the polymer produce a reduced chemical potential of water that leads to a gradient in the water chemical potential. Such a gradient can presumably create a driving force for the water molecules to diffuse into the overlap zones and push the polymer chains apart. The critical note regarding this mechanism is that a monotonic increment in the osmotic pressure was obtained even at salt concentrations >1 M, which makes this mechanism more plausible than electrostatic stabilization. Such an osmotic effect might also explain the observed conformational swelling of neutral polymers in the presence of weakly hydrated salts. For example, Wanless et al. investigated the effect of salts on polymer brush films in terms of the polymer film thickness and density profiles [202,208,209]. In one study, they demonstrated that the average thickness of an ethylene glycol-based polymer brush in the presence of 500 mM NaSCN is approximately twice that observed in a salt-free solution (Fig. 7c) [202]. The Debye screening length for such a high salt concentration is ~0.4 nm, suggesting the unlikelihood of such a drastic swelling solely due to electrostatic repulsions; however, it could be reasoned based on the osmotic effect.

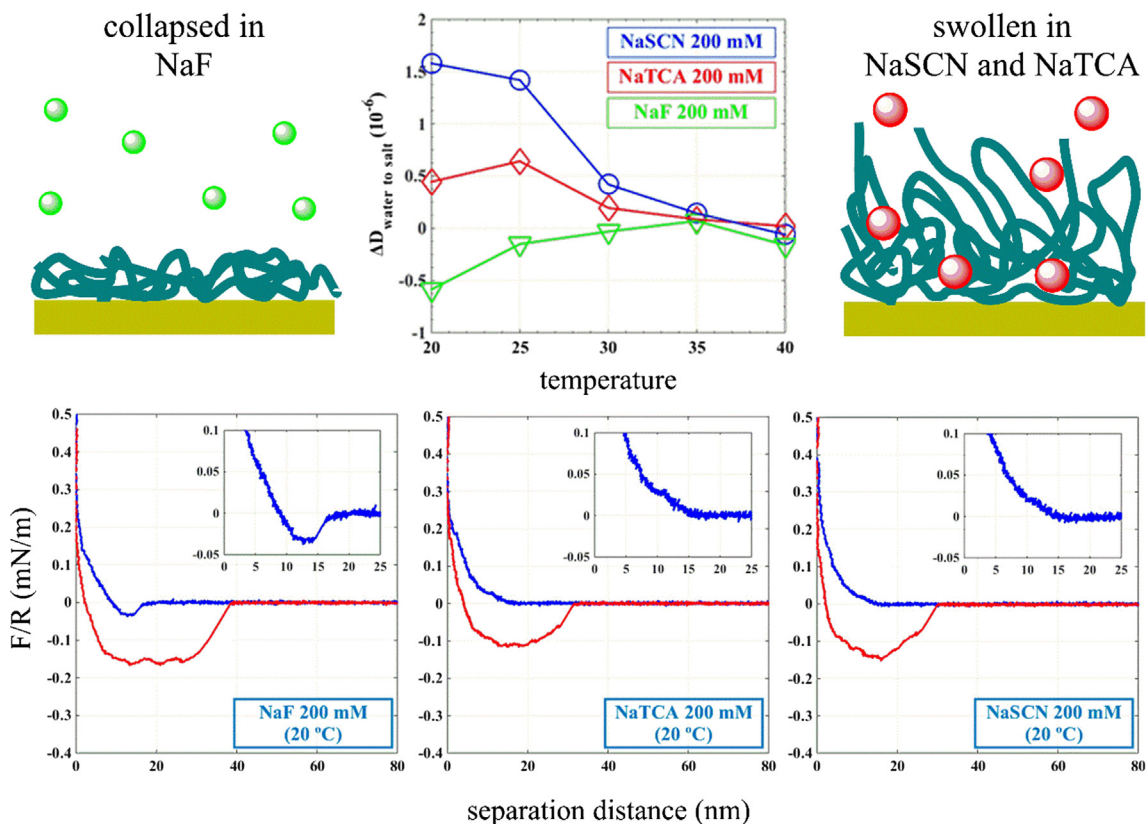
Aside from electrostatic and osmotic contributions, the other open question pertains to the additional effects of weakly hydrated salts on the hydration state and intermolecular forces of the polymers. As discussed in Section 2.1, ions are believed to influence the hydrophobic hydration of polymers by changing the surface tension at the nonpolar polymeric surface; an effect that has been regarded as the origin of the linear salting-out effect (at high salt concentrations) by weakly hydrated salts. It is however obscure under which conditions the effect of ions on the hydrophobic

hydration could lead to polymer stabilization. For example (Fig. 7b), the slope in high salt concentration regime is negative (destabilizing) for PNIPAM but positive (stabilizing) for PPO. As we will further discuss in the next section, the surface tension effect can lead to destabilization or stabilization, depending on the polymer chemistry. Regarding the effect of ions on the hydrophilic hydration of polymers, one can argue that a concentrated salt solution resembles polymer chains dispersed between the hydrated ions; hence, even though the ions supposedly cannot exhibit a long-range influence on the water structure, the idea of having a bulk water network seems impractical. Thus, one would expect a different situation for the polymer to withdraw hydration water from a pure water–water or chaotrope–water network. Thus, ion-specific variation in the “solvent quality” is probable. Regarding the effect of ions on polymer hydration, Liu et al. addressed a similar idea by assessing the effect of salts on PNIPAM in solvent mixtures [210–212]. They demonstrated that the reentrant (cononsolvency) behavior of PNIPAM in water–methanol mixtures is substantially suppressed in the presence of  $\text{SCN}^-$  and  $\text{ClO}_4^-$  ions, due to the structure breaking effects on the solvent complexes and solvent quality. Finally, the intra- and inter-chain attractive interactions (e.g., hydrophobic attraction and hydrogen bonding), which control the conformation and give rise to polymer chain collapse and aggregation, can be affected by ion–surface and solvent-mediated interactions, which will be discussed further in Section 3.2 below.

### 3.2. Transition from salting-in to salting-out: what are the sources of destabilization?

Another enigmatic behavior exhibited by weakly hydrated salts is the observed turnover and subsequent salting-out effect at relatively high salt concentrations. The essential consideration regarding this behavior is the polymer-specific nature. For example, NaSCN on PNIPAM exhibits a turnover at a salt concentration of ~400 mM, while such an effect is not observed for PPO, even at concentrations  $\leq 1.5$  M. It is accordingly conclusive that weakly hydrated salts can produce a destabilizing effect depending on the polymer type.

To test such dual behavior of the weakly hydrated anions, we previously examined the effect of three sodium salts, i.e., NaF, NaSCN, and NaTCA on the solution properties of PNIPAM [213]. For the investigated salt concentration (200 mM), three particular effects on the properties of PNIPAM were revealed, which are summarized in Fig. 8. Based on the calorimetry measurements on PNIPAM in bulk solution, NaF produces a decrement (salting-out) of  $-4.5$  °C in the phase separation temperature. When studying PNIPAM at an interface, the quartz crystal microbalance with dissipation (QCM-D) data suggest partial shrinkage of the polymer film and the AFM data demonstrate strong attractive polymer bridging forces, which agree with typical salting-out behavior. Conversely, the addition of NaSCN is characterized by an increment (salting-in) of  $1.2$  °C in the collapse temperature, partial swelling, and less significant polymer bridging attractions, which all together imply a stabilization effect. NaTCA demonstrates a combination of these two behaviors, i.e., a salting-out effect on the phase separation temperature ( $-1.2$  °C) but partial swelling of the film and weak polymer bridging interactions. The last two observations suggest that as a weakly hydrated anion,  $\text{TCA}^-$  is attracted to the polymer surface. The partial swelling might originate from osmotic pressure buildup due to excess salt within the PNIPAM film, while the weaker bridging forces could be due to steric effects by swelling or weaker attractive interactions. On the other hand, the observed drop in the collapse temperature implies that at this concentration, NaTCA produces simultaneous salting-in and salting-out effects.



**Fig. 8.** Hofmeister Effect of NaF, NaTCA, and NaSCN salts on poly(*N*-isopropylacrylamide) (PNIPAM) at the gold-water interface. (Adapted with permission from [213]. Copyright (2019) American Chemical Society). First row: quartz crystal microbalance with dissipation (QCM-D) shifts for a PNIPAM film when changing the solvent from water to the saline solutions. A positive dissipation shift ( $\Delta D$ ) for NaSCN and NaTCA suggests polymer layer swelling, while a negative  $\Delta D$  for NaF hints at polymer collapse. Second row: atomic force microscopy (AFM) force-distance curves between two PNIPAM-coated gold surfaces in the salt solutions at 20 °C. Strong attractive bridging between the layers is observed in the NaF solution, while in both the NaSCN and NaTCA solutions the attraction is significantly attenuated.

As discussed in Section 2, the salting-out effect generally emerges from the polarization of the polymer hydrophilic hydration shell, increment of the surface tension at the polymer-water interface, and collective binding. The polarization effect by weakly hydrated anions should not be pronounced since the ions are poorly hydrated and no correlation between their entropies of hydration and salting-out powers is inferable [89]. The idea of surface tension variation in the presence of ions is more sensible; however, further scrutiny is necessary to understand how ions affect the interfacial tension of polymers of various surface chemistries. In the literature, the salting-out power of weakly hydrated salts [slope of  $\Delta T(c)$  after the turnover point] is generally ascribed to their corresponding surface tension increment at the air-water interface [102]. One should, however, note that the air-water surface tension cannot describe the salt-induced changes in polymer solubility and conformation. Indeed, most of the salts (including NaSCN, NaClO<sub>4</sub>, and NaI) enhance the air-water interfacial tension, due to the strongly repulsive electrostatic image forces that promote an ion-depleted zone adjacent to the air surface. On the other hand, the weakly hydrated salts exhibit smaller effects presumably due to the opposite effect of these ions on the water cohesion forces and lesser depletion from the air surface. Indeed, Dér et al. suggested that the interfacial tension between a solute (polymer) and the saline solution depends on the nature of the exposed molecular surface, strength of hydrogen bonding between the water molecules, and excess surface concentration of the salt [214–217]. Accordingly, plotting the salting-out slopes against the air-water surface tension increment for each salt might provide an overall satisfactory trend (albeit not in all cases [104]) but is not the correct representation of the polymer interfacial

changes. There are sporadic studies evaluating the interfacial tension of water-oil in saline solutions that affirm interfacial tension drop in the presence of weakly hydrated anions such as I<sup>−</sup> and SCN<sup>−</sup> [218,219]. Nevertheless, information on the interfacial tension between water and the polymeric surfaces is scarce. As a noted work, Deyerle and Zhang inspected the effect of Hofmeister salts on the aggregation temperature of a PEO-PPO-PEO block copolymer [112]. The investigated copolymer is characterized by a two-step phase transition, i.e., a low-temperature micellization corresponding to a collapse of the PPO blocks as well as a high-temperature aggregation related to a collapse of the PEO blocks. The effects of the salts on these two transition temperatures were shown to be different, suggesting that each ion exerts distinctive effects on the PPO and PEO blocks. For both transitions, however, NaI and NaSCN presented positive slopes at high salt concentrations in contrast with NaBr, NaNO<sub>3</sub>, and NaCl (negative slopes, salting-out). The authors have accordingly speculated that I<sup>−</sup> and SCN<sup>−</sup> ions lower the PEO-water and PPO-water interfacial tensions. In addition, the effect on the PEO blocks was more pronounced, which was attributed to its more hydrophilic nature. The authors then estimated the change in the interfacial tension for each block in the saline solutions. The most significant conclusion of this work is the proposed relationship between the surface tension effect and surface polarity (dielectric constant). Accordingly, for the air-water interface, where air displays a very low dielectric constant, all the poorly hydrated salts increase the surface tension. At the hydrophobic interfaces in the hydrophobic collapse of the polymers or peptides such as PNIPAM and elastin-like peptides, the interfacial tension changes in the presence of weakly hydrated salts are moderately correlated to the surface tension

data at the air–water interface. With respect to the relatively hydrophilic solutes such as PPO and PEO, the most poorly hydrated salts such as NaI and NaSCN lower the interfacial tension, while salts with a relatively stronger hydration still destabilize the interface. For more hydrophilic systems with larger dielectric constants such as lysozyme, almost all the poorly hydrated salts lower the interfacial tension. Therefore, the authors proposed that the change in surface tension is mainly governed by the surface accumulation/exclusion of the ions since a correlation between the surface tension effect [slope of the linear  $\Delta T(c)$ ] and polarizability of the ions was observed.

In addition to the above discussions, the salting-out effect of some weakly hydrated salts seems too strong to merely originate from the surface tension effect. For example, the air–water surface tension increment by  $\text{NaClO}_4$  is 1.4 mN L/m mol, which is comparable to those of NaBr and NaCl. However, the salting-out power by  $\text{NaClO}_4$  at high salt concentrations is significantly larger than those of NaBr and even NaCl [89]. For such cases, the collective binding mechanism through which a crosslinking-like-effect occurs could be the most probable explanation (as seems to be the case for  $\text{TCA}^-$  [213]). However, this mechanism also requires further examination regarding its correlation to the polymer structure and chemistry, since such an effect by  $\text{NaClO}_4$  is not observed for all the polymer systems [200,201].

### 3.3. Role of the polymer and solvent properties

We have previously discussed that the origins of the salting-in and salting-out effects, specifically for weakly hydrated salts, are yet to be explored. One of the chief reasons for this scarcity is because the role of polymer properties in the specific ion effects has rarely been investigated in a systematic manner. A significant number of reports on how salts modify the collapse temperature of different thermo-responsive polymers have been reported in the literature; nevertheless, studies addressing the effect of salts on polymers with controlled variation in the structural properties are somewhat limited.

It is well established that several parameters such as polymer concentration, molecular weight, polydispersity, hydrophilicity, end groups, and chain architecture can affect the thermo-responsive behavior of polymers in salt-free solutions [220–225]. The effect of these parameters has been often interpreted in terms of the changes applied to hydration, interaction, and conformation of the investigated polymer. Accordingly, performing studies in which such parameters are varied in a controlled way can also clarify some of the obscurities surrounding the mechanisms of ion-specific effects. An example of a proper approach would be the investigation of the effect of salts on a polymer with controlled variation in the monomer hydrophilicity. By conducting such experiments over an extended range of salt concentrations and testing weakly hydrated salts, one can pursue how the binding isotherm and interfacial tension effects are dependent on the polymer hydrophilicity. As an example of such an approach, one can consider the work by Bloksma et al. in which the effect of salts on the cloud points of three poly(2-oxazoline)s with different side chains (different hydrophilicity) was investigated [226]. The authors concluded that specific ion effects are more pronounced (with regard to magnitude) on the more hydrophilic polymer; however, not all the observed trends were discussed in detail. For example, the salting-in effects by LiI and  $\text{NaClO}_4$  were reported to be stronger on the more hydrophobic polymer. In the same line, studying the behavior of nonionic block copolymers, e.g., PEO-PPO-PEO, in saline solutions could be another way to assess the role of polymer hydrophilicity on ion-specific effects [112].

In addition to the chemical structure, another approach to elucidate the mechanisms of ion-specificity is to vary the structural

properties of the polymer (e.g., the molecular weight) and investigate the correlation to the effects of salts [102,227]. By doing so, one can assume that ion–polymer interactions are not affected from a chemistry point of view, but will be able to ascertain the roles of the accessible surface area and polymer–polymer interactions. As a relevant example, Cremer et al. investigated the effects of salts on the cloud point temperatures of PNIPAM with four different molecular weights [102]. This work features essential results and conclusions; for example, with an increase in the PNIPAM molecular weight, the salting-in (binding) effect becomes weaker, the turnover point is shifted to lower salt concentrations, and the slope of the subsequent salting-out effect is almost unaffected. Accordingly, the authors reasoned that the surface-related binding is affected by the changes in polymer conformation and accessibility of the binding sites; however, the surface tension effect is not modified since the chemistry of the polymeric surface is unchanged. We have conducted a similar study on PPO, where the influence of the polymer molecular weight and concentration on the salting-in and salting-out effects was investigated [227]. The results revealed that generally, an increase in the molecular weight leads to weaker specific ion effects, while increasing the PPO concentration produced weaker salting-out but stronger salting-in effects. Wanless et al. stressed the influence of polymer architecture on specific ion effects by comparing the effect of salts on free polymer chains and those grafted as a brush layer [228]. They also investigated the specific ion effects on ethylene glycol-based comb-polymer brushes as a function of the copolymer composition [225]. They suggested that the confinement of polymer chains plays a significant role in the balance and magnitude of the specific ion effects.

Controlled variations of the solvent properties can be another alternative to inspect the role of solvent–solvent, solvent–ion, and solvent–polymer interactions. We have recently demonstrated that the effect of different salts on the phase separation temperature of PPO is influenced by changing the solvent from normal to heavy water. For example, the salting-in effect of NaSCN was notably stronger in deuterated water, probably due to the more chaotropic character of the anion in heavy water [229]. Similarly, studying the reentrant behavior of polymers in mixed water–alcohol solvents in the presence of salts could be an alternative way to study how solvation forces and solvent complexes can influence the specific ion effects [210]. Such measurements are typically interpreted in terms of the thermodynamic entropies and enthalpies of transition that can provide further understanding of the specific ion effects on polymer hydration.

Accordingly, regardless of the chosen approach, future studies on polymer–salt solutions should aim beyond cloud point measurements and monitor how salts affect other fundamental polymer properties. For example, the polymer coil size and polymer–solvent interaction quality in the presence of different salts can be examined through scattering techniques. Such data can be supplemented with osmotic pressure measurements to establish whether there is any correlation between the polymer coil size (swelling/shrinkage) and osmotic pressure effect. Structural changes in polymers (e.g., changes in water content and conformation) can also be monitored at the interfaces using surface-involved techniques such as QCM-D, spectroscopic ellipsometry (SE), and surface plasmon resonance (SPR). Measurements of this type can be combined with AFM colloidal probe measurements to inspect the polymer interactions.

### 3.4. Specific ion effects in salt mixtures: additivity vs. non-additivity

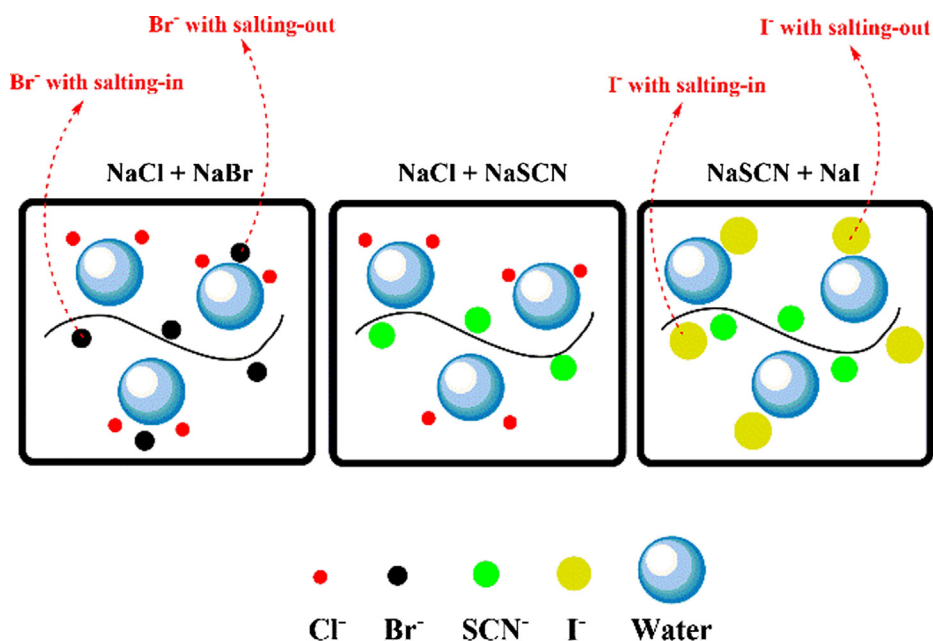
The examples of Hofmeister-related phenomena in biology are numerous. For example, the presence of chaotropic anions such as  $\text{SCN}^-$ ,  $\text{ClO}_4^-$  and  $\text{NO}_3^-$  can interfere with iodide transport to

negatively affect thyroid-related functions [230–232]. As another interesting case, the precipitation and formation of amyloid fibrils, one of the suspected origins of Alzheimer disease, have been attributed to changes in the ionic composition [233–235]. In addition, kosmotropes such as  $\text{Mg}^{2+}$  were shown to inhibit the growth of calcium oxalate crystals, which has enormous implications for the pathogenesis of urinary stones. The interested reader is referred to the relevant review paper by Lo Nostro and Ninham for more details on the specific ion effects in biology-, medicine- and food-related systems [165].

One of the primary reasons for studying the specific ion effects on model polymer systems is indeed to mimic and understand the role of ion-specificity in complex biological systems. For example, instead of investigating biopolymers with multiple stable structures and functionalities, PNIPAM is studied as a model thermo-responsive polymer with a rather similar structure. However, a critical factor that has been less discussed regarding such model studies is that biological systems always comprise a mixture of different ions. Accordingly, investigating the effects of salt mixtures on model polymers can be another critical step toward understanding the relevance of Hofmeister-related phenomena in biological systems. Equally important, it should be noted that comparing the effect of salt mixtures with the solutions of their constituents could be considered as a new touchstone to assess the molecular mechanisms behind the specific ion effects.

To our knowledge, few reports addressed the specific ion effects in salt mixtures [88,236–244]. For example, Bastos-Gonzales et al. investigated the electrophoretic mobility of charged PNIPAM particles in 10 mM  $\text{Na}_2\text{SO}_4$ , 10 mM  $\text{NaSCN}$ , and a 5 mM + 5 mM mixture of both [183]. Accordingly, they suggested an additive effect for the mixture of the two salts based on the measured surface charge values. In another relevant work, Vrbka et al. assessed the distribution of sodium, choline, chloride, and sulfate ions around two model proteins using MD simulation studies [240]. The authors detected an additive effect for most of the mixtures regarding the ion distribution around the surface of the protein. In a recent work, we have systematically examined the effect of three basic salt mixtures on the phase transition temperature of PPO [90]. The mixed salt solutions demonstrated both additive and non-additive effects,

depending on the salt type and concentration (Fig. 9). The mixture of two salts of considerably different behavior (salting-in and salting-out behavior) demonstrated an additive effect on the phase separation temperature. This implied that each anion applies its specific effect on the polymer stability, regardless of the presence or absence of the other ion. When mixing two salts with a salting-in effect, the stronger component (the anion with a higher propensity toward the polymeric surface) was shown to dominate the overall salting-in behavior of the mixture, while the other component inevitably produced a relative salting-out effect. Accordingly, a non-additive “competitive binding” mechanism can be deduced. When mixing two salts with a salting-out effect, the overall salting-out behavior of the mixture was surmounted by the stronger component (the anion with higher hydration strength), while the other component had a relative salting-in effect, implying a non-additive “competitive hydration” mechanism. The additive and non-additive mechanisms need to be subjected to more precise and rigorous measurements, to provide a better understanding on how polymer hydration, interaction, and conformation are affected in mixed saline solutions. In a recent notable work, Wanless et al. investigated the structure of a thermo-responsive polymer brush in mixed salt solutions containing  $\text{SCN}^-$  (salting-in) and  $\text{CH}_3\text{COO}^-$  (salting-out) [243]. The authors suggested that the relative influence of the ions in the mixed electrolyte environment is indeed temperature dependent. At temperatures well below the LCST, an additive and approximately equal effect of the  $\text{CH}_3\text{COO}^-$  and  $\text{SCN}^-$  ions was observed. On the other hand, it was demonstrated that the effect of the  $\text{CH}_3\text{COO}^-$  ions is diminished at higher temperatures resulting in an enhanced relative influence by the  $\text{SCN}^-$  ions. Vegt et al. recently investigated the effects of salt mixtures on PNIPAM using MD simulation and vibrational sum frequency spectroscopy [244]. They reported that for a fixed  $\text{Na}_2\text{SO}_4$  concentration, the addition of  $\text{NaI}$  leads to non-additive effects that can be summarized into three regimes: at low  $\text{NaI}$  concentrations (regime I), the  $\text{SO}_4^{2-}$  ions withdraw the  $\text{Na}^+$  ions into their counterion cloud leaving the  $\text{I}^-$  ions more hydrated than in the pure salt state. As a result, the  $\text{NaI}$  activity increases and a salting-out effect is found. At intermediate  $\text{NaI}$  concentrations (regime II), the  $\text{SO}_4^{2-}$  ions force the  $\text{I}^-$  ions out from



**Fig. 9.** Schematic illustration of the Hofmeister effect by salt mixtures. (Reproduced from [90] with permission from the PCCP Owner Societies) A mixture of two salts with a salting-out effect gives rise to competition for the polymer hydration shell, while a mixture of two salts with a salting-in effect leads to competition for the polymer surface area. The mixing two salts with salting-in and salting-out effects represents additive effects.



solution to the polymer interface, leading to enhanced binding and subsequent reentrant swelling (salting-in effect). At the highest NaI concentrations (regime III), NaI addition leads to a salting-out effect similar to that observed with a single salt, which the authors attributed to the surface tension effect.

Of equivalent importance is that there always exists a mixture of different biomacromolecules of various molecular weights and chemistries in complex bio-related systems. Therefore, another approach toward understanding the specific ion effects in “real” systems is to investigate multi-component model polymeric systems that can better mimic the composition of biological fluids. As a relevant case, various studies have demonstrated that macromolecular crowding effectively contributes to protein folding and enzymatic reactions [245–247]. Accordingly, one of several approaches toward elaborating the model systems is to study specific ion effects in a crowded environment, where some initial studies have already been conducted [248–250].

#### 4. Summary and conclusion

We have herein presented an overview of previous works and future research perspectives regarding specific ion effects in thermo-responsive polymer solutions. The knowledge gained from the currently existing literature together with follow up studies can be of great importance and use. On the one hand, by elucidating how different ions affect polymer stability, we can tune the interaction and conformation of stimuli-responsive polymers more effectively. This opens new windows and opportunities to the vast applications of stimuli-responsive polymers. On the other hand, a better understanding of the mechanisms governing ion–macromolecule systems can render us a deeper comprehension of biological systems where proper functioning depends on the presence of ions and their interplay with biomacromolecules.

With respect to the mechanisms, we have discussed how strongly and weakly hydrated ions interact with polymers in different ways. These differences not only depend on both the ionic properties (ion-specificity) but are also affected by the polymer features (polymer-specificity). The conducted works relevant to ion-specific effects in polymer solutions can be grouped into two fundamental schools of thought. The first group mainly focuses on understanding the ion–polymer interplay from a more molecular point of view to establish how ions affect the polymer stability in terms of hydration and conformation. The second group has adopted a more fundamental approach where ion–polymer interaction was investigated with respect to the origins of ion-specificity. While both approaches have been quite fruitful, it is indisputable that an attempt to further merge these ideas can provide a stronger opinion on the topic. This includes current obscurities surrounding the: (i) mechanisms of the salting-in and salting-out effects by weakly hydrated salts, (ii) correlation of salt effects with the polymer properties, and (iii) mechanisms of ion-specificity in complex crowded systems where multiple ions and solutes exist.

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