

Modifying Specific Ion Effects: Studies of Monovalent Ion Interactions with Amines

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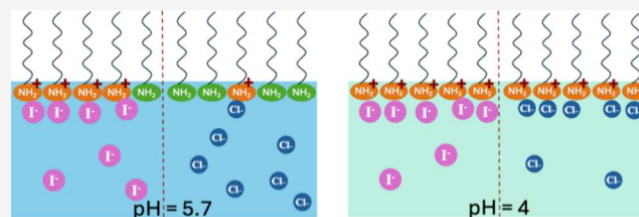


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ABSTRACT: Specific ion effects in the interactions of monovalent anions with amine groups—one of the hydrophilic moieties found in proteins—were investigated using octadecylamine monolayers floating at air–aqueous solution interfaces. We find that at solution pH 5.7, larger monovalent anions induce a nonzero pressure starting at higher areas/molecules, i.e., a wider “liquid expanded” region in the monolayer isotherms. Using X-ray fluorescence at near total reflection (XFNTR), an element- and surface-specific technique, ion adsorption to the amines at pH 5.7 is confirmed to be ion-specific and to follow the conventional Hofmeister series. However, at pH 4, this ion specificity is no longer observed. We propose that at the higher pH, the amine headgroups are only partially protonated, and large polarizable ions such as iodine are better able to boost amine protonation. At the lower pH, on the other hand, the monolayer is fully protonated, and electrostatic interactions dominate over ion specificity. These results demonstrate that ion specificity can be modified by changing the experimental conditions.



INTRODUCTION

It was first reported by Hofmeister in 1888 and confirmed in numerous other studies that ions with the same outer electron shell can exhibit different effects in physical,¹ chemical,^{2,3} and biological⁴ systems. A widely accepted ordering of these specific ion effects is called a Hofmeister series, usually referring to two separate series for anions and cations:⁵

Anions: $F^- > Cl^- > Br^- > NO_3^- > I^- > SCN^-$

Cations: $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+ > Ca^{2+} > Mg^{2+}$

Ions on the left side of the series tend to precipitate and stabilize proteins, while ions on the right side tend to dissolve and denature proteins.

However, these established sequences are not always followed. Modifications, deviations, and sometimes even reversal of the Hofmeister series have been reported.^{6–9} A major reason for the seemingly contradictory information is the complexity of the protein structures. Ion-specific effects can change when they interact with different parts of proteins under different conditions. Therefore, it is important to break down this problem into its component parts, i.e., with a reductionist view. In this study, we provide a detailed investigation of ion specificity near amines, a functional group that exists in many proteins and other molecules. To do so, we study the model system of monolayer films floating in aqueous solutions.

Even when a single organic moiety is studied, contradictions remain. In some studies, it was reported that smaller anions are more attracted to protonated groups,^{6,10,11} while others observed a stronger effect of larger anions on cationic

films.^{12,13} Measurements using NMR,⁶ Infrared Spectroscopy,¹⁴ and Sum Frequency Generation (SFG)¹³ have provided detailed information about the ions through indirectly observing the effects that ions have on water or organic molecules. Here, in addition to isotherm studies, we also report direct observations of the ions. We detected anion adsorption to floating monolayers using X-ray fluorescence near total reflection (XFNTR). We confirm the ion specificity near amine groups at pH 5.7, but we also find that this is substantially modified by reducing the pH. A possible explanation of this pH dependence is discussed below.

METHODS

Materials. Octadecylamine (ODA) solution was prepared by dissolving the ODA powder (Sigma-Aldrich, >99.0%) in chloroform (Fisher, 99.9%). The salts potassium fluoride (Sigma-Aldrich, 99.5%), potassium chloride (Sigma-Aldrich, ACS, 99.0–100%), potassium bromide (Sigma-Aldrich, ACS, >99%), potassium nitrate (Sigma-Aldrich, ACS, 99.0%), potassium iodide (Sigma-Aldrich, >99.5%), potassium thiocyanate (Sigma-Aldrich, 99%), potassium perchlorate (Thermo, 99%) and potassium tetrafluoroborate (Sigma-Aldrich, 99.99%) were used as received. The salt solutions were

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prepared by dissolving salts in ultrapure water with an 18.2 M Ω resistivity. For the low solubility salts KClO₄ and KBF₄, concentrated solutions of 20 mM were prepared and allowed to stand for at least 24 h until fully dissolved. Then the bulk solutions were diluted from the 20 mM stock. For all other salts, the solutions were prepared before each use. Hydrochloric acid (Fisher, 36.5–38%), hydroiodic acid (Sigma-Aldrich, 55%), and perchloric acid (Sigma-Aldrich, 60%) were used to adjust pH in the corresponding KCl, KI, and KClO₄ solutions in X-ray experiments in order not to introduce interference from irrelevant fluorescence emissions. The pH in all pressure–area isotherms was adjusted using trace amounts of HCl.

Langmuir Monolayer Isotherms. The Langmuir trough used in pressure–area isotherms shown is a KSV Teflon trough (20 cm length, 12 cm width, 1 cm depth). The ODA monolayers were formed by spreading 1 mM of ODA in a chloroform solution on the water surface. After 5 min of waiting to allow the solvent to evaporate, the monolayer was compressed with a Teflon barrier at 10 mm/min. A 10 mm wide paper Wilhelmy plate was used to measure the surface pressure. All the isotherms were recorded at a constant room temperature of 21 $\pm$ 1 $^{\circ}$ C.

The trough used in all X-ray experiments was a custom designed and fabricated Teflon trough (11.43 cm length, 7.62 cm width, and 0.41 cm depth). The ODA monolayers were formed by titrating 1 mM ODA in chloroform solution on the surface until the desired surface pressure was reached. The surface pressure was monitored using a 2 mm wide filter paper Wilhelmy plate. All the XFNTN measurements of the ODA samples were taken at a surface pressure of 1–11 mN/m, in the range of the tilted-condensed phase of the monolayer. The areas per molecule fluctuations were within 5% during each XFNTN scan.

XFNTN. XFNTN measurements were conducted at NSLS-II (Brookhaven National Lab) beamline 12 with an X-ray energy of 9.7 keV. The details of this technique are explained in the work of Bu et al.¹⁵ In brief, XFNTN profiles ion distribution near the surface utilizing the contrast of X-ray penetration depth below versus above the critical angle. When the incoming beam is incident from below the critical angle, it experiences total external reflection. Only ions in the interfacial region ($\sim$ 100 Å) are excited by the X-ray evanescent wave, while once the beam is above the critical angle, the penetration depth increases by 2–3 orders of magnitude, allowing emission from the ions in both the surface region and the bulk to be probed. With a known bulk ion concentration, the emitted fluorescence intensities from specific ions can be fitted to extract the ion population in the interfacial region. While the technique does not precisely locate the ions relative to the amine groups, the anion concentrations at the monolayer interface are much higher than in the bulk when there is a monolayer; and no interfacial enhancement is observed when there is no monolayer. This indicates that the ions detected by this method have been attracted to the interface by the monolayer. XFNTN data analysis was performed using software developed by ChemMatCARS (Argonne, Argonne, National Laboratory).

RESULTS

Modification of ODA Isotherms by Monovalent Anions. The addition of any monovalent salt will trigger charging of the amine group,¹³ thus modifying the isotherm of

a floating amine monolayer. We observed this modification in octadecylamine (ODA) monolayers at the air–water interface when monovalent salts are dissolved in the subphase. The pressure–area isotherm of the ODA with 0–1 mM KI in the subphase is shown in Figure 1a. The salts give rise to an

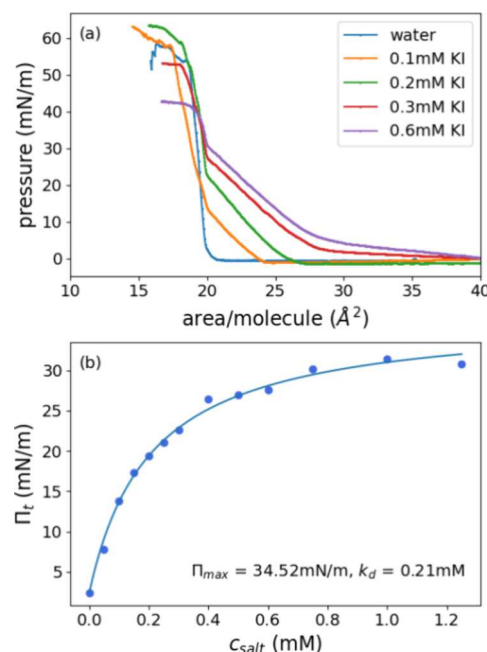


Figure 1. (a) Isotherms of ODA on the KI subphase at various concentrations. (b) Upper phase transition pressure in ODA isotherms plotted versus the bulk KI concentration and fitted with a Langmuir model (see text).

extended “tilted-condensed” phase in the isotherm, and the phase transition pressure to the most dense (“untitled”) phase as the salt concentration increases. Note that at the higher salt concentrations, the surface pressure starts to rise at a very high molecular area, implying high repulsive interactions between the headgroups.^{16,17} This is contrary to what was observed for anions under the fixed cationic film DPTAP, where iodine was found to lower the surface pressure by screening the charges.¹⁷ It is this same repulsive interaction that increases the pressure of the transition to the untitled phase.

The phase transition pressure as a function of the bulk salt concentration is plotted in Figure 1b. Since a saturating process is observed, we attempt to model the phase transition pressure Π_t versus bulk concentration with a Langmuir isotherm model:

$$\Pi_t = \Pi_0 + \frac{(\Pi_{max} - \Pi_0)[c]}{k_d + [c]} \quad (1)$$

where Π_0 is the phase transition pressure in the absence of salt ($[c] = 0$) and Π_{max} is the limiting phase transition pressure. $[c]$ is the molar bulk salt concentration. The model provides a good fit through the data points with the dissociation constant $k_d = 0.21$ mM.

XFNTN was used to determine how many ions are involved in the change in pressure–area isotherms. ODA monolayers on potassium iodide solutions with eight different concentrations were examined, and the integrated iodine fluorescence intensities from selected samples are displayed in Figure 2a. The fluorescence intensities reach a maximum at the critical

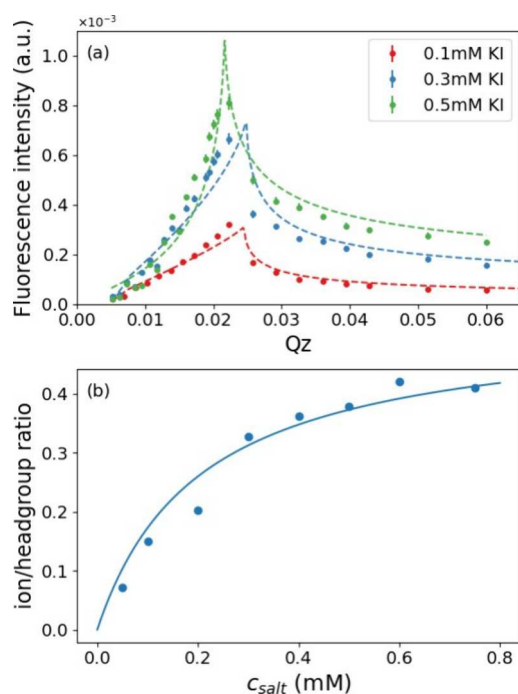


Figure 2. (a) Fluorescence intensity of iodine emission from selected samples and XFNR fits (lines). (b) Extracted iodine surface population normalized to ODA surface coverage as a function of bulk KI concentration. Solid line shows the Langmuir isotherm model with the same k_d as in Figure 1b.

angle and then drop as the beam penetrates into the bulk, which tells us that the ions are accumulating in the interfacial region. The extracted iodide ion populations adsorbed to ODA at different bulk concentrations, determined by data fitting, are shown in Figure 2b. Iodine adsorbed to the interface with respect to concentration shows a trend very similar to the change in upper phase transition pressure in isotherms. In both cases, the effect is a saturating process, with the change/adsorption slowing down at higher concentrations. The same k_d extracted from the phase transition pressure fits the ion population from fluorescence data. This suggests that the phase transition pressure is a macroscopic indicator of the degree of iodine adsorption. (Of course, the transition pressure also depends on other factors, such as temperature, but such factors were held fixed.) While we cannot prove that the same linkage exists for ions that we cannot see using the XFNR technique, we postulate such a linkage in order to extract k_d values from isotherm data in the presence of several other ions (see below).

It is to be noted that the saturation in amine monolayers occurs at a much lower solution concentration than the concentrations used in studying Hofmeister effects in biological systems or macromolecules in bulk, which are typically a few hundred mM.^{18,19}

Ion Specificity. Charging of monolayers on air–water interfaces has been reported in many studies, involving both cationic¹³ and acidic films,^{20,21} and the degree of charging is usually well described by the Gouy–Chapman (GC) model of charged surfaces. However, in our study, in contrast to what had been reported for acids on cation solutions (where ion identity made no difference),²⁰ we have found that the monovalent anions' effect on the amine monolayer is ion-specific. The ion specificity cannot be understood by the GC

model since it considers only ion valence. Figure 3 plots the phase transition pressure versus salt concentration for eight

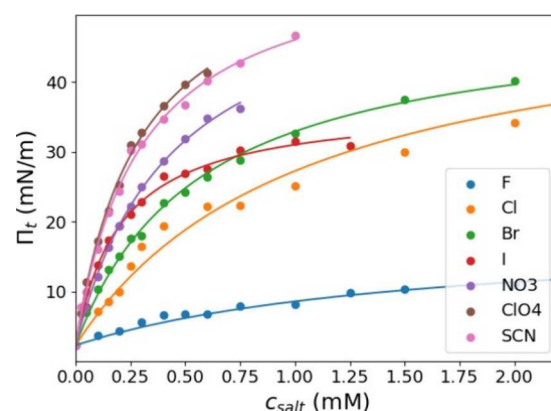


Figure 3. ODA monolayer upper phase transition pressure vs bulk ion concentration, with different anions in the subphase.

different potassium salts. The responses of the monolayers to different anions are distinctly different. With larger ions, the phase transition pressures rise quickly at low bulk concentrations, while for smaller ions, this happens much more slowly. Note that for all the ions, bulk concentration beyond a certain point will make the monolayer become so unstable that a condensed phase cannot be observed. Therefore, for smaller ions, the data was taken up until 2 mM, while for larger ions like ClO₄ and NO₃, data at concentrations beyond 0.75 mM could not be extracted.

Fitting the data with the Langmuir isotherm model (eq 1), a unique dissociation constant k_d is extracted for each ion and listed in Table 1. As noted previously, we postulate that the

Table 1. Fitted k_d from Kink Pressure as a Function of Salt Concentration, Using the Langmuir Isotherm Model (eq 1)

ion	k_d (mM)
F	1.58 ± 0.18
Cl	1.04 ± 0.12
Br	0.56 ± 0.027
NO ₃	0.45 ± 0.023
SCN	0.30 ± 0.018
ClO ₄	0.29 ± 0.021
I	0.21 ± 0.014

same dissociation constant applies to the number of ions adsorbed, with a smaller k_d indicating stronger adsorption. The association strength of these ions to amine closely follows the established Hofmeister series.

To confirm the ion specificity, XFNR was used to investigate ODA monolayers on three different salt solutions—KCl, KClO₄, and KI. This method is limited to atoms with fluorescence in an accessible range at the facility used, and thus the other ions used for isotherm studies could not be observed with XFNR. Very different ion populations near the surface are found for these ions when the bulk concentration is kept the same at 0.5 mM (Figure 4):

In agreement with the dissociation constant values extracted from isotherms and the Hofmeister series, perchlorate and iodine ions are found to be more adsorbed, followed by chlorine. Note that although k_d indicates a slightly stronger adsorption for iodine than perchlorate, while XFNR reports

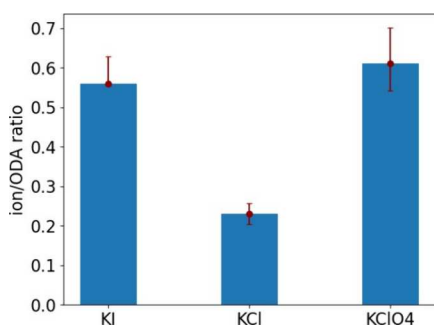


Figure 4. Ions adsorbed to the interface, normalized to the surface coverage of the ODA on 0.5 mM salt solutions. These results were extracted from XFNT data.

the opposite, the difference is not significant considering the error bars.

pH Dependence. ODA monolayers start to become soluble at subphase pH < 5 due to the charging of the headgroups.^{22,23} However, when salts are added to the subphase, the monolayers are stable at a lower pH. Figure 5

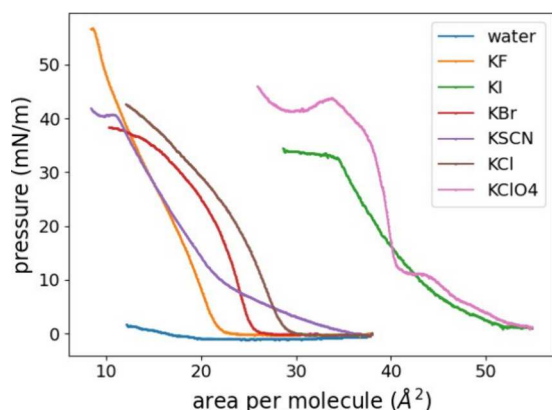


Figure 5. Isotherms of the ODA monolayers on pH 4 subphases with 1 mM of different anions.

shows the pressure–area isotherms of ODA at subphase pH 4 with different salts in bulk. 1 mM of all of the salts studied recovered observable surface pressures, but the isotherms had very diverse shapes for different anions. Larger anions caused pressure rise at a large area per molecule (around 40 Å²/molecule). For smaller anions, the isotherms reached an unreasonably small area/molecule, implying the dissolution of the ODA molecules into the bulk.

Unexpectedly, given the distinct difference between the isotherms, XFNT results showed that at 1 mM bulk concentration, the number of ions adsorbed to the interface is indistinguishable for different ion species. The ion/ODA ratio is close to one-to-one for all three ions (Figure 6).

XFNT also revealed that, unlike the case of subphase pH 5.7 (Figure 2), ion adsorption to the monolayer at pH 4 is not dependent on the subphase concentration (Figure 7). Iodine adsorbed to the film with a 0.1 mM bulk concentration does not differ from iodine adsorbed with a 5 mM bulk concentration, and for all cases, the adsorbed ions per spread molecule reached a ratio of near unity.

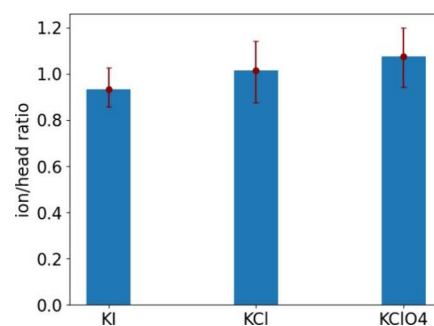


Figure 6. Anions adsorbed to the interface per ODA molecule spread on the water surface (from XFNT data).

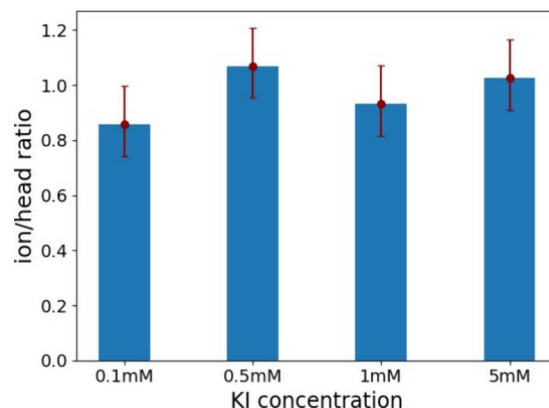


Figure 7. Iodine ions adsorbed to the interface per ODA molecule spread on the water surface at different subphase concentrations (from XFNT data).

DISCUSSION

The modification of film charge at the air–water interface by introducing salts has been observed in many other studies, including studies of both basic¹³ and acidic monolayers.^{20,21} Gouy–Chapman theory is usually used to explain these observations. In our study, XFNT confirms that (at pH 5.7) more anions are adsorbed to the film when the bulk salt concentration increases, in agreement with the increasing surface charge predicted by Gouy–Chapman’s model. Tyrode et al.²⁰ observed an analogous cation effect on acid deprotonation. In their study, the acid deprotonation fraction extracted from VSFG amplitudes versus the bulk salt concentration could be perfectly predicted by the Gouy–Chapman model. They suggested that at low ionic strength, the Gouy–Chapman approximation of treating ions as a point charge remains valid. Our study, on the contrary, reports a strong dependence of the amine charging behavior on the specific anion present at a similar ionic strength. We propose that ion specificity cannot be ignored even at low ionic strength, and Gouy–Chapman’s model is not sufficient. The independence of acid deprotonation on cation identity in Tyrode’s study may result from the particular pH and salt concentration chosen.

Recently, Gregory et al. proposed a very general measure of ion chaotropicity in water–radial charge density.²⁴ For monatomic anions, the order of ion–amine binding strength represented by the k_d we extracted is correlated with the sequence of β values calculated (Table S1 in Supporting Information). This suggests that although the Gouy–Chapman picture is oversimplified, the short-range Coulomb interactions

are the predominant forces in the system. The sequence does not hold for polyatomic ions SCN^- , ClO_4^- , and NO_3^- , indicating a more complex mechanism for these ions.

There are, of course, many computer simulations of such systems; however, we are not aware of any studies that predict or explain the information we report here. As one example, Schwierz et al.²⁵ reverse the Hoffmeister series in a simulation either by changing the sign of the surface charge or by changing the surface polarity from hydrophobic to hydrophilic. However, neither of these changes can be made in our experimental system.

To interpret the observed ion specificity, we consider two possibilities for the ion specificity at pH 5.7. It could be that all the ions enhance the charging of ODA to the same extent following Gouy–Chapman's prediction, but under the equally charged surface, chlorine is less adsorbed than iodine and perchlorate. Another possibility is that the larger ions have a stronger capacity to enhance amine protonation, resulting in a more positively charged ODA surface. Consequently, the more cationic surface attracts more anions with larger ions in the bulk compared with smaller ions.

The first hypothesis can be ruled out by looking at the ion population at pH 4 (Figure 6). At pH = 4 with 1 mM of salt, according to the Gouy–Chapman model, the monolayer is almost fully protonated (greater than 95% charged¹³). If the anions are adsorbed to equally charged films differently, different surface ion populations would have been seen by XFNTA at pH 4. However, XFNTA revealed similar adsorption to the surface for all three ions. Also, this hypothesis means better screening of the film charge by iodine than by chlorine. If that is the case, then with iodine in bulk, the repulsion between headgroups of the film would have been reduced. However, the isotherms showed a more extended tilted-condensed region for larger ions, which indicates not less but more repulsion between headgroups.¹⁷ In simulations where the surface charge is fixed, it is often found that smaller anions are more accumulated around cationic patches,^{6,10} which further refutes the possibility of more iodine adsorption than chlorine on surfaces with the same charge. We must conclude that in our case, the ion specificity does not come from the ions' different affinity to the amine surface when the charge is fixed.

The above reasoning makes the second proposal more plausible—larger anions have better ability to help protonate the amine film. Larger ions, such as iodine, are known to be more polarizable. The presence of the more polarizable ions may modify the apparent pK_a value of amines by modifying the interfacial region environment. It is widely recognized that large, polarizable ions are more prone to segregating to dielectric surfaces.^{26,27} At pH 5.7, using the Gouy–Chapman model, less than 10% of the monolayer is protonated.¹³ (It should be emphasized here that the ODA has a $\text{pK}_a \sim 10.6$, but the bulk pH is not a quantitative measure of the proton concentration at the surface.) The amine film acts mostly like an uncharged dielectric surface, and the larger, polarized anions are attracted to the surface due to the low electrostatic energy cost and high cavitation energy gain (energy gain from ions leaving the bulk and the cavities being reoccupied by water hydrogen bonds).²⁶ Then, as anions accumulate near the surface, more protons are drawn to the interfacial region, causing more facile protonation of the amines. Whether considering the monolayer as neutral or as slightly charged, the proton concentration in the surface region is smaller than in

the bulk pH.^{28,29} In the picture proposed above, the anions did not change the intrinsic pK_a value of the ODA but modified the proton availability within the interfacial region, appearing as though the ODA protonation is changed when bulk pH is unaltered. In a VSFG study of carboxylic acid monolayers, it was found that the presence of larger anions results in a higher surface potential and, consequently, a higher surface proton (H^+) concentration.³⁰ This further supports our proposed mechanism.

Moreover, ions may also modify the intrinsic surface pK_a value of the amines by affecting the strength of the binding of protons to amines. It was proposed in another study that protons can more readily unbind from acid groups under the presence of larger ions.²⁹ Similar effects could also interfere with proton-amine binding through modifying the mediated water molecules or through competitions among ion-amine interactions, ion-proton interactions, and amine-proton interactions.

At pH 4, on the other hand, since the film is already fully charged, the ions have no room to further promote the protonation through either mechanism. Then, at least for the low ionic strengths studied, all of the monovalent ions are similarly adsorbed because electrostatic attraction dominates. Note that even if the adsorbed ions are similar in amount, their effects on the ODA monolayer isotherm are very different (Figure 5). This may be because the larger ions have a better ability to penetrate through hydrophobic surfaces and thereby disturb the ordered conformation of the film.^{17,31} Our fluorescence data revealed that even when the number of ions adsorbed to the interface is identical, the way ions distribute within the interfacial region is crucial to the stability of macromolecules.

Unfortunately, the system described here is beyond the scope of simplified models using mean electric fields and ignoring co-ion interactions, i.e., any modified version of Gouy–Chapman theory. We hope our study stimulates interest in exploring the specific ion effect at protonatable groups using MD simulations using polarizable fields that can take more polarizability, hydronium ions, and water molecules into account.

CONCLUSIONS

Monovalent ion interactions with the ionizable surfactant ODA follow different mechanisms at two different pH levels. At pH 5.7, strong ion specificity was observed, and the number of ions adsorbed by the amines follows the Hofmeister series. We propose that larger, more polarizable anions, such as iodine, may have the ability to promote protonation of ODA near interfaces at this pH. Conversely, at pH 4, all the amines at the interface are already fully protonated with or without assistance from anions. Consequently, electrostatic interaction between ions and amines dominates, and specific ion effects are suppressed. Thus, our experiments at this pH revealed no ion specificity, and the number of ions accumulating near the interface reached a one-to-one ratio to the number of ODA molecules at the surface. The pH-induced change in ion-amine interactions also causes different behavior of the ODA isotherms at pH 5.7; adding salts into the subphase induces extended tilted regions in the ODA monolayer isotherms; and an excess amount of salt makes the monolayer unstable upon compression. At pH 4, on the other hand, the ions help “stabilize” the ODA monolayers. The observation reported in this study may provide a starting point for understanding the

modification or even reversal of the Hofmeister series under different conditions, as reported in the existing literature.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jpcb.4c02359>.

Pressure-area isotherms for octadecylamine on aqueous subphases with different salts at various concentrations; Langmuir isotherm fitting parameters k_d and $\Pi_{\max}$; and integrated X-ray fluorescence versus Qz , raw data from XFNR, and the best fit curves for ion surface coverage extraction (PDF)

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Notes

The authors declare no competing financial interest.

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