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Driving Forces for Oppositely Charged Polyion Association in Aqueous Solutions: Enthalpic, Entropic, but Not Electrostatic

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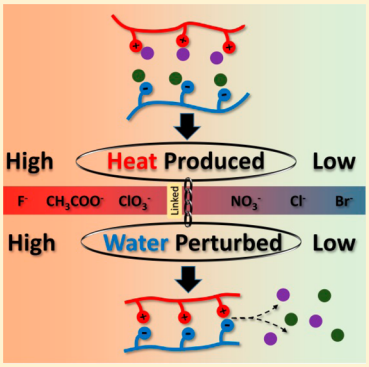
Supporting Information

ABSTRACT: Driving forces for association between oppositely charged biological or synthetic polymers in aqueous solution have long been identified as electrostatic in origin. This attraction is broken down into an entropic component, due to loss of counterions, and an enthalpic component, stemming from Coulombic attraction between opposite charges. While the balance between entropic and enthalpic contributions shifts according to the conditions, the presence of exotherms or endotherms on mixing, though small, are viewed as signatures of Coulombic interactions which support theories of polyelectrolyte association rooted in continuum electrostatics. Here, a head-to-head comparison is made between mechanisms based on electrostatics and those based on specific ion pairing, or ion exchange. Using a Hofmeister series of counterions for a common polycation, poly(diallyldimethylammonium), enthalpy changes on association with poly(styrenesulfonate) are shown to derive from changes in water perturbation, revealed by Raman scattering studies of water O−H vibrations. The free energy for complexation is almost completely entropic over all salt concentrations.



INTRODUCTION

Interactions between oppositely charged units on macromolecules assist in the formation of numerous condensed phases. In natural systems these interactions play a role in protein folding and molecular recognition.[1] Synthetic polyelectrolytes associate to yield dense polyelectrolyte complexes,[2] PECs, or more liquidlike coacervates.[3] Because most synthetic polyelectrolytes lack specific recognition elements, such as hydrogen-bonding, the driving force for association between polycation, Pol^+, and polyanion, Pol^-, repeat units appears to be the straightforward electrostatic attraction of opposite charges, represented by

$$Pol^+A^-_{aq} + Pol^-M^+_{aq} \rightarrow Pol^+Pol^-_s + A^-_{aq} + M^+_{aq} \quad (1)$$

Quantitative understanding of the electrostatic mechanism is immediately fraught with difficulty which stems from an incomplete theoretical description of the interactions within the starting materials themselves: the polyelectrolytes.[4] A closer look at the issues plaguing polyelectrolyte theory reveals that the culprits of confusion usually turn out to be the counterions and their exact location. For example, should each charged polymer repeat unit be accompanied by a counteranion A^- or cation M^+ as depicted in eq 1, or should only the fraction of ions "condensed" on the polyelectrolyte chain be included?[5] Despite decades of refinements to electrostatic analyses attempting to answer these questions, much experimental data is still not rationalized.[6] The central question for PECs is: how do counterions moderate the electrostatic attraction between Pol^+ and Pol^-?

A signature of net electrostatic (Coulombic) attraction would be an exotherm on polyelectrolyte association. Yet, from the early days of studies into polyelectrolyte complexes, it was remarked that no heat was generated upon complexation and therefore it must be entropically driven (by the "escaping tendency of the microions" as Michaels put it.[2c]) With the advent of more sensitive thermal methods, such as the isothermal calorimeter, small heats of complexation (a few kJ mol^{-1}) were measured.[7]

We have analyzed polyelectrolyte complexation using a site model where the state of association between polyelectrolytes is controlled only by the chemical potential (concentration) of salt MA.[8] Simple equilibrium expressions are sufficient to fit the data over a wide range. Using this ion exchange/pairing model, it was straightforward to explain differences in association for polyelectrolytes bearing different counterions across the Hofmeister series: a more hydrated counterion is easier to expel.[8c] Michaels initially used the ion pairing terminology[2b] but a few years later subscribed to the emerging electrostatics vocabulary and concepts,[2d] even though they were unable to explain the strong differences in association due to counterion identity.

Illustrated by the numerous morphologies in which polyelectrolyte complexes are found, association is not an all-or-nothing situation. A PEC in which all the repeat units are paired is rubbery, even glassy, in nature,[2c,9] whereas a PEC with few Pol^+Pol^- pairs yields a diffuse liquidlike material (coacervate). A carefully selected combination of PEC and salt allows access to the whole "continuum" of morphologies simply by changing salt concentration.[10] This degree of

Received: November 12, 2015
Published: January 15, 2016

DOI: 10.1021/jacs.5b11878
J. Am. Chem. Soc. 2016, 138, 980−990

association/dissociation controls all the properties of a PEC, such as modulus, ion selectivity, hydration, and permeability. Intramolecular association between opposite charges on the same chain are also controlled by salt concentration.[11] In biomacromolecules, as a protein folds, the fraction of charged peptides that pair (form "salt bridges") may increase.[1f]

There has recently been renewed interest in simple theories describing polyelectrolyte association. For example, a theory by Overbeek and Voorn[12] has been adapted by the Wageningen group[13] to describe phase boundaries in PEC formation. Negative enthalpies of complexation, though small, appear to support the role of electrostatics. Endothermic complexation cannot be rationalized by simple analytical theories,[12,13] but more recent molecular dynamics simulations[14] allow for positive or negative enthalpy changes. Theories relying on electrostatics do not describe the degree of association within a synthetic PEC. We have consistently avoided the use of electrostatics arguments to explain polyelectrolyte complexation and the response of PECs to solution ions. The term "ion pairing" invokes the essential concept of a positive and a negative polyelectrolyte repeat unit associating and allows prediction of the strength of interaction using simple arguments based on entropy. At the same time the driving force is still labeled "electrostatic" by almost all researchers in the field.

The electrostatic and ion pairing viewpoints are quite divergent, although they both predict weakening interactions with increasing salt concentration. The finding that there are enthalpic components to complexation continues to provide support, even if tentative, for the electrostatics picture of PEC formation. The purpose of the present work is to show what physically could be responsible, if not Coulombic interactions, for enthalpic changes when polyelectrolytes pair. In doing so, we provide a head-to-head comparison of electrostatics and ion pairing arguments, exploiting the Hofmeister series to emphasize the conclusion that the driving force does *not* derive from continuum electrostatics, as has been argued for at least 50 years.

RESULTS AND DISCUSSION

Enthalpies of complexation or association are obtained from calorimetric studies. Isothermal calorimetry (ITC), more familiar to biochemists measuring interactions between small molecules and proteins, has occasionally been employed to study complexation between synthetic polyelectrolytes[7] and between polyelectrolytes and ions.[15] These calorimetric studies have highlighted the major role of entropic driving forces for association in the presence of small enthalpic contributions. In ITC small aliquots of one component are added to a larger volume of a second component and the heat (endothermic or exothermic) is recorded during each addition. An example is seen in Figure 1A where 10 mM poly(diallyldimethylammonium chloride), PDADMAC, is added to 0.5 mM poly(styrenesulfonate, sodium salt), PSSNa, in the cell (this combination of polyelectrolytes has been used extensively in the field). Exothermic spikes are translated to ΔH in Figure 1B as a function of the molar ratio, r, of positively to negatively charged repeat units mixed. Small background signals from heats of PDAMDAC dilution and instrumental nonidealities, seen at $r > 1$, may be subtracted. These amount to less than 100 J mol^{-1}.[15]

For interactions of a small ligand with a (bio)macromolecule, interpretation of ITC results as in Figure 1B is usually done by assuming the ligand has one or two binding sites. The ΔH vs r is fit with a curve using a binding constant K_a which then yields the free energy change $\Delta G°$ through $\Delta G° = -RT \ln K_a$ and the remainder is $T\Delta S°$ (from $\Delta G = \Delta H - T\Delta S$). Polyvalent interactions between polyelectrolytes make the 1- or 2-site binding model inapplicable and complicate the fitting considerably. Various models have been used to analyze ITC data of polyelectrolyte complexation resulting in widely varying association constants K_a. It is difficult to establish whether these variations are due to differences in the models or in the materials (polyelectrolytes) and conditions. Some examples are as follows (K_a in parentheses): polyamidoamine/DNA (10^5);[16] polyallylamine/PSS (10^5–10^7);[7d] chitosan/DNA (10^9–10^{10});[7f] PDADMAC/DNA (10^5–10^6);[7g] polypeptides (10^4–10^5);[7h] PDADMAC/poly(acrylic acid) (10^3–10^5).[7j] In the present work, *no curve fitting* was performed on ITC data. The total heat evolved was simply integrated and the background subtracted; that is, the areas under each spike were summed. This sum is the enthalpy of complexation under the conditions (salt concentration) employed. The assumption that all polyelectrolyte is complexed at $r = 1$ is justified by the fact that no free polyelectrolyte is found at this point for any concentration of polymers mixed.

Ideally, heat is evolved on complexation until the ratio is 1.0. Figure 1 illustrates this expected output for a 1:1 complex of PSS and PDADMA. To obtain reliable thermodynamic data from ITC, one must be confident that the system is not biased

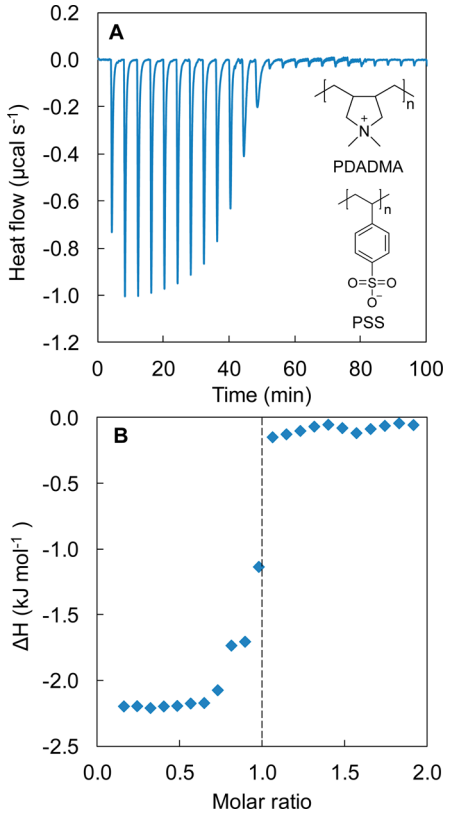


Figure 1. Heat flow per injection versus time for the injection of PDADMA(Cl) (10 mM) into PSS(Na) (0.5 mM). Both solutions contain 0.1 M NaCl. [A] Raw heat output versus time; a spike of heat evolves for each aliquot of titrant added to the reactor. [B] Heat per mole versus molar ratio r for each aliquot. The total enthalpy of reaction is obtained by summing heat from each injected aliquot until the background is reached (at $r \approx 1$) and subtracting the background due to the enthalpy of PDADMA(X) dilution seen at $r > 1$.

DOI: 10.1021/jacs.5b11878
J. Am. Chem. Soc. 2016, 138, 980–990

or compromised by kinetics. Polyelectrolyte complexes and compositions are often found to be kinetically trapped.[4] Early examples of polyelectrolyte combinations which exhibited labile or nonlabile association were presented in the pioneering work of the Moscow State group.[17] In another manifestation of kinetic control, the composition of PECs is notoriously dependent on mixing order.[18] The addition of salt is known to "unfreeze" PECs, allowing the chains to reconfigure and compact.[19]

Experimentally, there are two ways to ensure ITC interpretations of polyelectrolyte association are not compromised by kinetics. First, for strong binding of polymer to polymer, heat evolution should stop at r = 1.0, which suggests all the cationic repeat units have complexed with all the anionic ones. Second, the total heat evolved at r = 1.0 should not depend on the mixing order (whether Pol^+ is added to Pol^- or vice versa). A "reverse titration" was implemented by titrating PSS(Na) into PDADMA(Cl) in 0.1 M NaCl (Figure S1). The enthalpy of this reversed titration was −1.91 kJ mol^{-1}, which is close to the enthalpy (−1.88 kJ mol^{-1}) from the PDADMAC → PSS titration in Figure 1.

Salt Concentration Dependence of ΔH_{PEC}. Response to ionic strength (salt concentration) is a well-known and central property of polyelectrolyte solutions: coil size generally decreases as salt is added.[4,20] In polyelectrolyte complexation, salt counterions moderate the interaction between oppositely charged segments. The enthalpy of complexation, ΔH_{PEC}, between PDADMA and PSS was measured over the range [NaCl] = 0–2.0 M. No models were used to fit the binding. The total heat generated to complex an aliquot of PSS (PDADMA) in the cell was integrated to the point where no more heat above background was seen (close to r = 1). As shown in Figure 2, ΔH_{PEC} becomes less exothermic when the components are mixed in solutions of higher ionic strength. Increasing salt concentrations, converted to activities using tabulated activity coefficients, gave a broad span of ΔH_{PEC} between about −2 and 0 kJ. Data for mixing the two polyelectrolytes in salt-free solution (i.e., a_{NaCl} is undefined because the polymers generate NaCl as they pair) is shown by an open point (Figure 2).

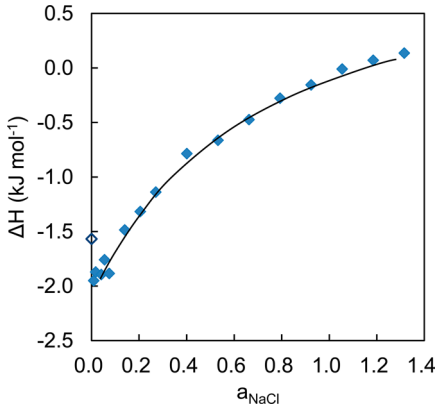
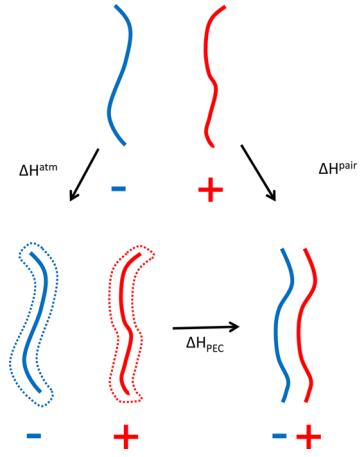


Figure 2. Enthalpy versus NaCl activity at room temperature for complexation of 10 mM PDADMA(Cl) added to 0.5 mM PSS. Point a_{NaCl} = 0, where no salt was mixed with polyelectrolyte, is shown as an open diamond. The solid line is a guide to the eye.

Models for Association. Two concepts will be compared to analyze the driving force for polyelectrolyte association. In the electrostatics model, electric fields driving attraction (between opposite charges) or repulsion (between like charges) compete with entropy loss of ions condensing on polyelectrolytes. The range of electric fields is set by the solvent dielectric constant and the ionic strength of the solution ("screening"). In the ion pairing model, interactions are controlled by the activities (concentrations) of the species competing among each other to form the following electrically neutral ion pairs: Pol^-Pol^+, Pol^-M^+, Pol^+A^-. Both of these models account for some observations, such as the dependence of interaction strength on salt concentration, but different vocabularies and concepts are used. The importance of counterion entropy is central to both models: it is known that polyelectrolytes lose their counterions, a driving force for association, when they complex. For example, analysis of bulk complexes[2b,c] or neutron scattering of solution macromolecules[21] show loss of counterions.

Electrostatic Model. In a continuum electrostatics model charged polyelectrolytes in solution collect an atmosphere of ions around themselves (see Scheme 1 on the left). An energy gain ΔH^{atm} by bringing oppositely charged ions close to the polymer counters a loss in entropy by taking them out of bulk solution and forcing them to reside next to the chain. Polyelectrolytes are now set up for complexation.

Scheme 1. Electrostatic Picture of Polyelectrolyte Complexation[a]



[a]Polymers lose their condensed atmosphere of ions (dotted lines) on association. Enthalpy, ΔH^{atm}, and entropy changes in "dressing" polyelectrolytes with counterions have been treated extensively by theory.[5b]

On complex formation, counterions are lost (costing $-\Delta H^{atm}$) and polyelectrolytes are paired (gaining ΔH^{pair}). The net enthalpy is ΔH_{PEC}. Estimates are available for the Coulombic energy, that is, the origin of ΔH^{atm}, for "dressing" a polyelectrolyte chain with counterions.[5b] The association of "bare" polyelectrolytes (in water) is less studied using electrostatic models. The decrease of exothermicity seen in Figure 2 is explained by screening of the oppositely charged polymer repeat units by counterions, thereby reducing the electrostatic (Coulombic) attractions.

In an effort to bypass the complexity (or lack) of analytical solutions, molecular dynamics methods have been pressed into service recently.[14,22] These sophisticated models still rely on the concepts from continuum electrostatics (interactions via Coulomb's law, uniform dielectric constant of medium, counterion is a sphere with a point charge, Bjerrum length,

DOI: 10.1021/jacs.5b11878
J. Am. Chem. Soc. 2016, 138, 980–990

counterion condensation, and Debye screening length) but allow the system to find its minimum energy in silico. Three pairwise interactions are pitted against each other in defining the net Coulomb energy of the system: polyion−polyion, polyion−counterion, and counterion−counterion, with attraction between opposites and repulsion between like charges.

Ou and Muthukumar,[14] OM, show the electrostatic energy (Coulomb energy), the source of ΔH_{PEC}, is a weak function of salt concentration for strongly charged polyelectrolytes (like DNA). As with many simulations, scaling predictions are made rather than absolute values, with arbitrary units for ΔH. The parameter of interest is the Coulomb strength parameter, Γ, which is the ratio of the Bjerrum length, l_b (about 0.7 nm in water at 25 °C), to the charge separation distance along a chain, l_o. Results derived from the molecular dynamics simulation of OM for 0.1 M NaCl are represented in Figure 3.

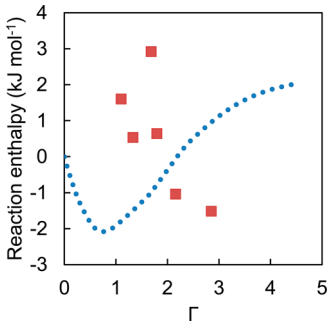


Figure 3. (Dotted line) Calculated scaling of Coulomb energy in 0.1 M NaCl, adapted from the molecular dynamics simulations of Ou and Muthukumar (ref 14) as a function of Coulomb strength parameter; (red square) experimental ΔH_{PEC} values from ITC data of Laugel et al.[7b] for a range of complexing polyelectrolytes in 0.15 M NaCl.

Laugel et al.[7b] provide experimental ΔH_{PEC} results, including exothermic and endothermic values, for a number of pairs of polyanions and polycations in 0.15 M NaCl. l_o was estimated by modeling the chain using the average of the distance between repeat units on the two chains (see Table S1) and is presented along with the data of Laugel et al. in Figure 3. Although OM account for both endothermic and exothermic complexation enthalpies, as can be seen in Figure 3 the scaling of predicted ΔH_{PEC} deviates strongly from experimental results.

Elder et al.[22] studied the binding of polylysine to DNA with molecular dynamics simulations and predicted a ΔH_{PEC} of about −43 kJ mol^{-1} with a $T\Delta S$ of about −14 kJ mol^{-1} (i.e., the association is entropically *disfavored*), whereas Ikonen et al.[23] measured ΔH_{PEC} to be much smaller: −3 kJ for association of DNA with polyethylenimine and smaller than ±1 kJ for complexation with polylysine, which implies an entropically driven process.

In these examples, the electrostatic model clearly does not correlate with experimental data. The failures of the electrostatic model continue with an inability to account for the strong dependence of polymer/polymer interactions on the type of ion, described further below. In addition, polyelectrolytes with identical values of Γ, such as poly(acrylic acid) and polyallylamine, have strongly different binding energies with oppositely charged polymers.[24] Of course, one could account for "specific" interactions with an additional interaction parameter but that would admit the insufficiency of the electrostatic description.

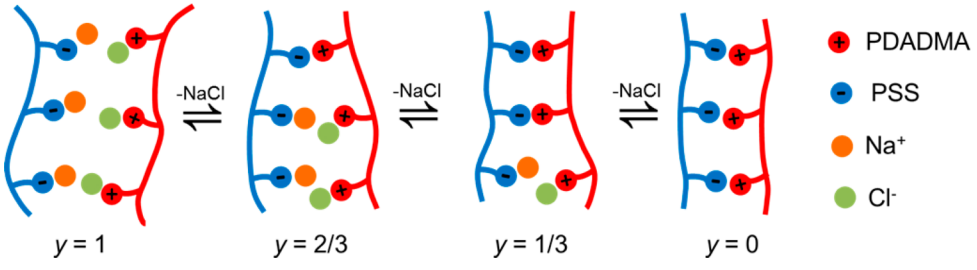
Ion Pairing Model. Ion pairing is a highly localized (within a couple of solvent molecules) phenomenon with chemical specificity. When competition is between different ions for the same site, it is equivalent to ion exchange.[25] In dilute salt, polyelectrolytes pair when mixed as in eq 1. The stepwise association of Pol^+ and Pol^- is illustrated by Scheme 2.

The representation of complex formation in Scheme 2 is simplified for the sake of clarity. In reality, the pairing is more random, with a mixture of ladder (between adjacent repeat units) and network (between repeat units on different chains or remote units on the same chain) contacts.[9] Polymer chains adopt compact, random coil conformations[26] in this amorphous "scrambled salt" composition.[2b]

With the addition of salt to solution, it is possible to reverse complexation and, if the association is not too strong, return polyelectrolyte chains to their fully separated, individual state. Between these extremes is a range of ion pairings defined by a "doping level," y, which is the fraction of ion pairs in the counterion-compensated ("extrinsic") form. The doping level controls all physical properties of PECs in their bulk or thin-film form. For example, when $y \rightarrow 1$, the PEC is highly swollen, is loosely associated, behaves like an elastic liquid, and is termed a "coacervate."[3c] Our discussion here is focused on the more highly paired form of a PEC, where $y \rightarrow 0$, and where the PEC has a more "cheeselike" bulk morphology.

Under the right conditions, for most PECs, polycations pair with all the polyanion repeat units when the two are mixed and the stoichiometry approaches 1:1. Off-stoichiometric compositions result when the PEC ion pairs are too strong and the salt concentration is too low.[17b] Our extensive experience with PSS and PDADMA has shown us they complex with 1:1 stoichiometry if their concentration is not too high.[27] Once formed, the ion content within a PEC is rapidly reversible (perhaps diffusion limited[28]).

Scheme 2. Complexation of an equimolar mixture of PDADMAC and PSS[a]



[a]The system starts on the left with isolated chains and a doping level of 1.0 (fully "extrinsic" charge compensation). As salt ions are progressively removed, more ion pairs are formed until, at [NaCl] = 0, the complex is fully paired (intrinsic compensation).

DOI: 10.1021/jacs.5b11878
J. Am. Chem. Soc. 2016, 138, 980−990

If the doping level is under equilibrium control, it should be possible to define an equilibrium constant that connects y to various salt concentrations. While the concentration of salt MA is easily translated to activity, the question of polymer "concentration" must be addressed with more care. Solution concentrations of synthetic polymers are provided in terms of the repeat unit because there is no unique molecular weight for chains, even for samples with narrow polydipersities. The use of monomer concentration, which does not account for connectivity within a polymer chain, is a classical conundrum, recognized at the outset by Flory and others as a failure of the "mean field" approximation for dilute polymer solutions.[29] In PEC formation, as soon as the first ion pair is made between polyelectrolytes ("first contact"), they have lost the small amount of solution translational entropy they had. At this point, the PEC is considered a separate phase and its composition is described by the degree of ion pairing, with $y = 0$ as the reference phase for fully paired PEC. Such a description of the state of a PEC is almost fully complete because of the long-chain nature of polymers. For example, when describing the state of association of a polyelectrolyte with 1000 repeat units, for over 99.9% of the possible interactions ($y = 0$–0.999) it is already bound to another polymer. To represent the states of association, eq 1 is modified slightly

$$\mathrm{PDADMA^+A^-_{pec}} + \mathrm{PSS^-M^+_{pec}} \rightleftharpoons \mathrm{PDADMA^+PSS^-_{pec}} + \mathrm{A^-_{aq}} + \mathrm{M^+_{aq}} \quad (2)$$

where the species on the left are counterion-compensated repeat units *within* the PEC. The equilibrium association constant of this reaction K_a can be expressed, in its simplest form, as follows,

$$K_a = \frac{(1-y)a_{MA}^{\ 2}}{y^2} \quad (3)$$

where a_{MA} is the mean activity of salt ions a_{M^+} and a_{A^-} (Figure 4). Reference states are $y = 1$ for the completely dissociated complex, $y = 0$ for completely associated complex. eq 3 does not account for the changing activities of Pol^+A^-, Pol^-M^+ and Pol^-Pol^+ with volume changes (swelling). Defining a swelling factor $\phi = V_{[NaCl]}/V_o$, where V_o is the PEC volume with no added salt and the volume with salt in solution is $V_{[NaCl]}$

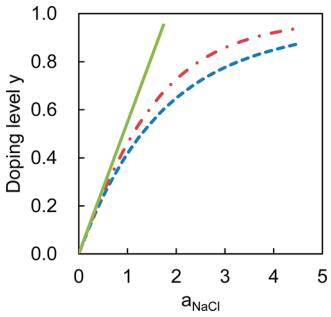


Figure 4. Calculated doping level versus salt activity for doping of PDADMA/PSS complex with NaCl at room temperature using a doping constant $K_{dop} = 1/K_a$ of 0.3 (from ref 28) and eqs 3 (doping without swelling, dashed line), 4 (doping with swelling, dash-dot line), and 5 (linear form of doping valid as $y \to 0$, solid line).

$$K_a = \frac{\phi(1-y)a_{MA}^{\ 2}}{y^2} \quad (4)$$

From prior work on the swelling of PDADMA/PSS thin films (multilayers) by salt,[24] the experimental relationship between ϕ and a_{NaCl} is $\phi = 1 + 0.31a_{NaCl}$.

As $[NaCl] \to 0$, $(1-y) \to 1$, and $\phi \to 1$,

$$K_a \to \frac{a_{MA}^{\ 2}}{y^2} \quad (5)$$

Strong association of the polymer, that is, association of the entire polymer chain over all conditions, is not a sign of thermodynamic irreversibility. Ion pairs must be reversible on the time scale of the experiment so that the thermodynamically proscribed degree of segmental association (i.e., eq 4) may be achieved.

Response of ΔH_{PEC} to a Hofmeister Series of Counterions. The counterion has a strong influence on PEC association. For example, along the series F^-, CH_3COO^- (Ac^-), ClO_3^-, Cl^-, NO_3^-, Br^-, I^-, ClO_4^-, SCN^-, known as a Hofmeister series, K_a varied from 125 to 0.3.[28] The physical significance of the Hofmeister series,[30] exhibited for anions more strongly than cations,[31] and its impact on a wide variety of small ion/molecule and macromolecular behaviors was, for a long time, associated with "breaking" and "making" (right to left in the $F^- \to SCN^-$ series above) water structure by "chaotropic" to "kosmotropic" ions, respectively.[32] This interpretation has been vigorously debated for decades.[33] That water structure is perturbed is generally accepted,[34] but the range of this effect may be limited,[35] probably to the first hydration shell.[36] The water content of PECs is low enough for most water molecules to be within a hydration-shell distance of the Pol^+Pol^- ion pair.

Ranking of a selection of ions in a Hofmeister series (there is no unique ranking since differences are observed depending on the technique[37]) also reveals a parallel trend in the numbers of waters of hydration: ions labeled as more chaotropic are also less hydrated (in general).[38] The number of water molecules per ion (hydration number)[8c,39] has been used to quantitatively rationalize differences in doping by different ions in PSS/PDADMA(X).[8c,28] Differences in hydrophobicity *also* apply to polyelectrolyte repeat units. For example, carboxylate is more hydrated than sulfonate so the former would complex more weakly with a quaternary ammonium like PDADMA.[8c]

Here, samples of PDADMA(X) with different counterions, X^-, were prepared by dialyzing PDADMA(Cl) against various sodium salts NaX (X = Br^-, Cl^-, NO_3^-, ClO_3^-, CH_3COO^-, F^-). Quantitative replacement of Cl^- by X^- was verified by X-ray fluorescence spectroscopy (see Supporting Information Figure S2). PDADMA(X) in a solution of 0.1 M NaX was titrated into PSS(Na) in 0.1 M NaX (the same conditions as in Figure 1). Raw ITC curves (Figures S3–S7) for the six PDADMA(X) Hofmeister series anions showed uncomplicated exothermic behavior except for Br^-. Any nonidealities in complexation would be expected to show up at the smallest heats generated. For PDADMA(Br) complexation individual aliquots of titrant generated less heat at first. The larger heat output toward the end of the titration (Figure S3), together with small endotherms, are probably signs of compaction of complex.[40] Again, no modeling of titration curves was performed: the heat output was simply integrated until the

DOI: 10.1021/jacs.5b11878
J. Am. Chem. Soc. 2016, 138, 980–990

reaction was complete (at r = 1, whereupon background only remains).

To ensure the ΔH_{PEC} (in 0.1 M NaX) results truly reflect the condition that [MA] → 0, calorimetry data for [MA] = 0.02 M are also shown in Table 1. ΔH_{PEC} for 0.1 and 0.02 M are within

Table 1. Enthalpy of Complexation ΔH_{PEC} of PDADMA(X) and PSS(Na) in 0.1 and 0.02 M NaX Solution at 25 °C[a]

	ΔH_{PEC} (kJ mol^{-1})		
anion X$^-$	0.1 M NaX	0.02 M NaX	PDADMA:PSS ratio, r
Br$^-$	−0.79	−0.98	1.01
Cl$^-$	−1.88	−1.87	1.06
NO_3^-	−2.17	−2.21	1.03
ClO_3^-	−2.48	−2.46	0.92
Ac$^-$	−4.00	−3.45	0.87
F$^-$	−4.19	−3.89	0.99
KBr[b]	−0.30	−0.24	1.09

[a]X refers to the anion (Br$^-$, Cl$^-$, NO_3^-, ClO_3^-, Ac$^-$, and F$^-$). Ratio of PDADMA/PSS when no heat above background is generated (see the dotted line in Figure 1). As [MA] → 0 and r = 1, all polymer ends up in the same (reference) state: pure PDADMA/PSS with y → 0. Ions at the hydrophobic end of the Hofmeister series, such as I$^-$, ClO_4^-, and SCN$^-$, could not be studied as they precipitated PDADMA. Data for KBr is provided as an example of a salt MA which generates ΔH_{PEC} approaching zero as closely as possible. [b]PDADMA(Br) titrated into PSS (potassium salt) in KBr.

experimental error and, along with Figure 2, give no indication that there are significant changes in ΔH_{PEC} as [MA] → 0. The stoichiometry is close to 1.0 with the exception of acetate ion, believed to be caused by the difficulty in drying PDADMA(Ac) completely. Because more hydrophobic ions I$^-$, ClO_4^-, and SCN$^-$ precipitated PDADMA (in line with Hofmeister's original experiments on proteins[30]), a more hydrophobic cation, K$^+$, was substituted for Na$^+$ in an effort to approach ΔH_{PEC} = 0 (see Figure S8). As seen in Table 1, this substitution did, indeed, bring the system to almost athermal mixing.

Qualitative Study of Water Perturbation by FTIR. Water hydrogen bonding stores a great deal of cohesive energy.[41] Thus, even small perturbations of the H-bonding network should translate to measurable enthalpic changes. The impact of a point dipole on the surrounding water may be observed spectroscopically from changes in the O−H vibrational spectra (3000−3500 cm^{-1}).[36b,42] First, for a qualitative idea of the differences of water structure between bulk and within a PEC, a piece of fully hydrated (by soaking in water) ion-free PDADMA/PSS PEC was pressed against a diamond internal reflectance assembly (ATR) and the ATR-IR spectrum recorded as shown in Figure 5 (with three bands from the C−H stretching of the polymer at 2884−2977 cm^{-1} subtracted). The O−H stretching envelope includes an asymmetric mode at 3550 cm^{-1}, a mode at 3396 cm^{-1} assigned to a disordered tetrahedral hydrogen-bonding network, and a symmetric stretch at 3250 cm^{-1} also assigned to the H-bonding network.[43]

The final state of PEC at [MA] → 0 is the same for all complexation reactions with different PDADMA(X). The initial state differs by the identity of the PDADMA counterion. Thus, the next step of the qualitative comparison was to compare IR spectra of solutions of PDADMA(X). This study was performed by placing a drop of 1.0 M PDADMA(X) on the ATR crystal and allowing the water to partially evaporate. The water content was referenced to a 1.0 M solution of

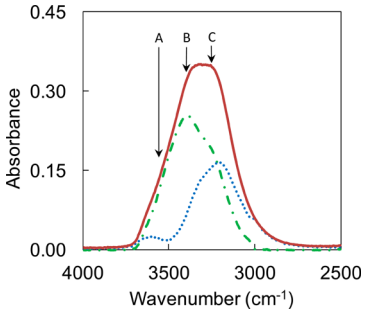


Figure 5. ATR-FTIR spectra of O−H stretching regions from water in bulk water (red solid line), PDADMA/PSS complex saturated with water (green dash-dotted line); and difference spectrum (blue dotted line). C−H stretching features at ca. 2900 cm^{-1} have been subtracted using dry complex. Arrows indicate the location of bands assigned to an O−H symmetric stretch (3550 cm^{-1}, A); disordered tetrahedral hydrogen bonding network (3396 cm^{-1}, B); symmetric H-bonding network (3250 cm^{-1}, C).

PDADMA(X) to obtain the ratio of water molecules to PDADMA repeat units. A comparison of the O−H stretching band for a water/PDADMA molar ratio of 5:1, with the C−H stretching features (mostly) subtracted is shown in Figure 6.

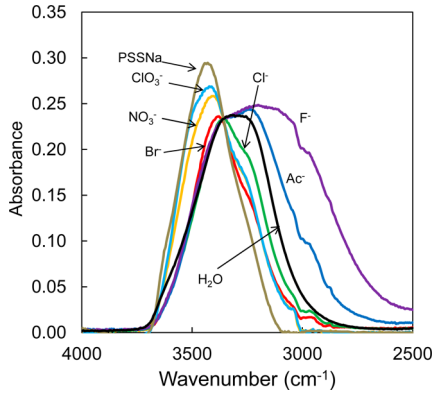


Figure 6. IR spectra comparison of PSS(Na) and PDADMA(X) (X = Br$^-$, Cl$^-$, NO_3^-, ClO_3^-, Ac$^-$, and F$^-$) when the molar ratio of water to polymer is around 5:1. Spectra are normalized at 3357 cm^{-1}.

Inasmuch as the shifts and intensity changes indicate changes in water structure, the qualitative trend in structure perturbation is clear and approximately tracks the trend in ΔH_{PEC} seen in Table 1. Figure S9 presents additional FTIR data.

Quantitative Study of Water Perturbation by Raman Spectroscopy. The IR results in Figures 5 and 6 support an apparent structural change of water as the possible cause of ΔH_{PEC}. Raman spectroscopy afforded a more quantitative estimate of the degree of water disruption, which indicates anions to be more effective than cations in this respect.[31] The method used here was introduced by Green et al.[44] to look at perturbations of water by LiCl,[45] and later extended by Kitano and co-workers to polymers in solution,[46] including polyelectrolytes[47] and polyzwitterions.[48] The analysis focuses on the highly polarized O−H band at around 3250 cm^{-1} assigned to the collective in-phase symmetric O−H stretch of strongly H-bonded water. Changes of the band intensity have been assumed to reflect perturbations (reinforcements or disruptions) of water H-bonding.[49]

DOI: 10.1021/jacs.5b11878
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Raman spectra of the O−H region are shown in Figure 7A for scattering perpendicular ($I_\perp$) and parallel ($I_\parallel$) to the

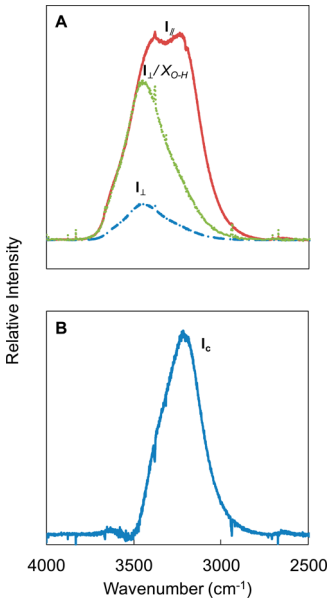

Figure 7. Raman spectra of water O−H stretching region. (A) $I_\parallel$ (solid line) and $I_\perp$ (dash-dot line) of water at room temperature. $I_\perp/X_{O-H}$ (dotted line) is the normalized $I_\perp$. (B) The collective band of water.

polarization of the incident beam.[50] The intensity of the collective band, I_c, was isolated by scaling up the intensity of the $I_\perp$ band by the depolarization ratio, σ_{O-H}, and subtracting the result from the $I_\parallel$ band[47]

$$I_c = I_\parallel - I_\perp/\sigma_{O-H} \quad (6)$$

The resulting I_c band is shown in Figure 7B. The next step is to normalize the area of the I_c band to that of the $I_\parallel$ band[45,48c,50a,51]

$$C(I_c) = \int I_c(\omega)\, d\omega / \int I_\parallel(\omega)\, d\omega \quad (7)$$

where ω is the Raman shift in cm^{-1}. The value of C in aqueous solutions, C_x, is then compared with that of pure water, C_w, to obtain what is termed the defect probability, P_d.[47,48]

$$P_d = \frac{C_w - C_x}{C_w} \quad (8)$$

Figure S10 shows that C_x decreases as the concentration of polyelectrolyte increases, as expected.[47]

If β is defined as the number of O−H oscillators per polymer repeat unit, the number of water "defects", N, per polymer repeat unit may be estimated

$$N = \beta P_d \quad (9)$$

Because water already contains a number of intrinsic defects, N is corrected using a C value for ice ($C_{ice} = 0.54$), where water is assumed to be free of H-bond defects.

$$N_{corr} = N\left(\frac{C_w}{C_{ice}}\right) \quad (10)$$

While N_{corr} is a specific value, the nature of these "defects" is not clear: how seriously is the structure of water perturbed by such a defect? A defect cannot be the complete loss of an H-bond according to the two-state model ("intact" or "broken") of Muller[52] because much larger enthalpic changes would result. Recognizing this, Kitano et al., in later work,[48c] emphasized that N_{corr} represents the *degree* of perturbation, not the number of H-bonds perturbed. Following the thesis of Smith et al. that changes in O−H intensities are limited to water molecules next to ions, and are a result of electric fields from point charges,[36b] "relative water perturbation factor" would be a more accurate description for N_{corr}.

The procedure described above was repeated for aqueous solutions of the PDADMA(X) series using a mole fraction of polyelectrolyte of 0.05. N_{corr} values for each PDADMA(X), representing the *relative* perturbation of water by a PDADMA-(X) repeat unit, are presented in Table 2. Positive(negative) values of N_{corr} align with the structure breaking (making) characterization of anions relative to pure water.

Table 2. Effect of Different Anions on the N_{corr} Values of PDADMA(X) and NaX[a]

	N_{corr}		
X^-	polymer PDADMA(X)	salt NaX	ΔN_{corr}
Br^-	6.35	8.09	1.75
Cl^-	3.33	6.94	3.61
NO_3^-	2.06	5.83	3.76
ClO_3^-	−1.33	3.28	4.61
Ac^-	−5.61	1.55	7.16
F^-	−10.92	−2.40	8.52

[a]Difference of N_{corr} value of NaX and PDADMA(X), ΔN_{corr}, for each anion. All solutions contain 0.05 mole fraction solute.

In order to correlate water perturbation to exotherms from calorimetry, the *change* in water perturbation around an anion, as it goes from compensating the polymer to release in solutions of NaX, must be determined. Therefore, the identical Raman scattering procedure for determining N_{corr} was performed with solutions of 0.05 mole fractions of NaX. The resulting $N_{corr,NaX}$ values listed in Table 2 are presented, along with the difference in values, $N_{corr,NaX} - N_{corr,PDADMA(X)} = \Delta N_{corr}$.

Finally, ΔN_{corr} values are plotted versus ΔH_{PEC} in Figure 8. We stress again that ΔN_{corr} is simply a relative difference of water perturbation between anions in a solution of NaX and anions as counterions for PDADMA. Another way to state this

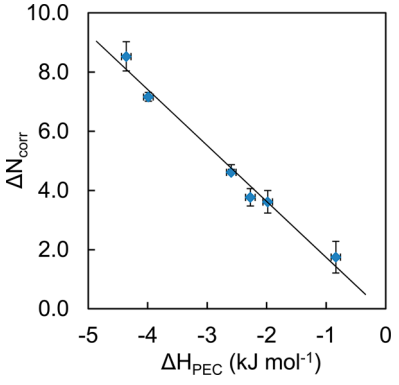

Figure 8. Relationship between PDADMA(X)-PSS(Na) complexation enthalpy ΔH_{PEC} as [MA] → 0 from Table 1 and ΔN_{corr}, a measure of the differences between relative extent of water structure perturbation between the counterion residing on PDADMA and free in solution.

DOI: 10.1021/jacs.5b11878
J. Am. Chem. Soc. 2016, 138, 980−990

is that if the water perturbations are the same in both environments, $\Delta N_{corr} \rightarrow 0$.

The comparison of the difference in water perturbation versus the enthalpy of complexation in Figure 8 follows some fascinating trends: first, ΔN_{corr} tracks ΔH_{PEC} well; second, as $\Delta N_{corr} \rightarrow 0$, $\Delta H_{PEC} \rightarrow 0$, which is expected if ΔH_{PEC} is a direct (and proportional, it seems) result of changes in water structure/perturbation. The physical reasons for the magnitude of ΔN_{corr} along a Hofmeister series are not understood at present, although they may stem from the increasing mismatch in size (and polarizability) between ion and PDADMA going from Br^- to F^-. Nevertheless, it is clear that the right anion, whether it exists, would generate zero enthalpy of association between polyelectrolytes. Unfortunately, ions more chaotropic than Br^-, such as I^-, ClO_4^-, and SCN^-, precipitated PDADMA and could not be used.

It is known that breaking water hydrogen bonds increases entropy and is endothermic. The enthalpy to break a hydrogen bond, ΔH_{HB}, at room temperature is about 8 kJ, and $T\Delta S_{HB}$ is about 6 kJ.[53] Under these opposing forces, the net ΔG of an H-bond approaches a small number (here, 2 kJ). This is an example of the well-known and much debated concept of enthalpy−entropy compensation.[54] If ΔN_{corr} were the number of H-bonds broken/made per polymer repeat unit, the slope of Figure 8 would indicate 0.5 kJ of ΔH per H-bond, which is much less[53] than the estimated 8 kJ. This mismatch is another clue that hydrogen bonds are not formally broken by ions.

The possibility that different ions "condense" or associate more strongly on polyelectrolytes (known as "regularization"[55]) was discounted by measuring the electrical conductivities of all PDADMA(X) solutions (see Figure S11) and extrapolating to infinite dilution Λ_∞. For all but Ac^-, PDADMA(X) conductivity Λ_∞ was 68 ± 4% of that of the pure anion (see Table S2), suggesting no trends in ion association. The abnormal high conductivity of PDADMA(Ac) could be the result of the hydrolysis of acetate anion, as the equivalent molar conductivity of OH^- is much higher (198.3 $S\ cm^2\ eq^{-1}$) than that of Ac^-.

Enthalpic and Entropic Driving Forces as a Function of Salt Concentration. The driving force for a particular set of conditions depends on how far away these conditions are from equilibrium. It is not given, as many cartoons depict, by taking a pair of bare polyelectrolytes separated in a medium of fixed dielectric by an infinite distance and bringing them together. Using eq 4 the following can be written for the driving force per polyelectrolyte repeat unit, ΔG_{PEC}, in kJ mol^{-1}

$$\Delta G_{PEC} = -RT \ln \frac{\phi(1-y)a_{MA}^{\ 2}y_{ne}^{\ 2}}{\phi_{ne}(1-y_{ne})a_{MA,ne}^{\ 2}y^2} = -RT \ln \frac{y_{ne}^{\ 2}}{\phi_{ne}(1-y_{ne})a_{MA,ne}^{\ 2}}K_a \quad (11)$$

The subscript "ne" denotes the nonequilibrium conditions that determine the driving force to go from a starting y_{ne} to the equilibrium y. The salt activities a_{MA} and $a_{MA,ne}$ would be the same if both polyelectrolytes have the same salt concentration. There appears to be a limit as $y \rightarrow 1.0$, $\Delta G_{PEC} \rightarrow \infty$. However, this is a nonphysical limit because the maximum y, where there is only ONE ion pair remaining on the whole chain of length n repeat units, is $1 - 1/n$. Beyond this, the polyelectrolytes are separated. Thus, to model the association of two chains of length n, it is possible to start with $y_{ne} = 1-1/n$ and estimate the driving force using eq 11 to plot ΔG_{PEC} as a function of n (or y_{ne}) keeping the salt concentration constant, or to keep n constant and vary the salt concentration. These respective limits, and the following approximation, are used in Figure 9A and B:

$$\Delta G_{PEC} \approx -RT \ln \frac{n}{\phi_{ne}a_{MA,ne}^{\ 2}}K_a \text{ for large } n \quad (12)$$

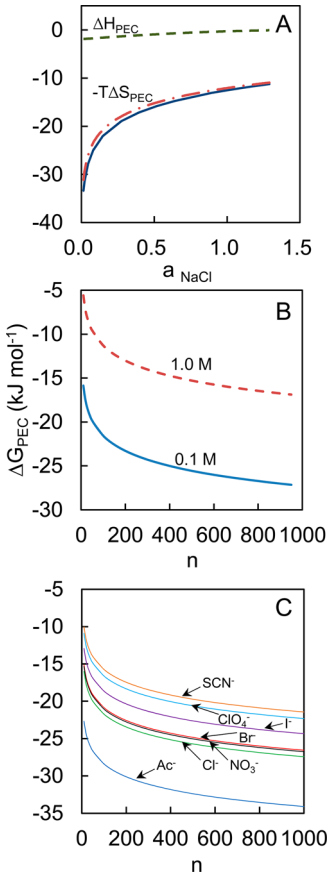

Figure 9. (A) Calculated free energy of complexation ΔG_{PEC} using eq 12 of PDADMA/PSS PEC from dissolved polymer as a function of a_{NaCl} assuming a chain length n of 400 repeat units (solid line), ΔH_{PEC} from Figure 2 (dashed line) and $-T\Delta S_{PEC}$ as the difference (dash-dotted line). Entropic driving forces far outweigh enthalpic ones. (B) ΔG_{PEC} vs n when [NaCl] = 0.1 M (solid line) and [NaCl] = 1 M (dashed line). (C) ΔG_{PEC} vs n in the presence of various 0.1 M NaX using K_a values from ref 28.

Instead of simply ΔG_{PEC}, more pertinent information could be added: $\Delta G^{[MA]}_{n,Pol^-/Pol^+}$, for example, $\Delta G^{0.1MNaCl}_{n=100,PSS/PDADMA}$, means the driving force for formation of a complex from n = 100 PSS and PDADMA in 0.1 M NaCl. An estimate for ϕ_{ne}, the swelling coefficient for the PEC as $y \rightarrow 1$, is needed. From studies on the same polyelectrolytes in KBr it is known that the concentration of PDADMA/PSS complex is about 0.3 M at $y \rightarrow 1$,[10] while the concentration of PEC in the undoped polyelectrolyte is about 2.56 M (assuming 32% water and a density of PEC of 1.2 g cm^{-3}) which means ϕ_{ne} is 8.5. ΔH_{PEC} is provided directly from the experimental data in Figure 2. These data are used to separate out ΔH_{PEC} and $T\Delta S_{PEC}$ contributions to the driving force in Figure 9. Equation 12 implies a greater driving force for complexation of longer chains, or preferential

DOI: 10.1021/jacs.5b11878
J. Am. Chem. Soc. 2016, 138, 980−990

binding of longer chains over shorter chains if there is an excess of competing polyelectrolyte, which is observed experimentally.[56]

Under standard conditions (e.g., $a_{NaCl} = 1$), $\Delta G = \Delta G^{\circ}$ may even be positive for the weaker ion pairs, such as those involving (poly)carboxylates,[24] which means complexes do not form (or formed complexes dissociate[57]).

CONCLUSIONS

Over the range 0.1−2 M NaCl, the driving force for complex formation between PSS and PDADMAC is between 90% and 100% entropic. Small enthalpic contributions to ΔG_{PEC} are ascribable to water perturbation by point source electric fields of counterions rather than Coulombic interactions between charged species. The strength of interaction between Pol^+ and Pol^- is correlated with, but not caused by, differences in ΔH_{PEC}, since the "driving force" is related to the release of water molecules along with polymer counterions. For example, a small counterion like F^- is highly hydrated and provides a strong gain in entropy when released, but when it *is* released its low polarizability and small size perturb the O−H bonds of any additional water that directly surrounds it. Thus, correlations between ΔH_{PEC} and the strength of complexation are observed.[7b]

Continuum electrostatics models are not appropriate for highly condensed systems, where the local (within a distance of two or three water molecules) charge density from polyelectrolyte repeat units greatly exceeds that from any salt ions in the vicinity. For example, if the average distance between repeat units, either of same charge (Pol^-/Pol^-) or opposite charge (Pol^-/Pol^+), is on the order of a Bjerrum length, it would require at least 2 M of salt to have, on average, at least one salt ion between the charges. At lower concentrations, it is difficult to see how salt modifies electric fields. Put another way: the assumption that interactions can be described by these continuous electric fields fails when it is needed the most−when the charges approach each other closely. At the shortest ranges, the "chemical" aspects of charges, for example, how hydrated they are, take over from longer range interactions modeled by extensions of vacuum electrostatics. Only the logic of the entropic component of electrostatic theories survives this scrutiny. The conclusions above are not affected by the controversy over whether and how much water structure "breaking" or "making" occurs in a Hofmeister series. Again, ion hydration numbers and observations of supposed structural impacts parallel each other.

EXPERIMENTAL SECTION

Poly(diallyldimethylammonium chloride) (PDADMAC, molar mass = 400 000−500 000 g mol^{-1}), poly(4-styrenesulfonic acid sodium salt) (PSS, molar mass = 7.5×10^4 g mol^{-1}), potassium bromide (KBr), sodium chloride (NaCl), and sodium bromide (NaBr) were from Sigma-Aldrich; sodium chlorate ($NaClO_3$) and sodium acetate ($NaCH_3COO$) from Mallinckrodt; sodium nitrate ($NaNO_3$) and sodium fluoride (NaF) from Fisher Scientific.

Six PDADMA(X) samples with different anions (X = Br^-, Cl^-, NO_3^-, ClO_3^-, $CH_3COO_3^-$, F^-) were prepared by dialysis followed by lyophilization. A volume of 15 mL of PDADMA(Cl^-) solution was transferred to a 15 cm dialysis tube (3500 MW, Thermo Scientific). This PDADMA was dialyzed sequentially against three batches of 1 L of 0.1 M NaX for 24 h for each batch. This was followed by 3 days of dialysis against deionized water, replacing the water every 24 h. After dialysis, PDADMA(X) solution was frozen using dry ice and dried under lyophilization. Dry, purified PDADMA(Cl) and PSS(Na) samples were prepared by dialyzing the PDADMA(Cl) or PSS(Na) solution from Aldrich against water for 3 days followed by lyophilization.

An Epsilon 3 (Panalytical) energy dispersive X-ray spectrometer was used to compare the amounts of Cl and Br in PDADMA(X) samples after dialysis. The amount of 0.5 g of dry PDADMA(X) powders was well spread on the bottom of the sample holder. Samples were measured with a Ti filter while spinning using a rhodium X-ray source. Liquid helium was used for cooling, and the measurement was conducted at a voltage of 12 kV and a current of 25 μA.

Isothermal calorimetry was performed with a VP-ITC (MicroCal Inc.) instrument. A solution of 300 μL of reactant, approximately 10 mM PDADMA(X), based on the polyelectrolyte repeat unit, in 0.1 M NaX in a rotating (310 rpm) syringe was injected into a sample cell with a volume of 1.4545 mL filled with a solution of PSS(Na) (approximately 0.5 mM) in 0.1 M NaX in sequential 6 μL aliquots at a rate of 1 aliquot every 4 min. The heat flow was recorded as a function of time. All solutions were degassed at 18 °C for 5 min prior to each trial. All heat of complexation measurements were recorded at 25.0 °C.

Attenuated total reflectance infrared (ATR-IR) spectra were recorded using a Bruker Alpha FTIR spectrometer with a Platinum ATR Quick Snap sampling module (single reflection diamond crystal). Spectra were collected from 400−4000 cm^{-1} at a resolution of 4 cm^{-1}. Six PDADMA(X) samples and dialyzed PSS(Na) solutions were prepared at a concentration of 1 M (based on the polyelectrolyte repeat unit). A 5 μL droplet of solution was placed on the surface of the ATR crystal, and spectra were taken as the water in the droplet evaporated. Measurements were terminated when no change was observed in two sequential spectra. A 2.5 cm × 2.5 cm piece of dried PDADMA/PSS PEC was soaked in water for 24 h then forced down on the crystal.

Raman spectra from 2500 to 4000 cm^{-1} at a spectral resolution of 8 cm^{-1} were recorded for the 1 M PDADMA(X) polymers solution and 0.05 mole fraction NaX solution. Raman spectra were obtained using a JY Horiba LabRam HR800 micro-Raman spectrograph with a 17 mW 633 nm Melles-Griot HeNe laser (model 25-LHP-925−249) as a light source. After passing through a bandpass filter, the beam was coupled into the microscope (Olympus BX30) by total reflection. The beam was directed through the liquid sample using a macro sample cuvette holder using a 75 mm focal length lens and curved back mirror to allow a double pass which also collected the back scattered radiation. Rayleigh scattering was filtered out by a Semrock edge filter with Raman scattering coupled into the 800 mm focal length spectrograph through a confocal hole. A grating (600 lines/mm, 76 × 76 mm^2) dispersed the light onto a 1024 × 256 element open CCD detector (Wright, 26 μm square pixels). Macrosample optics coupled the microscope to a thermoelectrically temperature-controlled cuvette holder (Quantum Northwest TLC 50F) to maximize the Raman signal in a transparent sample. Laser power at the sample was 3 mW. Polarization studies were carried out using Glan−Thompson polarizers and a polarization scrambler placed in the scattered light path. Polarization ratios ($I_\perp/I_\parallel$) were calculated from the integrated intensity of the peaks obtained from Raman spectra in which the scattered radiation was collected parallel ($I_\parallel$) and perpendicular ($I_\perp$) to the polarization of the excitation beam.

Conductivities were measured with a calibrated Thermo Scientific Orion 3 star conductivity meter equipped with a water jacketed cell controlled to 25 ± 0.1 °C. Various concentrations of PDADMA(X) solutions were added to the cell.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11878.

X-ray fluorescence example; ITC titrations for various PDADMA(*X*); ITC titration of PDADMA(Br) into PSS(K); additional FTIR and Raman data; conductivity data for PDADMA(X) series (PDF)

DOI: 10.1021/jacs.5b11878
J. Am. Chem. Soc. 2016, 138, 980−990

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by grants from the National Science Foundation (DMR1207188 and DMR1506824). The authors thank Dr. Bert van de Burgt for help with Raman scattering measurements.

REFERENCES

(1) (a) Kim, P. S.; Baldwin, R. L. *Annu. Rev. Biochem.* **1990**, *59*, 631. (b) Sindelar, C. V.; Hendsch, Z. S.; Tidor, B. *Protein Sci.* **1998**, *7*, 1898. (c) Marqusee, S.; Baldwin, R. L. *Proc. Natl. Acad. Sci. U. S. A.* **1987**, *84*, 8898. (d) Walther, T. H.; Ulrich, A. S. *Curr. Opin. Struct. Biol.* **2014**, *27*, 63. (e) Loo, T. W.; Clarke, D. M. *Biochemistry* **2013**, *52*, 3194. (f) Anderson, D. E.; Becktel, W. J.; Dahlquist, F. W. *Biochemistry* **1990**, *29*, 2403.

(2) (a) Fuoss, R. M.; Sadek, H. *Science* **1949**, *110*, 552. (b) Michaels, A. S.; Miekka, R. G. *J. Phys. Chem.* **1961**, *65*, 1765. (c) Michaels, A. S. *Ind. Eng. Chem.* **1965**, *57*, 32. (d) Bixler, H. J.; Michaels, A. S. In *Encyclopedia of Polymer Science and Technology*; Mark, H. F., Gaylord, N. G., Bikales, N. M., Eds.; Interscience: New York, 1969; Vol. *10*. (e) Markley, L. L.; Bixler, H. J.; Cross, R. A. *J. Biomed. Mater. Res.* **1968**, *2*, 145. (f) Tsuchida, E. *J. Macromol. Sci., Part A: Pure Appl.Chem.* **1994**, *31*, 1. (g) Thünemann, A. F.; Müller, M.; Dautzenberg, H.; Joanny, J. F. O.; Löwen, H. *Adv. Polym. Sci.* **2004**, *166*, 113.

(3) (a) Bungenberg de Jong, H. G.; Kruyt, H. R. *Proc. Sect. Sci. K. Ned. Akad. Wet.* **1929**, *32*, 849. (b) Michaeli, I.; Overbeek, J. T. G.; Voorn, M. J. *J. Polym. Sci.* **1957**, *23*, 443. (c) Veis, A. *Adv. Colloid Interface Sci.* **2011**, *167*, 2. (d) Kayitmazer, A. B.; Seeman, D.; Minsky, B. B.; Dubin, P. L.; Xu, Y. *Soft Matter* **2013**, *9*, 2553. (e) Gucht, J. v. d.; Spruijt, E.; Lemmers, M.; Cohen Stuart, M. A. *J. Colloid Interface Sci.* **2011**, *361*, 407. (f) Spruijt, E.; Cohen Stuart, M. A.; van der Gucht, J. *Macromolecules* **2013**, *46*, 1633. (g) Perry, S. L.; Li, Y.; Priftis, D.; Leon, L.; Tirrell, M. *Polymers* **2014**, *6*, 1756.

(4) Dautzenberg, H.; Jaeger, W.; Kötz, J.; Philipp, B.; Seidel, C. H.; Stscherbina, D. *Polyelectrolytes: Formation, Characterization and Applications*; Hanser: Munich, 1994.

(5) (a) Manning, G. S. *J. Chem. Phys.* **1969**, *51*, 924. (b) Sharp, K. A. *Biopolymers* **1995**, *36*, 227. (c) Stigter, D. *Biophys. J.* **1995**, *69*, 380.

(6) Collins, K. D. *Biophys. Chem.* **2012**, *167*, 43.

(7) (a) Oppermann, W.; Schulz, T. *Makromol. Chem., Macromol. Symp.* **1990**, *39*, 293. (b) Laugel, N.; Betscha, C.; Winterhalter, M.; Voegel, J. C.; Schaaf, P.; Ball, V. *J. Phys. Chem. B* **2006**, *110*, 19443. (c) Bucur, C. B.; Sui, Z.; Schlenoff, J. B. *J. Am. Chem. Soc.* **2006**, *128*, 13690. (d) Bharadwaj, S.; Montazeri, R.; Haynie, D. T. *Langmuir* **2006**, *22*, 6093. (e) Feng, X.; Leduc, M.; Pelton, R. *Colloids Surf., A* **2008**, *317*, 535. (f) Ma, P. L.; Lavertu, M.; Winnik, F. M.; Buschmann, M. D. *Biomacromolecules* **2009**, *10*, 1490. (g) Alatorre-Meda, M.; Taboada, P.; Krajewska, B.; Willemeit, M.; Deml, A.; Klosel, R.; Rodriguez, J. R. *J. Phys. Chem. B* **2010**, *114*, 9356. (h) Priftis, D.; Laugel, N.; Tirrell, M. *Langmuir* **2012**, *28*, 15947. (i) Alonso, T.; Irigoyen, J.; Iturri, J. J.; Larena, I. L.; Moya, S. E. *Soft Matter* **2013**, *9*, 1920. (j) Vitorazi, L.; Ould-Moussa, N.; Sekar, S.; Fresnais, J.; Loh, W.; Chapel, J. P.; Berret, J. F. *Soft Matter* **2014**, *10*, 9496.

(8) (a) Farhat, T. R.; Schlenoff, J. B. *Langmuir* **2001**, *17*, 1184. (b) Farhat, T. R.; Schlenoff, J. B. *J. Am. Chem. Soc.* **2003**, *125*, 4627. (c) Schlenoff, J. B.; Rmaile, A. H.; Bucur, C. B. *J. Am. Chem. Soc.* **2008**, *130*, 13589.

(9) Jaber, J. A.; Schlenoff, J. B. *J. Am. Chem. Soc.* **2006**, *128*, 2940.

(10) Wang, Q. F.; Schlenoff, J. B. *Macromolecules* **2014**, *47*, 3108.

(11) Kudaibergenov, S. E.; Ciferri, A. *Macromol. Rapid Commun.* **2007**, *28*, 1969.

(12) Overbeek, J. T. G.; Voorn, M. J. *J. Cell. Comp. Physiol.* **1957**, *49*, 7.

(13) Spruijt, E.; Westphal, A. H.; Borst, J. W.; Cohen Stuart, M. A.; van der Gucht, J. *Macromolecules* **2010**, *43*, 6476.

(14) Ou, Z. Y.; Muthukumar, M. *J. Chem. Phys.* **2006**, *124*, 154902.

(15) Sinn, C. G.; Dimova, R.; Antonietti, M. *Macromolecules* **2004**, *37*, 3444.

(16) Ehtezazi, T.; Rungsardthong, U.; Stolnik, S. *Langmuir* **2003**, *19*, 9387.

(17) (a) Kabanov, V. M.; Zezin, A. B. *Pure Appl. Chem.* **1984**, *56*, 343. (b) Bakeev, K. N.; Izumrudov, V. A.; Kuchanov, S. I.; Zezin, A. B.; Kabanov, V. A. *Macromolecules* **1992**, *25*, 4249.

(18) (a) Huglin, M. B.; Webster, L.; Robb, I. D. *Polymer* **1996**, *37*, 1211. (b) Chen, J. H.; Heitmann, J. A.; Hubbe, M. A. *Colloids Surf., A* **2003**, *223*, 215. (c) Leclercq, L.; Boustta, M.; Vert, M. *J. Bioact. Compat. Polym.* **2011**, *26*, 3. (d) Reisch, A.; Tirado, P.; Roger, E.; Boulmedais, F.; Collin, D.; Voegel, J. C.; Frisch, B.; Schaaf, P.; Schlenoff, J. B. *Adv. Funct. Mater.* **2013**, *23*, 673.

(19) (a) Dautzenberg, H. *Macromolecules* **1997**, *30*, 7810. (b) Dautzenberg, H.; Karibyants, N. *Macromol. Chem. Phys.* **1999**, *200*, 118. (c) Dautzenberg, H.; Rother, G. *Macromol. Chem. Phys.* **2004**, *205*, 114.

(20) *Physical Chemistry of Polyelectrolytes*; Radeva, T., Ed.; M. Dekker: New York, 2001; Vol. *99*.

(21) Gummel, J.; Cousin, F.; Boué, F. *J. Am. Chem. Soc.* **2007**, *129*, 5806.

(22) Elder, R. M.; Emrick, T.; Jayaraman, A. *Biomacromolecules* **2011**, *12*, 3870.

(23) Ikonen, M.; Murtomäki, L.; Kontturi, K. *Colloids Surf., B* **2008**, *66*, 77.

(24) Dubas, S. T.; Schlenoff, J. B. *Langmuir* **2001**, *17*, 7725.

(25) Helfferich, F. G. *Ion Exchange*; McGraw-Hill: New York, 1962.

(26) Markarian, M. Z.; Hariri, H. H.; Reisch, A.; Urban, V. S.; Schlenoff, J. B. *Macromolecules* **2012**, *45*, 1016.

(27) Shamoun, R. F.; Reisch, A.; Schlenoff, J. B. *Adv. Funct. Mater.* **2012**, *22*, 1923.

(28) Ghostine, R. A.; Shamoun, R. F.; Schlenoff, J. B. *Macromolecules* **2013**, *46*, 4089.

(29) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, NY, 1953.

(30) Hofmeister, F. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1888**, *24*, 247.

(31) Terpstra, P.; Combes, D.; Zwick, A. *J. Chem. Phys.* **1990**, *92*, 65.

(32) Collins, K. D.; Washabaugh, M. W. *Q. Rev. Biophys.* **1985**, *18*, 323.

(33) Zhang, Y. J.; Cremer, P. S. *Annu. Rev. Phys. Chem.* **2010**, *61*, 63.

(34) Marcus, Y. *Chem. Rev.* **2009**, *109*, 1346.

(35) Gurau, M. C.; Lim, S.-M.; Castellana, E. T.; Albertorio, F.; Kataoka, S.; Cremer, P. S. *J. Am. Chem. Soc.* **2004**, *126*, 10522.

(36) (a) Kropman, M. F.; Bakker, H. J. *J. Am. Chem. Soc.* **2004**, *126*, 9135. (b) Smith, J. D.; Saykally, R. J.; Geissler, P. L. *J. Am. Chem. Soc.* **2007**, *129*, 13847. (c) Collins, K. D.; Neilson, G. W.; Enderby, J. E. *Biophys. Chem.* **2007**, *128*, 95.

(37) Diamond, J. M.; Wright, E. M. *Annu. Rev. Physiol.* **1969**, *31*, 581.

(38) Parsons, D. F.; Bostrom, M.; Lo Nostro, P.; Ninham, B. W. *Phys. Chem. Chem. Phys.* **2011**, *13*, 12352.

(39) Collins, K. D. *Biophys. Chem.* **2006**, *119*, 271.

(40) Huang, Y.; Lapitsky, Y. *J. Phys. Chem. B* **2013**, *117*, 9548.

(41) Lazaridis, T. *Acc. Chem. Res.* **2001**, *34*, 931.

(42) (a) Kujumzelis, T. G. *Eur. Phys. J. A* **1938**, *110*, 742. (b) Buijs, K.; Choppin, G. R. *J. Chem. Phys.* **1963**, *39*, 2035. (c) Choppin, G. R.; Buijs, K. *J. Chem. Phys.* **1963**, *39*, 2042. (d) Max, J. J.; de Blois, S.; Veilleux, A.; Chapados, C. *Can. J. Chem.* **2001**, *79*, 13. (e) Liu, D. F.; Ma, G.; Levering, L. M.; Allen, H. C. *J. Phys. Chem. B* **2004**, *108*, 2252. (f) Nickolov, Z. S.; Miller, J. D. *J. Colloid Interface Sci.* **2005**, *287*, 572. (g) Perera, P. N.; Browder, B.; Ben-Amotz, D. *J. Phys. Chem. B* **2009**, *113*, 1805.

DOI: 10.1021/jacs.5b11878
J. Am. Chem. Soc. 2016, 138, 980−990

(43) (a) Schnitzer, C.; Baldelli, S.; Campbell, D. J.; Shultz, M. J. *J. Phys. Chem. A* **1999**, *103*, 6383. (b) Allen, H. C.; Raymond, E. A.; Richmond, G. L. *J. Phys. Chem. A* **2001**, *105*, 1649.
(44) Green, J. L.; Lacey, A. R.; Sceats, M. G. *Chem. Phys. Lett.* **1986**, *130*, 67.
(45) Green, J. L.; Lacey, A. R.; Sceats, M. G. *Chem. Phys. Lett.* **1987**, *134*, 385.
(46) (a) Maeda, Y.; Tsukida, N.; Kitano, H.; Terada, T.; Yamanaka, J. *J. Phys. Chem.* **1993**, *97*, 13903. (b) Maeda, Y.; Kitano, H. *Spectrochim. Acta, Part A* **1995**, *51*, 2433.
(47) Tsukida, N.; Muranaka, H.; Ide, M.; Maeda, Y.; Kitano, H. *J. Phys. Chem. B* **1997**, *101*, 6676.
(48) (a) Kitano, H.; Imai, M.; Sudo, K.; Ide, M. *J. Phys. Chem. B* **2002**, *106*, 11391. (b) Kitano, H.; Imai, M.; Mori, T.; Gemmei-Ide, M.; Yokoyama, Y.; Ishihara, K. *Langmuir* **2003**, *19*, 10260. (c) Kitano, H.; Nagaoka, K.; Tada, S.; Gemmei-Ide, M. *J. Colloid Interface Sci.* **2007**, *313*, 461.
(49) (a) Rice, S. A.; Sceats, M. G. *J. Phys. Chem.* **1981**, *85*, 1108. (b) Hare, D. E.; Sorensen, C. M. *J. Chem. Phys.* **1990**, *93*, 25.
(50) (a) Green, J. L.; Lacey, A. R.; Sceats, M. G. *J. Phys. Chem.* **1986**, *90*, 3958. (b) Green, J. L.; Lacey, A. R.; Sceats, M. G.; Henderson, S. J.; Speedy, R. J. *J. Phys. Chem.* **1987**, *91*, 1684.
(51) Green, J. L.; Sceats, M. G.; Lacey, A. R. *J. Chem. Phys.* **1987**, *87*, 3603.
(52) Muller, N. *Acc. Chem. Res.* **1990**, *23*, 23.
(53) Silverstein, K. A. T.; Haymet, A. D. J.; Dill, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 8037.
(54) (a) Chodera, J. D.; Mobley, D. L. *Annu. Rev. Biophys.* **2013**, *42*, 121. (b) Starikov, E. B.; Nordén, B. *Chem. Phys. Lett.* **2012**, *538*, 118.
(55) Hua, J.; Mitra, M. K.; Muthukumar, M. *J. Chem. Phys.* **2012**, *136*, 134901.
(56) Karibyants, N.; Dautzenberg, H. *Langmuir* **1998**, *14*, 4427.
(57) Dubas, S. T.; Schlenoff, J. B. *Macromolecules* **2001**, *34*, 3736.

DOI: 10.1021/jacs.5b11878
J. Am. Chem. Soc. 2016, 138, 980−990