Role of Electrostatic Interactions in Charge Regulation of Weakly Dissociating Polyacids

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Abstract

We investigate theoretically charge regulation of weakly dissociating polyacids by potentiometric titration of their aqueous solutions. By treating deprotonation and cation binding to the polyacids as reversible reactions in our model, the ionization constant of acid groups along the polyacid chain is adjusted from its intrinsic value by electrostatic correlations. If electrostatic correlations are modeled with a Debye-Hückel electrostatic free energy that ignores the connectivity of acid groups, the theory follows Henderson-Hasselbalch behavior for monoacids at low polyacid concentrations, and does not capture the shift of the ionization constant from its intrinsic value with increasing pH. Using a random phase approximation (RPA) that captures the chain connectivity, the shift of the ionization constant is predicted, which is found to directly originate from the electrostatic repulsions along the polyacid chain. We make predictions for titration of rodlike and Gaussian coil polyacids, and find that the former is followed by hydrophilic poly(acrylic acid), while the latter is followed more closely by hydrophobic poly(acrylamido-2-methyl-1-propanesulfonic acid). The results suggest that development of more advanced free energy models that allow chain configurations to self adjust with changing pH and chain hydrophobicity could provide accurate a priori modeling of charge regulation of polyacids.

Keywords: Polyacids, Charge regulation, Electrostatic correlations, ionization constant

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ABBREVIATIONS

AMPS	Acrylamido 2methyl 1propanesulfonate
DH	Debye-Hückel
HH	Henderson-Hasselbalch
iPMA	Iso-tactic poly(methacrylic acid)
PAA	Poly(acrylic acid)
PAMPS	Poly(acrylamido 2methyl 1propanesulfonate)
PB	Poisson-Boltzmann
PE	Polyelectrolyte
PEA	Poly(ethacrylic acid)
PMA	Poly(methacrylic acid)
RPA	Random phase approximation

1. Introduction

Weakly dissociating polyelectrolytes (PEs) are chains of ionizable functional groups, and include ubiquitous natural polyelectrolytes, such as DNA, RNA, and proteins, and technologically important synthetic ones, such as poly(alkylacrylic acid)s. Tuning the degree of ionization of weak polyelectrolytes with pH offers a myriad of novel applications such as viscosity modification [1], encapsulation of therapeutics and nano medicines [2] and, in particular, pH dependent drug or gene delivery vehicles, which respond to local pH changes near target cells [3–6].

The ionization behavior of a solution of small monoacids is traditionally studied within the framework of the Henderson-Hasselbalch (HH) theory, giving

$$pK_{A}^{0} = pH + \log \frac{1 - \alpha_{A}}{\alpha_{A}}$$
(1)

where the degree of ionization of each monoacid, α_A , as a function of pH, is governed only by a fixed *intrinsic* ionization constant, pK_A^0 , which solely depends on the nature of the monoacids.

In contrast to small monoacids, the ionization behavior of polyacids (i.e. chains of monoacids) is much more complicated. The ionization (or more appropriately, deprotonation) of an acid group along the polyacid chain can be described as,

$$AH + H_2 0 \Longleftrightarrow A^- + H_3 0^+$$
⁽²⁾

where (AH) and (A⁻) denote the protonated and deprotonated states of the polyacid monomer, respectively.

The deprotonation of monomers of polyacid chains in a solution has been described empirically by a simple adjustment of the HH theory of monoacids,

$$pK_{A}^{eff} = pH + \log \frac{1 - \alpha_{A}}{\alpha_{A}}$$
(3)

Because of electrostatic interactions arising from their proximity, monomers along a polyacid chain do not deprotonate with the same strength (pK_A^0) as their monoacid counterparts do in aqueous solutions [7,8]; the monomers along the chain deprotonate with an *effective* ionization constant, pK_A^{eff} , that differs from the pK_A^0 of the corresponding monoacid by a complicated function of the degree of deprotonation [9], type and concentration of salt [10], and the chain hydrophobicity and configuration. All these physiochemical factors *regulate* the (de)protonation of chain monomers and therefore, the charge of polyacids. For instance, it is known that a homo polyacid becomes harder to deprotonate as the degree of ionization of the polyacid increases [11]. The shift of pK_A^{eff} (from its intrinsic value) with pH is of great interest to the biochemical community, due to its importance in biomolecular processes [12–14]. Although in the present study we investigate charge regulation of (synthetic) homo polyacids in homogeneous solution, because of their relative simplicity, the ideas and results developed here are applicable to biomolecular hetero polyacids.

The shift of pK_A^{eff} from pK_A^0 for polyacids in solution is usually attributed to the electrostatic free energy cost for separating a proton from the polyacid, ΔG_{elec} , according to [15,16],

$$pK_{A}^{eff} = pK_{A}^{0} + \frac{\Delta G_{elec}}{2.3 k_{B}T}$$

$$\tag{4}$$

Most prior studies on charge regulation, and specifically on pK_A^{eff} , have been based on mean-field electrostatic theories. In homogeneous solutions, the mean-field electrostatic potential is zero due to the electroneutrality of the solution. However, a mean-field approach, known as the Poisson-Boltzmann (PB) theory, can be made to apply to a single polyacid molecule in solution by modeling the polyacid chain as a charged cylinder, which provides a non-homogenous charge distribution outside of the cylinder. By solving for charge distribution and electrostatic potential, one would be able to determine the contribution of electrostatic free energy to pK_A^{eff} [10,12,15,17,18]. Specifically Nagasawa et al. [15], Sadeghpour et al. [10] and others assumed that the free energy cost for separation of a proton from a polyacid in Equation (4) is $\Delta G_{elec} = e\psi$, where *e* is the proton charge (= the elementary charge) and ψ is the electrostatic potential on the surface of the cylinder. Nagasawa et al. found that the PB approach yields reasonable agreement with experimental titration data for poly(acrylic acid), and, at high degrees of ionization, for poly(methacrylic acid) [15]. However, these theories treat the electrostatic interactions at a mean field level and suffer from important deficiencies, such as neglect of electrostatic correlations in chain configurations [19]. Furthermore, the charged species are treated as point charges, and so ion specific effects, which manifest themselves near the polyelectrolytes, cannot be accounted for [20]. Despite the shortcomings, these theories have remained the only approaches to treat the electrostatic interactions in polyacid solutions.

One way of including local charge correlations in chains, absent in mean-field theories, is through a site-binding model in which, in place of the cost ΔG_{elec} in Equation (4), a "penalty" to the ionization constant is added to capture the effect of electrostatic repulsions arising from ionization of the nearest neighbors of a monomer [21]. For long chains, these nearest neighbor "pair-interactions" have been formulated using the Transfer Matrix technique [21,22]. Nevertheless, in addition to needing to assign a value to the penalty, this method contains no electrostatic correlations beyond nearest neighbors along the chain. A recent review by Koper and Borkovec provides a comparison of charge regulation models for weak PEs in solution [21].

Mean-field theories of charge regulation have also been developed by Szleifer and co-workers for weak PEs grafted to a surface [23–25]. In their approach, a set of polymer configurations, generated for example by computer simulations, is incorporated into a mean-field expression for free energy that includes electrostatic

contributions. The method allows calculation of polyelectrolyte monomer concentration as a function of distance from the grafting surface, neglecting electrostatic fluctuations. In this study, however, we will focus on polyacids in solution (rather than tethered ones) with no source of heterogeneity and with an explicit account of connectivity of ionizable groups along polyacid chains in our treatment of electrostatic correlations.

Here, we present a theory to explain charge regulation of polyacid chains in solution that combines a random phase approximation (RPA) for the electrostatic correlations with reversible equilibrium reactions for (de)protonation and small cation binding to polyacids. We discuss how the shift in pK_A^{eff} from its intrinsic value pK_A^0 in Equation (4) for various polyacid configurations is obtained self consistently from the contribution of the electrostatic correlations given by the RPA to the (de)protonation equilibrium. Analyzing the potentiometric titration of polyelectrolytes bearing carboxylic or sulfonic groups, including poly(acrylic acid) or PAA, poly(methacrylic acid) or PMA, poly(ethacrylic acid) or PEA, and poly(acrylamido 2methyl 1propanesulfonate) or PAMPS, we elucidate the role of electrostatic correlations in the shifts of ionization constant in a unified manner. This study builds upon prior work by Salehi and Larson [11] on the charge regulation of weak polyacids, who employed a Debye-Hückel (DH) theory to treat the electrostatic interactions.

2. Theory

In this section, we briefly recap the equilibrium reaction model of polyelectrolytes by Salehi and Larson [11] and incorporate into it an RPA formulism for electrostatic interactions, developed by Friedowitz and Qin [26] in our recent work. We consider an aqueous solution, containing polyacid (A), its associated proton (H⁺), hydronium (H₃O⁺), hydroxide (OH⁻), salt anion (S⁻) and cation (S⁺), and water (W). Monomers of the polyacid and salt ions are assumed to be monovalent. Each (monomeric) unit of the species *i* with *i* = A, H₃O⁺, OH⁻, and S[±] occupies a molecular volume of v_i , which can be divided by the molecular volume of water, $v_W = 29.7$ Å³, leading to a normalized molecular volume of $\omega_i = v_i/v_W$.

The Helmholtz free energy density, f, of the system is [11],

$$\frac{v_{\rm W}F}{k_{\rm B}TV} \equiv f = f^{\rm T} + f^{\rm rxn} + f^{\rm comb} + f^{\rm corr}$$
(5)

where V is the system volume. Equation (5) contains a contribution from the mixing (or translational) entropy of the species,

$$f^{\mathrm{T}} = \sum_{i=A,H_{3}O^{+},OH^{-},S^{+},W} \frac{\phi_{i} \ln \phi_{i}}{N_{i}\omega_{i}}$$

$$= \frac{\phi_{A}}{N_{A}\omega_{A}} \ln \phi_{A} + \frac{\phi_{H_{3}O^{+}}}{\omega_{H_{3}O^{+}}} \ln \phi_{H_{3}O^{+}} + \frac{\phi_{OH^{-}}}{\omega_{OH^{-}}} \ln \phi_{OH^{-}} + \frac{\phi_{S^{+}}}{\omega_{S^{+}}} \ln \phi_{S^{+}} + \phi_{W} \ln \phi_{W}$$
(6)

 N_i (*i* = A) represents the degree of polymerization of the polyacid, and ϕ_i the volume fraction of species *i*. Here and in next equations, ϕ_A represents the volume fraction of all polyacid monomers, whether ionized, protonated, or bound by salt cation. We note that free cations (and not those ions bound to the polyacid) contribute to the translational free energy in Equation (6).

The hydronium ions and cations can reversibly bind to the polyacid, as described by the following reactions,

$$A^{-} + H_3 0^{+} \Longleftrightarrow AH + H_2 0 \tag{7}$$

$$A^- + S^+ \Longleftrightarrow AS \tag{8}$$

$$2H_20 \Leftrightarrow 0H^- + H_30^+ \tag{9}$$

The protonation reaction given in Equation (7) is simply the reverse of the deprotonation reaction in Equation (2). The water self-dissociation reaction in Equation (9) is also included for completeness. These association/dissociation reactions give rise to the free energy contribution f^{rxn} ,

$$f^{\rm rxn} = \frac{\phi_{\rm A}}{\omega_{\rm A}} \alpha_{\rm AH} \,\Delta G_{\rm AH} + \frac{\phi_{\rm A}}{\omega_{\rm A}} \alpha_{\rm AS} \,\Delta G_{\rm AS} + (\phi_{\rm W}^0 - \phi_{\rm W}) \,\Delta G_{\rm W} \tag{10}$$

Here, α_{AH} (= 1 – α_A) and α_{AS} represent the degrees of protonation and cation binding, defined as the fractions of total polyacid monomers that are protonated and cation bound, respectively. ΔG_{AH} and ΔG_{AS} represent the specific (or intrinsic) free energy due to protonation of a monoacid and cation binding to a monoacid in infinite dilution, respectively. In Equation (10), ΔG_W is the water dissociation free energy, and ϕ_W^0 is the water concentration of the solution before inserting the polyacid into it, and since it is a constant, it is not of thermodynamic importance and one can neglect it.

The protons and cations bound to the polyacid can move along the polyacid backbone and/or can exchange with the hydronium and cations in the solution, respectively. This gives rise to a combinatorial entropy, captured by the free energy contribution f^{comb} [11],

$$f^{\text{comb}} = \frac{\phi_{\text{A}}}{\omega_{\text{A}}} [\alpha_{\text{AH}} \ln \alpha_{\text{AH}} + \alpha_{\text{AS}} \ln \alpha_{\text{AS}} + (1 - \alpha_{\text{AH}} - \alpha_{\text{AS}}) \ln(1 - \alpha_{\text{AH}} - \alpha_{\text{AS}})]$$
(11)

Lastly, the electrostatic interactions among charged species, including the ionized polyacid monomers, free salt ions, and the hydronium and hydroxide ions in the solution, are accounted for using an expression for electrostatic free energy. In this work, we employ either the Debye-Hückel (DH) free energy, which will be introduced later, or a version of the random phase approximation (RPA), developed by Friedowitz et al. [26]. The contribution due to the RPA electrostatic correlations is,

$$f^{\rm corr} = \frac{1}{4\pi^2} \int_0^\infty q^2 \ln\left(1 + \frac{\tilde{k}^2(q)}{q^2}\right) dq$$
(12)

with,

$$\tilde{k}^{2} = 4\pi \frac{l_{\rm B}}{\ell} \left(\frac{\phi_{\rm H_{3}O^{+}}}{\omega_{\rm H_{3}O^{+}}} \hat{\Gamma}^{2}(q, a_{\rm H_{3}O^{+}}) + \frac{\phi_{\rm OH^{-}}}{\omega_{\rm OH^{-}}} \hat{\Gamma}^{2}(q, a_{\rm OH^{-}}) + \frac{\phi_{\rm S^{+}}}{\omega_{\rm S^{+}}} \hat{\Gamma}^{2}(q, a_{\rm S^{+}}) + \frac{\phi_{\rm S^{-}}}{\omega_{\rm S^{-}}} \hat{\Gamma}^{2}(q, a_{\rm S^{-}}) \right. \\ \left. + \frac{\phi_{\rm A}}{\omega_{\rm A}} N_{\rm A} \sigma_{\rm A}^{2} \hat{\Gamma}^{2}(q, a_{\rm A}) \, g_{\rm D} \right)$$

$$(13)$$

Here, $l_{\rm B} = e^2/4\pi\epsilon_0\epsilon k_{\rm B}T$ is the Bjerrum length, with ϵ being the dielectric constant of the medium, which is set to that of water ($\epsilon = 79$). In Equation (13), ℓ is a reference length ($\ell = v_{\rm W}^{1/3}$) and $\sigma_{\rm A} = 1 - \alpha_{\rm AH} - \alpha_{\rm AS}$ represents the net charge density of the polyacid. In this version of the RPA, we follow Ermoshkin and de la Cruz

[27], Wang [28], and Delaney and Fredrickson [29], by smearing out the charge of the ionizable unit *i* using a Gaussian function, $\hat{\Gamma}(q, a_i)$, across a width a_i , taken to be the radius of the unit *i*, $a_i = v_i^{1/3}$ [26,28]. It is worth noting that the approach by Szleifer and co-workers does not require this smearing of charges, because in their simulations excluded volumes are explicitly considered [23,24].

The effect of the polyacid structure on electrostatic correlations is captured by the form factor g_D , which will be discussed in depth in the Results section.

Minimization of the free energy in Equation (5) with respect to the extents of reactions, α_{AH} (or α_A), α_{AS} , and $\xi_W = \phi_W^0 - \phi_W$ in Equations (7) – (9), respectively, under the constraints of incompressibility and electroneutrality, yields three mass action equations,

$$K_{\rm AH} = \frac{\alpha_{\rm AH} \, \phi_{\rm W}}{\left(1 - \alpha_{\rm AH} - \alpha_{\rm AS}\right) \, \phi_{\rm H_30^+}} = \exp\left[-\Delta G_{\rm AH} - \mu_{\rm AH}^{\rm corr}\right] \tag{14}$$

$$K_{A+} = \frac{\alpha_{AS}}{(1 - \alpha_{AH} - \alpha_{AS}) \phi_{S^+}} = \exp[-\Delta G_{AS} - \mu_{AS}^{\text{corr}} + 1]$$
(15)

$$K_{\rm W} = \frac{\phi_{\rm H_3O^+} \,\phi_{\rm OH^-}}{\phi_{\rm W}} = \exp[-\Delta G_{\rm W} - \mu_{\rm W}^{\rm corr}] \tag{16}$$

Here, μ_{AH}^{corr} and μ_{AS}^{corr} represent the contributions of the electrostatic correlations to protonation and cation binding to the polyacid, respectively. These contributions are non-specific and depend on the polyacid configuration (captured by g_D within the RPA), as opposed to ΔG_{AH} and ΔG_{AS} , which denote the intrinsic, specific effects that do not depend on the chain structure. Similarly, μ_W^{corr} contains the effect of the electrostatic correlations on the water dissociation constant. The expressions for μ_{AH}^{corr} , μ_{AS}^{corr} and μ_W^{corr} are available in the Appendix. The equilibrium constants in Equations 14 and 15 resemble those in a prior work by Szleifer and coworkers [30]. However, we do not expect the equilibrium constants from our work to be the same as theirs, because ours include a direct effect of electrostatic correlations, while theirs do not (because of the mean-field assumption).

We compute potentiometric titration curves for polyacids and compare the predictions with the existing experimental data in the literature. To adjust the pH of the solution in our calculation of the titration curves, we use a strong acid or base (for instance, HCl or NaOH), taking the anion or cation from, respectively, the acid or base to be the same as the added salt ions.

For a given set of molar concentrations of polyacid (in its acidic form) and total cation and anion in an aqueous solution, respectively designated by C_{AH}^0 , $C_{S^+}^0$ and $C_{S^-}^0$, (de)protonation and binding of salt cations to the polyacid and water dissociation continue until the system reaches equilibrium. We solve Equations (14) – (16) along with the electroneutrality and incompressibility constraints to obtain the volume fractions of hydronium $\phi_{H_3O^+}$, hydroxide ϕ_{OH^-} , free cations ϕ_{S^+} , water ϕ_W , and the degree of protonation α_{AH} at equilibrium. The mass balance equation for cations allows us to replace the degree of cation binding α_{AS} with an expression involving ϕ_{S^+} . Also, each molar concentration (designated by " C_i ") can be converted into its volume fraction using $\phi_i = C_i \omega_i / C_W^0$, with C_W^0 being the water concentration at standard conditions ($C_W^0 = 55.56$ M). Note that the water dissociation equilibrium constant is $\mathcal{K}_W = [H_3O^+][OH^-] = 10^{-14}$ M², which can be nondimensionalized with $C_W^0 = 55.56$ M and expressed in terms of the water dissociation free energy, leading to $\Delta G_W = -\ln[\mathcal{K}_W/55.56^2] = 40.2 k_B T$.

3. Results and Discussion

3.1 Connection to Existing Literature

First, let us examine how our mass action equation for protonation in Equation (14) is related to Equations (3) and (4) in the Introduction, which are commonly used in the literature to describe charge regulation of polyacids. Noting that protonation is a reverse deprotonation reaction and that here the polyacids are initially inserted in their acidic form into the solution, we have $\alpha_{AH} = 1 - \alpha_A$ and can rewrite Equation (14) as,

$$K_{\rm A} = \frac{(1 - \alpha_{\rm A}) \phi_{\rm W}}{(\alpha_{\rm A} - \alpha_{\rm AS}) \phi_{\rm H_3O^+}} = \exp[\Delta G_{\rm A} + \mu_{\rm A}^{\rm corr}]$$
(17)

with $\Delta G_A = -\Delta G_{AH}$, and $\mu_A^{\text{corr}} = -\mu_{AH}^{\text{corr}}$. Taking the logarithm from both sides of Equation (17) leads to,

$$pK_{A} = \log\left(\frac{1-\alpha_{A}}{\alpha_{A}-\alpha_{AS}}\right) + \log\left(\frac{\phi_{W}}{\phi_{H_{3}O^{+}}}\right) = (\Delta G_{A} + \mu_{A}^{\text{corr}})\log(e^{1})$$
(18)

where the "log" is a base 10 logarithm. At this point, as in ref [11], we replace the degree of cation binding α_{AS} with $\alpha_{AS} = \alpha_A \gamma_{AS}$, where γ_{AS} is simply another representation for the degree of cation binding, defined as the fraction of the *deprotonated* monomers that are cation bound. Further, we recognize that $\log\left(\frac{\phi_W}{\phi_{W-OT}}\right) =$

$$-\log\left(\frac{\phi_{\rm H_3O^+}}{\phi_{\rm W}}\right) = -\log(\omega_{\rm H_3O^+}) + \text{ pH. Using these in Equation (18) we obtain,}$$
$$pK_{\rm A} = \log\left(\frac{1-\alpha_{\rm A}}{\alpha_{\rm A}}\right) + pH = \frac{\Delta G_{\rm A}}{2.3} + \frac{\mu_{\rm A}^{\rm corr}}{2.3} + \log(1-\gamma_{\rm AS}) + \log(\omega_{\rm H_3O^+})$$
(19)

Now, in Equation (19) we recognize the intrinsic ionization constant of the polyacid monomers as $pK_A^0 = \frac{\Delta G_A}{2.3}$, and since the ionization constant pK_A is shifted from this intrinsic value, we rename it pK_A^{eff} ,

$$pK_{A}^{eff} = \log\left(\frac{1-\alpha_{A}}{\alpha_{A}}\right) + pH$$
$$= pK_{A}^{0} + \frac{\mu_{A}^{corr}}{2.3} + \log(1-\gamma_{AS}) + \log(\omega_{H_{3}O^{+}})$$
(20)

The first equality above is the same as Equation (3) and the second one is equivalent to Equation (4). Thus, in our model the contribution of electrostatic interactions to the shift of the (effective) ionization constant from its intrinsic value is given by the expression $\mu_A^{\text{corr}}/2.3 + \log(1 - \gamma_{AS})$ in Equation (20).

In Equation (20), as $\alpha_A \rightarrow 0$, corresponding to little deprotonation and hence weak electrostatic interactions, the contribution from the electrostatic interactions to the ionization constant, i.e. μ_A^{corr} , decreases and thus pK_A^{eff} interestingly approaches its intrinsic value, pK_A^0 , suggesting similar deprotonation behavior for monomers in this limit as that for monoacids in aqueous solutions. We note that α_{AS} and γ_{AS} approach zero in the limit $\alpha_A \rightarrow 0$.

Next, using the titration of polyacids we focus on the significance of the contribution of electrostatic interactions to deprotonation (μ_A^{corr}), determined from either the Debye-Hückel theory, or from the afore mentioned RPA approach for different polyacid configurations g_D .

3.2 No chain connectivity – Debye Hückel free energy

Here, we incorporate the Debye-Hückel (DH) free energy of electrolytes into the model to treat electrostatic interactions in the titration of polyacids. To do so, we replace f^{corr} in Equation (12) with the DH free energy,

$$f^{\rm DH} = -\frac{\bar{\kappa}^3}{12\pi} \tag{21}$$

with $\bar{\kappa}$ denoting the nondimensional inverse Debye length, $\bar{\kappa} = \left[4\pi \frac{l_B}{\ell} \left(\frac{\phi_{H_3O^+}}{\omega_{H_3O^+}} + \frac{\phi_{OH^-}}{\omega_{OH^-}} + \frac{\phi_{S^+}}{\omega_{S^+}} + \frac{\phi_{S^-}}{\omega_{S^-}} + \frac{\phi_A}{\omega_A}\sigma_A\right)\right]^{1/2}$ [11]. With this, one can easily calculate the contribution of the DH free energy to deprotonation, cation binding,

and also water dissociation, namely $\mu_A^{\text{corr}} = \mu_A^{\text{corr,DH}}$, $\mu_{AS}^{\text{corr}} = \mu_{AS}^{\text{corr,DH}}$, and $\mu_W^{\text{corr}} = \mu_W^{\text{corr,DH}}$, respectively. The expressions for these contributions are provided in the Appendix.

Figure 1 exhibits the model predictions using the DH free energy compared against the experimental data for the potentiometric titration of poly(acrylic acid) or PAA, which are used as reference data, at zero added salt concentration. The only fitting parameter within the DH free energy is the strength of cation binding to the polyacid, ΔG_{AS} , to which the predictions are insensitive over the values of parameters studied in this work.

As can be seen in Figure 1, the DH informed model obviously cannot capture the titration behavior of PAA. Interestingly, since the DH free energy does not account for the chain connectivity and higher order electrostatic correlations, the predicted titration curve here falls on the Henderson-Hasselbalch (HH) titration curve for isolated *monocarboxylic* acids.



Figure 1. Theoretical predictions compared to experimental data for potentiometric titration of PAA polyacid with HCl and NaOH. The yellow symbols correspond to the experimental data: circles \bigcirc are from ref [31] and squares \square from ref [32]. The theoretical predictions are plotted with lines: dashed line _____ corresponds to the Henderson-Hasselbalch (HH) equation, line with circles _____ to the model with DH free energy, and in b) line with open circles _____ represents the contribution of electrostatic interactions within the DH free energy to the effective ionization constant, i.e. $\mu_A^{\text{corr,DH}}$. Here, a) shows the degree of deprotonation α_A as a function of pH, and b) replots the results of a) in terms of pK_A^{eff} as a function of α_A . Within the DH free energy, the only fitting parameter is the strength of cation binding to the polyacid, ΔG_{AS} (here, $\Delta G_{AS} = 0 \ k_B T$), but the results are insensitive to ΔG_{AS} at least over the range -3 to $3 \ k_B T$. Other parameters used for the theory are experimentally determined ones: the PAA concentration $C_{AH}^0 = 1.35 \ \text{mM}$ [10], the monomer diameter of PAA $d_A = 2 \times (3 \nu_A / 4 \pi)^{1/3} = 5.8 \ \text{Å}$ (or $\omega_A \approx 3.0$) obtained from the molar volume of the polyacid ($\approx 55 \ \text{mL/mol}$) [33,34], the degree of polymerization $N_A = 1000 \ [10], \ pK_A^0 = 4.35 \ \text{from the monoacid}$. We used a hydration number of 2 for both H_3O^+ and the anion (chloride here) [35–37], and 3 for OH⁻ and the cation (sodium here) [35–37], which give volumes relative to water

molecules of $\omega_i \approx 3.0$ for $i = H_3 0^+$, OH^- , and S^{\pm} . Note that the predictions are insensitive to ω for the anion and hydroxide ions. Unless otherwise mentioned, in the following Figures ΔG_{AS} is set to 2 $k_B T$. [31], Copyright 2005. Adapted with permission from American Chemical Society. [32], Copyright 2003. Adapted with permission from American Chemical Society.

Within the DH free energy and over the parameter values in this work, there is almost no contribution from the electrostatic interactions to the effective ionization constant through $\mu_A^{\text{corr,DH}}$ (≈ 0) as shown in Figure 1b, and hence, each monomer along the polyacid chain deprotonates with the same intrinsic strength of $pK_A^{\text{eff}} \approx pK_A^0$ (see Equation (20)), with nearly complete disregard for the electrostatic interactions with other monomers along the chain. However, we note that Friedowitz et al. demonstrated that the DH free energy generally enhances ion dissociations [26], whose contribution becomes negligible at low polyelectrolyte concentrations (say, < 50 mM) [26]. Therefore, owing to the negligible contribution of the DH to deprotonation at low polyelectrolyte concentrations, which is reflected as $\mu_A^{\text{corr,DH}} \approx 0$ in Figure 1b, the titration curve follows that predicted by Henderson-Hasselbalch theory for monoacids. Note that pK_A^{eff} in Figure 1b is an equivalent representation of the information in Figure 1a, and that the intrinsic ionization constant, pK_A^0 , is fixed at 4.35, which roughly equals that of a monocarboxylic acid [10].

Noting the clear deficiencies of the DH theory in modeling of titration of polyacids, in the next sections we employ the RPA with various structure factors g_D to investigate the role of electrostatic correlations in charge regulation of polyacids.

3.3 Rodlike structure

Here, we explore how rodlike structure for polyacids within the RPA affects their (de)protonation behavior. Plotted in Figure 2 are the predictions of the model for the titration of rodlike polyacids at zero added salt concentration. In contrast to the DH theory, here we observe that treating the electrostatic correlations using the RPA approach and modeling the polyacid structure as a rodlike chain, allows variation of the (effective) ionization constant with the degree of deprotonation (Figure 2b). Interestingly, the model produces a nearly linear variation of the ionization constant with the degree of deprotonation, α_A , mimicking the experimental trend for PAA and fitting it nearly quantitatively through adjustment of the parameter ΔG_{AS} . In the literature, however, this linear variation of p K_A^{eff} with α_A is usually either incorporated in an *ad hoc* manner [11], or obtained within the PB theory [10,15,17,21].

Nevertheless, we note that fitting to experimental data is not the focus of this work, as our work takes the first step toward developing a unified model for weakly dissociating polyacids in solution, and here we merely attempt to elucidate the role of electrostatic correlations in titration and charge regulation of polyacids in a general fashion.



Figure 2. The same as Figure 1, except that instead of the DH theory, a rodlike chain structure within the RPA approach is used to treat electrostatic interactions. The symbols are the same experimental data given in Figure 1. The only fitting parameter is the strength of cation binding to the polyacid, ΔG_{AS} (here, $\Delta G_{AS} = 2k_BT$). The length of the chain is obtained as $L = d_A \times N_A$, where d_A and N_A , and also other parameters, are the same as in the caption of Figure 1.

The increase of the ionization constant with α_A (or with pH) in Figure 2b means that the polyacid "resists" deprotonation, in that with increasing α_A , the (positive) ionization constant becomes larger, and so further deprotonation becomes more unfavorable. This is a consequence of the increased electrostatic repulsions among the *ionized* monomers along the polyacid that arise from deprotonations, making it increasingly hard to dissociate protons from the chain [38,39]. We note that this charge regulation mechanism is clearly absent in the acid-base equilibria of isolated monoacids in solutions (dashed red curves in Figure 2b), and due to this, they can deprotonate more easily than their monomer counterparts in the chains (see Figure 2a).

The repulsion between the ionized monomers in a polyacid chain is part of the self-energy of the system. The self-energy of a polyacid solution is the energy required to transfer each ionizable group (including acid groups and other ions) from the vacuum into the solution and *form* the system, including assembling acid groups into a chain to form polyacids [19,26,28]. Hence, Figure 2b shows that the shifts in pK_A^{eff} or, equivalently, the "resistance" of the polyacid to deprotonation, comes from the electrostatic correlations and self-energy, here captured by the μ_A^{corr} contribution at the level of RPA electrostatics.

The agreement in Figure 2 may seem surprising, given the PAA chains transition reversibly from a highly expanded configuration at high pH to a coil configuration upon decrease of pH [40–43], while we employed a rodlike structure for the polyacid at all pH values. However, we note that our assumption of rodlike chains for the polyacid is supported by an earlier work by Friedowitz et al. who found that counterion binding, described as a reversible reaction similar to our protonation reaction, when applied to chains with adaptive, flexible structure, resulted in a binding behavior that closely resembled that obtained for a fixed rodlike chain [26]. Hence, we conjecture that polyacids with negligible (intrinsic) hydrophobicity promptly expand upon deprotonation and take on the maximum possible extended configurations to reduce the electrostatic repulsions along the chain. Therefore, this, and possibly other deficiencies and assumptions of the model that counteract each other, might be responsible for the quantitative agreement between theory and experiment in Figure 2. In the Supporting Information (SI), we discuss the titration of PAA at different salt concentrations, showing easier deprotonation of the polyacid at higher salt concentrations, in agreement with recent work by de la Cruz and co-workers, and others.[10,15,44,45]

In addition, in the SI we investigate how the titration curves vary if the strength of cation binding to the rodlike polyacid changes when there is no added salt. Figure S2 shows that, not surprisingly, when a base with a more strongly binding cation is used to tune the pH, the polyacid more easily deprotonates at high pH. It would be interesting to explore this finding using experiments in the future.

3.4 Gaussian coil structure

In the previous section we highlighted the importance of the connectivity of monomers along polyacid chains in the titration of polyacids with negligible intrinsic hydrophobicities. Polyacids with high intrinsic hydrophobicity, on the other hand, have unfavorable chain water interactions, and to minimize these interactions, chains maintain a compact configuration (between a dense globule and a coil) even at high pH. This behavior stands in contrast to that of polyacids with negligible intrinsic hydrophobicity, including PAA, which *promptly* expand upon ionization.

First, by assuming a fixed Gaussian coil configuration for a compact polyacid within the RPA approach, we explore titration of these polyacids. Setting the Kuhn length of the Gaussian coil equal to the diameter of monomers of the rodlike chains and using the same input parameters as in Figure 1, we show in Figure 3 that the dissociation of protons from the Gaussian coil polyacids is much harder than from the rodlike polyacids. The polyacid thus builds a significant "resistance" to deprotonation over an increase in pK_A^{eff} by 4 units (from around $pK_A^{\text{eff}} \approx 5$ to $pK_A^{\text{eff}} \approx 9$ in this case) when it is coiled, which directly arises from the steep increase in the contribution from the electrostatic correlations μ_A^{corr} (Figure 3b).



Figure 3. a) and b) are the same as Figure 1, except showing a comparison of the predictions for Gaussian coil polyacids (lines with squares) and for dense spherical polyacids (lines with triangles) against that for rodlike polyacids (lines with circles). Except for the Kuhn length which is set equal to the diameter of monomers $b = d_A = 5.8$ Å, the rest of parameters are the same as in Figure 1. The radius of the spherical polyacids is obtained through equating its volume to that of a polyacid chain, leading to R = 35.9 Å. Note that, the radius of gyration of the coil polyacids is $R_g = 74.78$ Å. The inset plot in a) shows the experimental titration curve from ref. [46] in the backward and forward pH-directions for iso-tactic poly(methacrylicacid) (iPMA). [46], Copyright 1972. Adapted with permission from American Chemical Society.

For a given degree of ionization, the electrostatic repulsions and self-energy in the Gaussian chain are stronger than in the rodlike chain [19,26]. Hence, the polyacid suppresses dissociation of protons more strongly to relieve

these repulsions in the Gaussian chains. With increasing pH of the solution (> 8), however, the cations in the solution start binding and neutralizing the Gaussian polyacids, enabling the dissociation of protons without causing buildup of charge on the polyacids (see Figures 3a and S3). At this point, the Gaussian polyacid ceases to manifest further resistance to deprotonation, yielding the observed near plateau in the ionization constant (see Figure 3b), due to an increase in γ_{AS} (see Figure S3 and Equation (20)).

The most compact, hypothetical, state of a polyacid corresponds to a tightly compacted sphere containing only the polyacid monomers. Obviously, this does not represent physically realistic systems, but does provide insight into the deprotonation behavior of compact polyacids. Approximating the form factor of such a polyacid by that of a homogeneous sphere, we illustrate in Figure 3 that, interestingly, the titration curve and the ionization constant qualitatively mimic those of the Gaussian coils. However, since the electrostatic interactions are enhanced in the compact sphere configuration, the polyacid shows stronger resistance to deprotonation than does a Gaussian coil.

Figure 3 shows that the charge regulation of a polyacid strongly depends on its configuration. Forward and backward titrations of a polyacid generally coincide with each other, but there are exceptions. For instance, isotactic poly(methacrylicacid) (iPMA) shows hysteresis in its charge upon increase and decrease of pH (see inset of Figure 3a), apparently owing to a kinetic barrier to transitions between a low-pH compact state and a more expanded state high-pH state. For iPMA, the source of this barrier is likely the formation of "microgel-like aggregates" at low pH and low charge, which presumably resist swelling when pH is raised [47,48]. Hysteresis in polyelectrolyte swelling and other properties has also been reported in polyelectrolyte films subjected to changes in pH [49–51]. Such hysteretic behavior shows that the titration curve is indeed sensitive to chain configuration, as our model predicts.

Hereafter, owing to the similarity of the charge regulation of the spherical and Gaussian coil polyacids, we restrict ourselves to the Gaussian coil to model qualitatively the titration behavior of compact polyacids. The effect of the strength of cation binding to the Gaussian polyacids on the titration curve is studied in Figure S4, where, similar to that for the rodlike polyacids in Figure S2, stronger cation binding yields easier dissociation of protons from the polyacid, and therefore less resistance to deprotonation at high pH.

To investigate further the role of electrostatic correlations in the charge regulation of compact polyacids, we now consider Gaussian chains with varying lengths (or degrees of polymerization). As shown in Figure 4, upon decrease of the length of the polyacid, the sharp resistance of the polyacid to ionization gradually disappears.



Figure 4. a) and b) are the same as Figure 1, except showing the effect of the length of the Gaussian chains on the titration behavior. Except for the Kuhn length which is set equal to the diameter of monomers $b = d_A = 5.8$ Å and the degree of polymerization N_A , the other parameters are the same as in Figure 1.

Interestingly, for very short Gaussian chains (eg. with only 25 monomers), pK_A^{eff} varies almost linearly with the degree of deprotonation, α_A , mimicking that of rodlike polyacids. This clarifies that in the extreme limit of short Gaussian chains, the electrostatic repulsions are diminished (but not eliminated), and that only *long* Gaussian chains could yield the sharp resistance to deprotonation.

Polyacids in general have a wide spectrum of acidic properties depending on their intrinsic ionization constants pK_A^0 , with lower pK_A^0 usually corresponding to stronger polyacids such as sulfonate based polyacids (eg. $pK_A^0 = 1$ for poly(styrene sulfonate)). Here, we show the effect of the intrinsic ionization constant on the titration of Gaussian coil polyacids. As expected, we observe in Figure 5 that a smaller value of pK_A^0 leads to easier dissociation of protons from the polyacids, enhancing the acidity of the solution.



Figure 5. a) and b) are the same as Figure 1, except showing the effect of the intrinsic ionization constant of monomers pK_A^0 on the titration behavior of Gaussian polyacids. Except for the Kuhn length which is set equal to the diameter of monomers $b = d_A = 5.8 \text{ Å}$ and pK_A^0 , the rest of parameters are the same as in Figure 1.

That said, with decrease of pK_A^0 , the sharp increase in the effective ionization constant, or equivalently the presence of the plateau region of the degree of deprotonation at low pH, still persists, suggesting that the polyacid still resists losing its *weakly associated* protons because this would increase the electrostatic repulsions in the coil. In fact, with a decrease in pK_A^0 , the compact polyacid's resistance shifts more toward the nonspecific electrostatic correlations, captured by μ_A^{corr} (see Figure 5b and Equation 20).

One of the sulfonate-based polyacids that manifests a sharp resistance in its deprotonation behavior is poly(acrylamido-2-methyl-1-propanesulfonic acid), or PAMPS, with pK_A^0 of 3.0, corresponding to that of an AMPS monoacid [52,53]. PAMPS is a polyacid containing intrinsically hydrophobic groups of amide and methyl in its AMPS groups, promoting compactness of the polyacid structure. It was suggested that the polyacid takes on a configuration between a "compact coil" at low pH and an "open coil" at high pH [52]. In the experimental data in Figure 6, we see a strong resistance of the polyacid to deprotonation for pH values up to $pK_A^{eff} \approx 10$, which is well beyond the small value of the pK_A^0 of the AMPS groups ($pK_A^0 = 3.0$) [52,53]. In other words, PAMPS

behaves as a weak polyacid, although the pK_A^0 of the polyacid monomers is small. In the light of the discussion of Fig. 5 and as shown below, this charge regulation behavior arises from strong intra-chain electrostatic correlations in chains that are highly compacted due to high intrinsic hydrophobicity of the polyacid, which manifests itself through the large ionization constant.

Here, we crudely model titration of the polyacid PAMPS using a fixed Gaussian coil configuration. Figure 6 presents the titration predictions for chains with two different Kuhn lengths against the experimental data. Figure 6 shows that only when the Kuhn length is artificially small, around 4.0 Å which is even smaller than the PAMPS monomer diameter (≈ 8.2 Å, obtained from its molecular volume of ≈ 172.5 mL/mol), does the prediction come close to agreeing with the experimental data, at least for $\Delta G_{AS} = 4 k_B T$. In addition, weaker (specific) binding of cations to the polyacid, represented by more positive ΔG_{AS} , further increases the polyacid's resistance to deprotonation (see Figure S4), which also yields predictions closer to the data. Both these effects (i.e. smaller Kuhn length and more positive ΔG_{AS}) act in the same way and promote the electrostatic repulsions in the polyacid chain. Given that the typical Kuhn length of polyelectrolytes is usually more than 10 Å and longer than their monomer size [54], the predictions in Figure 6 could indicate that perhaps the configuration of the PAMPS polyacid should be modeled as a compact coil/globule, due to the hydrophobicity of the polyacid, rather than a Gaussian coil. Nevertheless, the qualitative agreement here clearly demonstrates the important role of intra-chain electrostatic repulsions in the polyacid's resistance to deprotonation (as inferred from μ_A^{corr} in Figure 6b), supporting Chandrasekar and Baskar's inference that the proximity of the AMPS groups to each other is responsible for the high pK_A^{eff} of the polyacid [52].



Figure 6. The same as Figure 1, except for poly(acrylamido-2-methyl-1-propanesulfonic acid) or PAMPS, with experimental data from ref [52], modeled as a fixed Gaussian coil within RPA. The fitting parameters are the strength of cation binding to the polyacid ΔG_{AS} and the Kuhn length of the coil *b*. Here, $\Delta G_{AS} = 4 k_B T$ and b = 5.8 Å (blue line) and b = 4.0 Å (black line). We used the experimental values of $C_A^0 = 4.5$ mM and pK_A^0 of 3.0 [52,53], while other parameters are the same as in Figure 1. [52], Copyright 2006. Adapted with permission from John Wiley & Sons Inc.

3.5 Titration of moderately hydrophobic poly(alkylacrylic acid)s

So far, we used either fixed rodlike or Gaussian coil/sphere configurations to investigate the charge regulation of polyacids with negligible or high intrinsic hydrophobicities, respectively. In this section, we attempt to study

further the role of chain structure on titration curves of polyacids within our model, by focusing on (atactic) poly(alkylacrylic acid)s, namely poly(ethylacrylic acid) (PEA), poly(methacrylicacid) (PMA), and poly(acrylic acid) (PAA). These poly(alkylacrylic acid)s share the same acidic group, namely acrylic acid COOH, and only differ in the length of alkyl group in their monomers, which influences the properties of these polyacids. In particular, the intrinsic hydrophobicity of the polyacids increases with the size of the alky group, as PAA < PMA < PEA.

Figure 7 depicts the titration curves for these polyacids, where following the aforementioned order of increasing hydrophobicity, the appearance of a small peak at low pH becomes more prominent, indicating a more compact configuration, especially for the most hydrophobic polymer, PEA [55,56]. The titration curves nearly converge at high pH and show the familiar linear increase of pK_A^{eff} with the degree of deprotonation, characteristic of a highly expanded chain configuration [55,56].



Figure 7. Effective ionization constants pK_A^{eff} from experiments for PAA \bigcirc , PMA \bigcirc , and PEA \bigcirc from refs. [57], [42], and [58], respectively, at 10 mM NaCl. The chain configurations of polyacids like PEA are shown in the three regions. [57], Copyright 2001. Adapted with permission from Springer. [42], Copyright 2015. Adapted with permission from John Wiley & Sons Inc. [58], Copyright 1983. Adapted with permission from Springer.

In the light of the predictions in Figures 3b and 6b, one can analyze the titration behavior of polyacids like PEA as follows: at low pH in region I (before the peak), the high hydrophobicity of PEA causes the polyacid to take a compact configuration. Thus, similar to the sharp resistance to deprotonation of compact polyacids in Figure 3b or that of PAMPS in Figure 6b, the carboxylic groups in PEA do not easily give up their protons at low pH, since doing so would create high electrostatic repulsions in the compact polyacid. However, increasing pH gradually drives incremental deprotonations and leads eventually to the expansion of the chain to reduce the electrostatic repulsions (region II). Thus, in this region the PEA opens up as it overcomes the hydrophobic interactions with water [57]. Intriguingly, although the degree of ionization of protons. This is because expansion of the PEA configuration beyond its compact configuration in region I reduces electrostatic repulsions between ionized groups in the chain. Nevertheless, further deprotonation and ionization of the polyacid chain in region III (corresponding to $\alpha_A > 0.5$) again increases the electrostatic repulsions along the open chain, leading to a gradual, linear, increase in its resistance to deprotonation, similar to that observed for the rodlike polyacids in Figure 2b. In this limit, as inferred from the titration curves for the poly(alkylacrylic acid)s, the (intrinsic)

hydrophobicity of the chains plays little role in their titration behavior. Thus, the titration of PEA at low and high pH values corresponds well to the titration behavior of compact polyacids at low pH and rodlike polyacids at high pH, respectively, clearly demonstrating the configurational transition of PEA upon increase of pH. Predicting this behavior even qualitatively may require a model in which chain configuration is determined self consistently with degree of deprotonation and chain hydrophobicity at each pH, and should be a priority for future research.

4. Conclusions and Prospective

We investigate the role of electrostatic interactions in the charge regulation and ionization constant of polyacids, using a model that describes the protonation and cation binding to polyacids as reversible reactions. The contribution of the electrostatic interactions to protonation (and cation binding) is obtained through an electrostatic free energy contribution. Using the simplest Debye-Hückel (DH) free energy, the prediction matches that from the Henderson-Hasselbakch (HH) theory of *monoacids* (at low polyacid concentrations), because at the DH level, neither chain connectivity nor higher order correlations are taken into account, and therefore, each polyacid monomer deprotonates with the same (intrinsic) strength, without regard to the electrostatic repulsions in the polyacid chain.

To remedy the deficiencies of the DH theory, we incorporated into the model a random phase approximation (RPA) that captures the effect of polyacid chain connectivity on the electrostatic correlations [26]. From this, we determined the *effective* ionization constant of polyacids with various configurations, and rationalized their charge regulation behavior based on the electrostatic repulsions (or self-energy) in the chain:

- With rodlike chain configuration, used for PAA chains which have negligible intrinsic hydrophobicity, the model yields a gradual increase of the (effective) ionization constant pK_A^{eff} with the degree of deprotonation, α_A . This increase in the ionization constant with α_A originates from the rise in the electrostatic repulsions between deprotonated monomers in the chain, which disfavors further deprotonation and leads to an accumulating "resistance" to deprotonation.
- A polyacid with Gaussian coil configuration, on the other hand, exhibits a significantly higher ionization constant in its titration than does a rodlike chain. The high resistance of the Gaussian polyacid to deprotonation arises from the fact that for a given degree of ionization, the electrostatic repulsions in the Gaussian polyacid are much stronger than in rodlike polyacids, and hence, to relieve these repulsions, the polyacid suppresses the dissociation of protons from the monomers more strongly. PAMPS, although a sulfonate-based polyacid, is an example of a compact polyacid, which behaves as a weak polyacid by manifesting an unusually high ionization constant.

By comparing the titration curves of PAMPS and PAA as well as those of two other poly(alkylacrylic acid)s, namely PMA and PEA, we take the first step towards development of a unified theory for the charge regulation of polyacids. The resistance of a polyacid to deprotonation, reflected in the shift in the pK_A^{eff} from its intrinsic value to more positive values, mainly arises from the electrostatic correlations of the polyacid chain: the more compact the polyacid chain, produced for example by higher hydrophobicity, the more the chain resists deprotonation, and the more the polyacid behaves like a weak polyacid. Thus, increased proximity of acid groups in a polyacid causes higher electrostatic repulsion (and self-energy), which can be relieved by suppression of deprotonation.

This insight can help rationalize the observed shifts in the ionization constants of complex biomolecules, such as RNA, proteins, etc. For instance, our results support the intuition of Honig and coworkers, who proposed that local proximity of the phosphate groups in RNA is responsible for elevation of the ionization constant of the macromolecule [14]. In parallel, Imoto et al. concluded that the hydrophobic environment of Glutamic acid in lysozyme contributes to an abnormally high ionization constant for the protein [59].

Thus, including the chain structure in electrostatic correlations allows us to capture the important trends in the charge regulation data of polyacids. Clearly, there are limitations in our work, including uncertainties in our parameter values, and most importantly our assumption of a fixed structure factor for polyacid configurations and the neglect of higher order electrostatic fluctuations, which are inherent to the RPA approach. Extending the theory to include an adaptive chain structure that self-adjusts in response to both ionization and intrinsic hydrophobicity of the chain will allow the model to be tested more precisely, and should lead eventually to accurate predictions without the need to preselect a fixed chain structure. An exciting, alternative idea is to extract chain structures from neutron scattering and/or molecular simulations and feed them into the RPA. Another possibility is to incorporate our charge regulation formulism in the model of Szleifer and co-workers [24,30,44,60]. In this way, not only would one be able to find an optimum structure from their model, given that a minimization of free energy is performed over all available configurations, but also the electrostatic correlations among ionizable groups in PE chains should be more accurately captured. In fact, this approach could be easily generalized to account for charge regulation of weak polyelectrolytes under different conditions, thus, introducing new research directions into this field.

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Declaration of Interests

There is no conflict of interest to be considered.

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5. Appendix

The contributions of electrostatic interactions to the equilibrium constants in Equations (14) - (16) can conveniently be obtained through the derivative of electrostatic free energy f^{corr} with respect to the extent of the reactions [26,61],

$$\mu_{ij}^{\rm corr} = \frac{\omega_i}{\phi_i} \partial f^{\rm corr} / \partial \xi_{ij} \tag{A1}$$

Here, the extent of reaction ξ_{ij} denotes α_{AH} , α_{AS} , or $\xi_W = \phi_W^0 - \phi_W$, and hence, $\mu_{ij}^{corr} = \mu_{AH}^{corr}$, μ_{AS}^{corr} or μ_W^{corr} , respectively. Depending on the expression for f^{corr} , its contribution to the equilibrium constants varies.

Within the Debye-Hückel (DH) free energy, i.e. $f^{\text{corr}} = f^{\text{DH}}$ given in Equation (21), one obtains,

$$\mu_{\rm AH}^{\rm corr,DH} = \mu_{\rm AS}^{\rm corr,DH} = -\mu_{\rm W}^{\rm corr,DH} = \bar{\kappa} \frac{l_{\rm B}}{\ell}$$
(A2)

with $\bar{\kappa}$ denoting the nondimensional inverse Debye length, given in the main text. The equality of the magnitude of the three contributions in Equation (A2) is not surprising, as it reflects the absence of chain connectivity within the DH free energy. Of course, since $\alpha_A = 1 - \alpha_{AH}$, the contribution of the DH to deprotonation is simply the negative of that for protonation, i.e. $\mu_A^{\text{corr,DH}} = -\mu_{AH}^{\text{corr,DH}}$.

Alternatively, one can feed the RPA free energy into the model. The RPA approach treats the electrostatic correlations up to the 2nd order in electrostatic fluctuations, hence capturing pair correlation functions and chain structure factors [19]. Using the RPA free energy given in Equation (12) yields,

$$\mu_{\rm AH}^{\rm corr} = \frac{\omega_{\rm A}}{\phi_{\rm A}} \frac{\partial f^{\rm corr}}{\partial \alpha_{\rm AH}}$$
$$= -\int_0^\infty \frac{1}{\pi} \cdot \frac{l_{\rm B}}{\ell} \left(2N_{\rm A} \sigma_{\rm A} \hat{\Gamma}^2(q, a_{\rm A}) \, g_{\rm D}(x) + \hat{\Gamma}^2(q, a_{\rm H_3O^+}) \right) / \left(1 + \frac{\tilde{k}^2(q)}{q^2} \right) \, \mathrm{d}q \tag{A3}$$

$$\mu_{\rm AS}^{\rm corr} = \frac{\omega_{\rm A}}{\phi_{\rm A}} \frac{\partial f^{\rm corr}}{\partial \alpha_{\rm AS}}$$
$$= -\int_0^\infty \frac{1}{\pi} \frac{l_{\rm B}}{\ell} \left(2N_{\rm A} \sigma_{\rm A} \hat{\Gamma}^2(q, a_{\rm A}) \, g_{\rm D}(x) + \hat{\Gamma}^2(q, a_{\rm S^+}) \right) / \left(1 + \frac{\tilde{k}^2(q)}{q^2} \right) \, \mathrm{d}q \tag{A4}$$

and,

$$\mu_{W}^{\text{corr}} = \frac{\omega_{A}}{\phi_{A}} \frac{\partial f^{\text{corr}}}{\partial \xi_{W}}$$
$$= \int_{0}^{\infty} \frac{1}{\pi} \cdot \frac{l_{B}}{\ell} \left(\hat{\Gamma}^{2}(q, a_{H_{3}O^{+}}) + \hat{\Gamma}^{2}(q, a_{OH^{-}}) \right) / \left(1 + \frac{\tilde{k}^{2}(q)}{q^{2}} \right) dq$$
(A4)

The contribution of electrostatic correlations generally promotes ion bindings (or opposes ion dissociations), because upon ion binding, the electrostatic repulsions between like charge ions are relieved, leading the system to reach a more favorable state. This can be clearly seen in Equations (A3) and (A4), where a negative sign before

the integral enhances ion binding [26]; especially, μ_A^{corr} (= $-\mu_{AH}^{\text{corr}}$) is positive based on Equation (A3), showing the unfavourability of deprotonation due to electrostatic interactions.

Within the RPA, a fixed structure factor for the polyacid is employed. To model the polyacid chain as a rod with length *L*, we use the structure factor, $g_D(x) = \frac{2}{x} \int_0^x \left(\frac{\sin(t)}{t} - \frac{1 - \cos(x)}{x}\right) dt$ with x = qL, which at high *q* reduces to $g_D(x) = \pi/x$. To model the compact configuration of polyacids, one can use the Gaussian coil configuration with the structure factor: $g_D(x) = 2(x - 1 + e^{-x})/x^2$. Here, $x = q^2 R_g^2$ and R_g is the radius of gyration of the Gaussian coil $(R_g^2 = N_A b^2/6)$, with *b* being the Kuhn length of the polyacid) [62]. Alternatively, the structure factor of a compact globule can be approximated by that of a homogeneous sphere: $g_D(x) = 9(\sin x - x \cos x)^2/x^6$ with x = qR and *R* being the radius of the sphere. In Figure 3, we find this radius simply by equating the volume of the sphere with that of a polyacid chain.

Supporting Information (SI)

The Supporting Information is available free of charge at DOI:

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