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Estimation of pK_a shifts in weak polyacids using a simple molecular model: effects of strong polybases, hydrogen bonding and divalent counterion binding

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Abstract

The pK_a values of ionizable groups in macromolecules can be significantly different than those of the isolated groups in solution. We have estimated theoretically the changes in the dissociation constant of a weak acid (*a*) in the vicinity of another ionizable group (*b*) on the basis of the theoretical approach by Hill (J. Am. Chem. Soc. 78 (1956) 3330) for matching pairs of interacting sites on two large molecules. Three cases are considered for group *b*: the strong base, the same weak acid as group *a* with hydrogen bonding between them, and the same weak acid as group *a* with divalent counterion binding. The pK_a shifts are evaluated in each case as a function of the interaction energy between the two ionizable groups and the external salt concentration. The theoretical results provide qualitative explanations for the pK_a shifts observed in many experimental systems with weak polyacids (polyampholyte systems like gels and ion exchange membranes, polyelectrolyte multilayers and biological membranes).

1. Introduction

The pK_a values of ionizable groups in macromolecules can be significantly different than those of the isolated groups in solution because of interactions between neighboring ionizable groups, solvation effects, and conformational changes. The electrostatic interactions between negative and positive fixed charge groups are responsible for many of the observed phenomena in amphoteric surfaces [1], polyampholyte systems like gels [2], membranes [3] and conducting polymers [4,5], and polyelectrolyte multilayers [6–8]. Electrostatic interactions play also a key role in the determination of the pK_a values of the acid and basic residues that control the permeability of ion channels to charged solutes [9,10]. Weakly acid and basic groups are of particular importance because the charge balance (and then the ionic selectivity of the system) can be controlled by the pH and salt concentration of the external solution [2,3,8,10]. Therefore, the theoretical estimation of the apparent dissociation constant of a weak polyacid in the vicinity of a basic group is of great interest for the above systems.

The effective pK_a of an acid group can also be changed due to hydrogen bonding interactions [11–13]. Protonated fatty acids appear to form stable acid–anion pairs with deprotonated fatty acids through strong hydrogen bonds [11]. The resultant acid-anion dimer has a single negative charge shared by the four oxygens of the headgroups, and the two apparent pK_a values of the resulting dimer are significantly different from the pK_a^0 of the monomer [11]. Also, when polyampholyte copolymer gels with randomly distributed strongly basic and weakly acid fixed charge groups are immersed in an electrolyte aqueous solution, hydrogen bonding between two neutral acid groups may appear [12,13]. This effect must be taken into account in the modeling of the swelling equilibrium of the gel [13], and leads to an effective dissociation constant of the acid in the collapsed gel lower than that in absence of hydrogen bonding. Divalent ion binding is also reported to shift the pK_a of the polyacid groups in ion exchange fibers used for controlled drug delivery [14,15] and lipid bilayers [16].

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The calcium binding appears to reduce the interaction between neighboring acid groups, and thus the apparent pK_a of the weak acid is significantly decreased in the presence of added calcium. This pK_a shift may affect the drug release from the ion exchange fiber [14,15].

We consider here a simple molecular model to estimate the pK_a shifts of a weak acid *a* close to another ionizable group *b* which is based on Hill's theory for matching pairs of interacting sites on two large molecules [17,18]. This approach has the advantage of simplicity at the price of introducing a limited amount of structural information and provides some molecular background for the empirical dissociation constants used in thermodynamic studies concerning weak polyacids in polyelectrolyte multilayers [8]. The wide applicability of the model is shown here in three case studies for group *b* that are relevant to many experimental systems [2–16]. In the first case, this group is a strong base interacting electrostatically with the weak polyacid group *a*. In the second and third cases, groups *a* and *b* are constituted by the same weak acid, and the effects of hydrogen bonding interactions and divalent counterion binding on the apparent pK_a of the polyacid are analyzed. The pK_a shifts are evaluated as a function of the interaction energy between the two relevant groups and the external salt concentration, and the theoretical results are compared qualitatively with previous experimental data. Although some of the above cases were considered in the original study by Hill, not all of the relevant states for the matching pairs were taken into account [17]. More recent, related work addressing the cooperative aspects of the binding of particles to two-site experimental systems different from those considered here has been carried out by Hill [19] and Ben-Naim [20,21].

2. Theoretical approach

We assume that the pK_a shifts of the weak polyacid can be estimated by considering only the interactions between the two relevant ionizable groups located on two large molecules. These interacting groups are treated as independent pairs of binding sites uniformly distributed in the system. Conformational changes, solvent effects, and the particular nature of the hydrocarbon chain of the polyacid are not considered. Finally, the interaction energies are input parameters of the model and no attempt is made to obtain them from local dielectric constants and effective interaction distances. Some of the effects ignored here have previously been explored by Ben-Naim [20,21] and Hill [17–19].

In each of the cases considered here, the different terms in the grand partition are obtained from the relevant states for the hydrogen and salt ions occupation of groups *a* an *b*, which are assumed to constitute effective binding sites for the mobile ions. The matching charge state is energetically favored respect to other manners of occupation of the groups and all the microscopic states are averaged over to obtain the properties of the system using the statistical thermodynamics formalism of the grand partition function [19–21]. The pH and salt concentration values within the polyelectrolyte system are assumed to be equal to those in the external solution, an admittedly crude assumption due to the presence of fixed charges [2,22]. Finally, we consider p$K_a^0 = 4$ for the free polyacid dissociation in aqueous solution in all cases.

2.1. Polybase effects

The four relevant states for the hydrogen and salt ions (sodium and chloride here) occupation of the acid (carboxyl) *a* and basic (ammonium) *b* groups are shown in Fig. 1 together with the respective contributions to the grand partition. Note that the matching charge state is energetically favored by the interaction energy *u*. The particular value of pK_b is not relevant here: the basic (ammonium) group remains always protonated because p$K_b \gg$ pH for the pH range considered in the calculations. As to the salt ions, binding constants of sodium cations bound to carboxyl groups in different macromolecules appear to be in the range 0.1–10 M^{-1} [16,23,24]. For the sake of simplicity, we assume the same value p$K_c = 0.2$ for the binding of sodium to the carboxyl group and the binding of chloride to the ammonium group (see Fig. 1) which leads to $10^{pK_c} = 1.6\ M^{-1}$.

Note that although the model introduces an effective binding constant for the ion pair formed by the salt ions and fixed charge groups in Fig. 1, no particular molecular mechanism is invoked for this pair. It is likely that contact ion pairs between the fixed and mobile charges do not exist in some systems, and thus every salt ion will

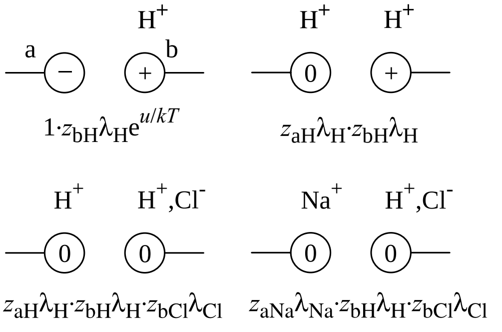

Fig. 1. The four relevant states for the hydrogen, sodium and chloride occupation of the acid (carboxyl) *a* and basic (ammonium) *b* groups together with the respective contributions to the grand partition function. The matching charge state is energetically favored by the interaction energy *u* respect to other manners of occupation of the sites.

still have some limited translation over the region close to the oppositely charged group. What the model assumes implicitly is that the proximity of the salt ion to the oppositely charged fixed charge effectively screens this charge. Therefore, increasing the salt concentration contributes to the effective neutralization of the fixed charge groups. (No continuous Debye screening [2] is invoked here because the distance between oppositely charged fixed groups could be relatively small.)

In principle, the system in Fig. 1 has a total number of $3 \times 3 = 9$ possible states: the acid group can be negatively charged (unprotonated) or in neutral form (either protonated or unprotonated but forming an ion pair with sodium) and the basic group can be positively charged (protonated) or in neutral form (either unprotonated or protonated but forming an ion pair with chloride). However, the requirements imposed by the series $\mathrm{p}K_\mathrm{c} < \mathrm{p}K_\mathrm{a}^0 < \mathrm{p}K_\mathrm{b}$ on the hydrogen and salt ions occupation of the groups together with the pH and salt concentration values considered here reduces the number of available states down to only 4 in practice. For example, the states with group *b* unprotonated but group *a* protonated can be neglected: they are highly unlikely because $\mathrm{p}K_\mathrm{a}^0 \ll \mathrm{p}K_\mathrm{b}$. Likewise, the state with a sodium bound to group *a* but no chloride bound to group *b* may also be excluded if the binding constants of the salt ions are assumed to be equal. Similar considerations apply to the other excluded states.

The states shown in Fig. 1 can now be averaged over to obtain the properties of the system using the statistical thermodynamics formalism of the grand partition function [19–21,25]. This leads to the different grand partition function contributions shown below each state in Fig. 1, where z_ij (i = a and b, j = H, Na and Cl) are the partition functions (including the binding energy) of ion j bound to site i and λ_H, λ_Na and λ_Cl are magnitudes proportional to the absolute activities of the ions. They are defined as [17,18] $z_\mathrm{aH}\lambda_\mathrm{H} = 10^{\mathrm{p}K_\mathrm{a}^0-\mathrm{pH}}$, $z_\mathrm{bH}\lambda_\mathrm{H} = 10^{\mathrm{p}K_\mathrm{b}-\mathrm{pH}}$, $z_\mathrm{aNa}\lambda_\mathrm{Na} = 10^{\mathrm{p}K_\mathrm{c}}c(\mathrm{M})$, and $z_\mathrm{bCl}\lambda_\mathrm{Cl} = 10^{\mathrm{p}K_\mathrm{c}}[c(\mathrm{M}) + 10^{-\mathrm{pH}}]$ where $c(\mathrm{M})$ and $[c(\mathrm{M}) + 10^{-\mathrm{pH}}]$ are the dimensionless sodium and chloride concentrations expressed in M units, respectively. Note that the term corresponding to an unoccupied group is taken as unity (a reference value) in Fig. 1 because this factor is not relevant in the model (see Eq. (2) below). The first state depicted in Fig. 1 corresponds to the matching charge state, which is energetically favored by a factor $\mathrm{e}^{u/kT} > 1$, where u is the interaction energy between oppositely charged groups, k is the Boltzmann constant and T is the absolute temperature, respect to other manners of occupation of the groups.

The fraction of protonated polyacid can be calculated from the grand partition function of the system q as $(1 - \alpha) = \lambda_\mathrm{H}(\partial \ln q/\partial\lambda_\mathrm{H})$, where q is given by the sum of all the terms shown in Fig. 1. In terms of pH and salt concentrations, the final results are

$$q = 10^{\mathrm{p}K_\mathrm{b}-\mathrm{pH}}\mathrm{e}^{u/kT} + 10^{\mathrm{p}K_\mathrm{a}^0+\mathrm{p}K_\mathrm{b}-2\mathrm{pH}} + 10^{\mathrm{p}K_\mathrm{a}^0+\mathrm{p}K_\mathrm{b}+\mathrm{p}K_\mathrm{c}-2\mathrm{pH}}[c(\mathrm{M}) + 10^{-\mathrm{pH}}] + 10^{\mathrm{p}K_\mathrm{b}+2\mathrm{p}K_\mathrm{c}-\mathrm{pH}}c(\mathrm{M})[c(\mathrm{M}) + 10^{-\mathrm{pH}}] \quad (1)$$

and

$$\alpha = [\mathrm{e}^{u/kT} + 10^{2\mathrm{p}K_\mathrm{c}}c(\mathrm{M})[c(\mathrm{M}) + 10^{-\mathrm{pH}}]]10^{\mathrm{p}K_\mathrm{b}-\mathrm{pH}}/q \quad (2)$$

for the fraction of unprotonated polyacid. Note that the factor $10^{\mathrm{p}K_\mathrm{b}-\mathrm{pH}}$ in Eq. (1) cancels out in the ratio of Eq. (2). Finally, the fraction of unprotonated free polyacid in aqueous solution is given by

$$\alpha = 1/(1 + 10^{\mathrm{p}K_\mathrm{a}^0-\mathrm{pH}}). \quad (3)$$

The present model extends the original study by Hill [17] by considering pH and salt effects simultaneously in Eqs. (1) and (2).

2.2. Hydrogen bonding effects

The states for hydrogen occupation of the two acid (carboxyl) *a* and *b* groups are shown in the highly idealized scheme of Fig. 2. The respective contributions to the grand partition function are included below each state. The matching hydrogen bond state is energetically favored by the interaction energy *v* respect to other manners of occupation of the groups. The state with charges of the same sign is discouraged by a factor $\mathrm{e}^{-u/kT}$. For simplicity, no salt effects are considered in this case. Related work addressing the cooperative aspects of the binding of particles to two-site systems has previously been carried out by Hill [19] and, especially, by Ben-Naim who considered the influence of the hydrocarbon chain on the apparent $\mathrm{p}K_\mathrm{a}$ of a weak acid group as well as the correlations between the groups

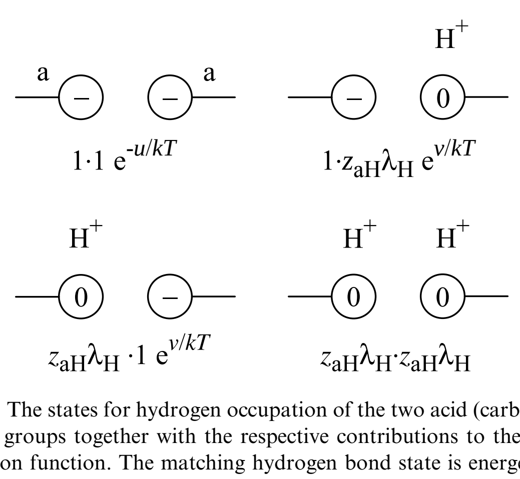

Fig. 2. The states for hydrogen occupation of the two acid (carboxyl) *a* and *b* groups together with the respective contributions to the grand partition function. The matching hydrogen bond state is energetically favored by the interaction energy *v* respect to other manners of occupation of the sites. The state with charges of the same sign is discouraged by the factor $\mathrm{e}^{-u/kT}$. If hydrogen bonding between the neutral groups –COOH and –COOH is more likely than between the groups –COOH and $–\mathrm{COO}^-$, then the energy factor $\mathrm{e}^{v/kT}$ will favor the fourth state instead of the second and third states.

present in dicarboxylic acids, diamines and amino acids [20].

The fraction of protonated polyacid can be calculated from the grand partition function of the system q as $(1-\alpha) = (1/2)\lambda_H(\partial \ln q/\partial\lambda_H)$, where q is given by the sum of all the terms shown in Fig. 2. In terms of pH and salt concentrations, the final results are

$$q = e^{-u/kT} + 2\cdot 10^{pK_a^0-pH}e^{v/kT} + 10^{2(pK_a^0-pH)} \tag{4}$$

and

$$\alpha = (e^{-u/kT} + 10^{pK_a^0-pH}e^{v/kT})/q \tag{5}$$

for the fraction of unprotonated polyacid.

Let us consider now a different (but related) case. If hydrogen bonding between the neutral groups –COOH and –COOH is more likely than between the groups –COOH and –COO$^-$, then the energy factor $e^{v/kT}$ will favor the fourth state instead of the second and third states in Fig. 2. Therefore, the grand partition function for this new case is

$$q = e^{-u/kT} + 2\cdot 10^{pK_a^0-pH} + 10^{2(pK_a^0-pH)}e^{v/kT} \tag{6}$$

and the fraction of unprotonated polyacid is now

$$\alpha = (e^{-u/kT} + 10^{pK_a^0-pH})/q. \tag{7}$$

Compare Eqs. (4) and (5) with Eqs. (6) and (7), respectively.

2.3. Divalent cation binding effects

The states for hydrogen and calcium occupation of the two acid (carboxyl) a and b groups are shown in Fig. 3 together with the respective contributions to the grand partition function. Analogously to the first case, we define $z_{aCa}\lambda_{Ca} = 10^{pK_c}c(M)$ where $c(M)$ is now the dimensionless calcium concentration (expressed in M units). The matching charge state is energetically favored by the interaction energy u respect to other manners of occupation of the sites. The state with charges of the same sign is discouraged by the factor $e^{-u/kT}$. For simplicity, no hydrogen bonding effects are considered in this case. The model of Fig. 3 extends previous work by Hill [17] by including the pH effects on the counterion binding.

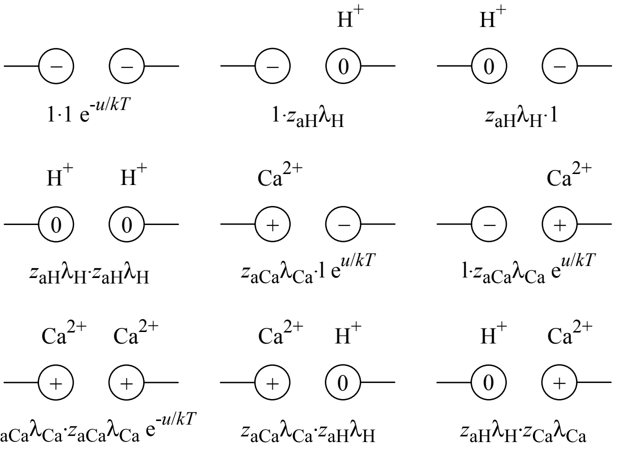

Fig. 3. The states for hydrogen and calcium occupation of the two acid (carboxyl) a and b groups together with the respective contributions to the grand partition function. The matching charge state is energetically favored by the interaction energy u respect to other manners of occupation of the sites. The state with charges of the same sign is discouraged by the factor $e^{-u/kT}$.

The fraction of protonated polyacid can be calculated from the grand partition function of the system q as $(1-\alpha) = (1/2)\lambda_H(\partial \ln q/\partial\lambda_H)$, where q is given by the sum of all the terms shown in Fig. 3. In terms of pH and salt concentrations, the final results are

$$\begin{aligned} q = {} & e^{-u/kT} + 2\cdot 10^{pK_a^0-pH} + 10^{2(pK_a^0-pH)} \\ & + 2\cdot 10^{pK_c}c(M)e^{u/kT} + [10^{pK_c}c(M)]^2e^{-u/kT} \\ & + 2\cdot 10^{pK_a^0-pH}10^{pK_c}c(M) \end{aligned} \tag{8}$$

and

$$\begin{aligned} \alpha = {} & [e^{-u/kT} + 10^{pK_a^0-pH} + 2\cdot 10^{pK_c}c(M)e^{u/kT} \\ & + [10^{pK_c}c(M)]^2e^{-u/kT} + 10^{pK_a^0-pH}10^{pK_c}c(M)]/q \end{aligned} \tag{9}$$

for the fraction of unprotonated polyacid. Calcium is known to adsorb strongly to carboxyl groups with binding constants in the range 1–10^3 M^{-1} [14–16]. We will assume $pK_c = 1$, which leads to a binding constant $10^{pK_c} = 10$ M^{-1}.

3. Results and discussion

Fig. 4 shows the calculated fraction α of unprotonated polyacid vs. the solution pH when group b is a

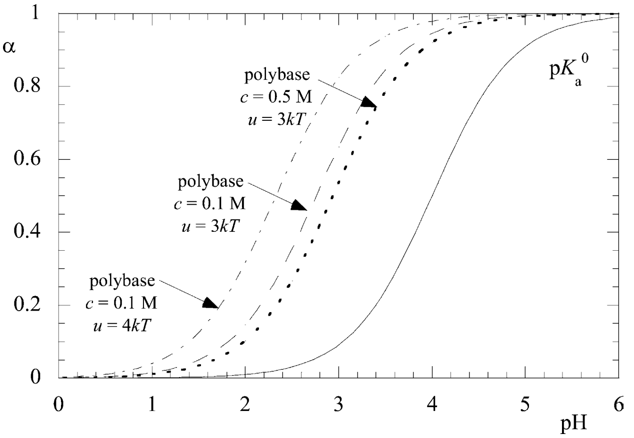

Fig. 4. The calculated fraction α of unprotonated polyacid vs. the solution pH when group b is a strong base. In the pK_a^0 curve α is calculated from Eq. (3) for the free polyacid dissociation in aqueous solution. The other curves correspond to the weak polyacid in the vicinity of the basic (ammonium) group for two NaCl concentrations, $c = 0.1$ and 0.5 M, and two electrostatic interaction energies, $u = 3kT$ and $4kT$, with $pK_a^0 = 4$ and $pK_c = 0.2$.

strong base. In the curve denoted by pK_a^0, α is calculated from Eq. (3) for the free polyacid dissociation in aqueous solution. The other curves correspond to the weak polyacid group in the vicinity of the basic (ammonium) group. In this case, α is calculated from Eq. (2) with $pK_c = 0.2$ for two NaCl concentrations, $c = 0.1$ and 0.5 M, and two electrostatic interaction energies, $u = 3kT$ (7.5 kJ/mol at $T = 300$ K) and $4kT$ (10 kJ/mol at $T = 300$ K). The values of u could simulate, e.g. different hydrophobic environments for the ionizable groups [8].

The theoretical results obtained using Eqs. (1)–(3) can now be compared with recent experiments concerning polyelectrolyte multilayers [6–8]. The experimental data (see, in particular, Fig. 1 of [8]) show that when a monolayer incorporating a strongly dissociated quaternary ammonium polycation is combined with the original monolayer incorporating a weak polycarboxylic acid to form a polyelectrolyte multilayer, the measured titration curve is shifted by 1.1 pH units relative to the free polyacid in aqueous solution. Indeed, the creation of a negatively charged group in the polyacid makes possible the formation of an energetically favorable ion pair with the ammonium and, since protonation removes this interaction, the polyacid in the multilayer should be more difficult to protonate (the apparent pK_a decreases with respect to that of the free polyacid in aqueous solution [8]). However, when the multilayer is immersed in a 0.5 M instead of the original 0.1 M NaCl solution, the new titration curve is shifted by only 0.75 pH units relative to the free polyacid in aqueous solution: increasing the salt concentration causes the number of polyelectrolyte ion pairs to decrease because more charged groups in the polymers are now compensated by the respective salt counterions (see Fig. 1). Therefore, the number of energetically favorable polymer/polymer ion pairs decreases and this makes the acidity of the polyacid to decrease, which explains the now positive shift in the apparent pK_a respect to the the case of the multilayer in a 0.1 M NaCl solution [8]. The theoretical curves of Fig. 4 reproduce qualitatively these experimental trends.

If a more hydrophobic polyelectrolyte incorporating positively charged groups is combined with the original weak polycarboxylic acid to form the multilayer, the measured titration curve is shifted now by 1.5 pH units relative to the free polyacid in aqueous solution: the ammonium and carboxyl groups are solvated by water, a highly favorable interaction for these fixed charges, and the relatively low water content of the new multilayer is expected to give more tightly bound ion pairs in comparison with the more hydrophilic original multilayer [8]. In the present model, this effect is simulated by the interaction energy of the first state in Fig. 1, which is increased from $u = 3kT$ to $4kT$ in the respective theoretical curves of Fig. 4. The apparent pK_a of the polyacid is thus shifted to even lower values in the case of the more hydrophobic multilayer. Therefore, the theoretical results of Fig. 4 reproduce the observed phenomena, that were previously analyzed on the basis of a thermodynamic formalism based on empirical equilibrium constants [8], providing additional molecular insights. Some electrostatic effects reported recently for the ionization and acid–base equilibria of weak polyelectrolytes in multilayer thin films [6,7] could also be qualitatively understood on the basis of the results in Fig. 4.

Estimation of the interaction energies from the local dielectric constants and effective interaction distances [17,20,21] characteristics of each experimental system could improve the applicability of the model. However, the fact is that in addition to the decrease in the coulombic energy due to the formation of ion pairs, other factors may also influence the monolayer formation and stability [6–8] (in particular, the entropy increase associated to the liberation of the small mobile counterions following ion pairing between the oppositely charged groups in the polyelectrolytes and the hydrophobic interaction between polymer segments [26]).

Fig. 5 shows the calculated fraction α of unprotonated polyacid vs. the solution pH when groups *a* and *b* are the same weak acid and hydrogen bonding effects are present. As in Fig. 4, the curve denoted by pK_a^0 makes reference to the free polyacid in aqueous solution. The other curves are calculated from Eq. (5) (dashed curve) and Eq. (7) (dotted curve) and include the effect of the hydrogen bonding between the ionized and neutral acid groups and between two neutral acid groups, respectively. In both cases, the hydrogen bonding energy is

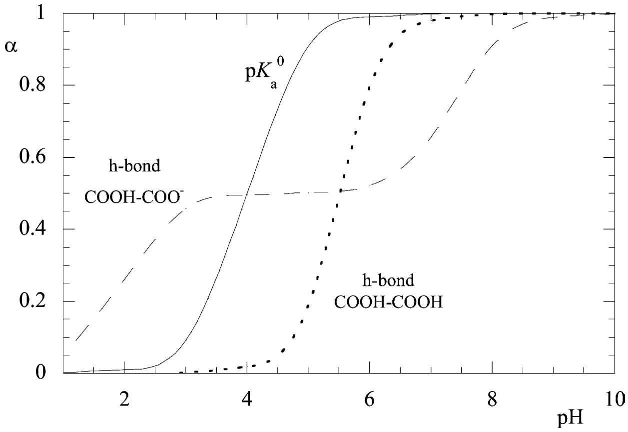

Fig. 5. The calculated fraction α of unprotonated polyacid vs. the solution pH when groups *a* and *b* are the same weak acid and hydrogen bonding interactions are present. The pK_a^0 curve corresponds to the free polyacid in aqueous solution while the other curves show the effect of the hydrogen bonding between the ionized and neutral acid groups (α calculated from Eq. (5), dashed curve) and between two neutral acid groups (α calculated from Eq. (7), dotted curve). In both cases, the hydrogen bonding energy is $v = 4kT$ and the electrostatic interaction energy is $u = 3kT$ with $pK_a^0 = 4$.

$v = 4kT$ (10 kJ/mol at $T = 300$ K) and the electrostatic interaction energy is $u = 3kT$.

The theoretical results of Fig. 5 can be compared with relevant experimental data. It has been proposed that anionic lipid headgroups form a proton-conducting pathway along the surface of biological membranes [11]. Studies on the protonation states of the fatty acids of liposomes with entrapped water showed that the bilayer contains mixtures of protonated and deprotonated carboxylates. The protonated fatty acids appear to form stable acid-anion pairs with deprotonated fatty acids through strong hydrogen bonds. The resultant acid–anion dimer has a single negative charge shared by the four oxygens of the headgroups, and the two apparent pK_a values of the resulting dimer are significantly different from the pK_a^0 of the monomer, so that the dimer is stable over a wide pH range [11]. The results of Fig. 5 can provide a simple theoretical justification for this behavior (compare the full curve resulting from Eq. (3) with the dashed curve resulting from Eq. (5)), although it must be mentioned that electronic effects in the chain length of the polyacid [20,27] and phase transitions [11] not taken into account here may also influence the apparent pK_a values observed.

A different situation appears when hydrogen bonding between the neutral groups –COOH and –COOH is more likely than between the groups –COOH and $–COO^-$, since in this case the factor $e^{v/kT}$ will favor the fourth state instead of the second and third states in Fig. 2. This could be the case when a polyampholyte copolymer gel with randomly distributed strongly basic and weakly acid fixed charge groups is immersed in an electrolyte aqueous solution [12,13]. For instance, acrylic acid can form hydrogen bonds to another acrylic acid. If the solution contains enough salt cations to compensate for the ionized acid groups, hydrogen bonding between two neutral groups may appear [12], and this bonding changes the swelling equilibria of the gel [13]. The result of this interaction is that the effective dissociation constant of acrylic acid in the collapsed gel decreases significantly respect to the value in absence of hydrogen bonding and, therefore, the apparent pK_a increases. This is indeed the effect shown by the theoretical results: compare the full curve, obtained with Eq. (3), with the dotted curve, obtained with Eq. (7), in Fig. 5.

Fig. 6 shows the calculated fraction α of unprotonated polyacid vs. the solution pH when groups a and b are constituted by the same weak acid group in presence of counterion binding. Again, the pK_a^0 curve corresponds to the free polyacid in aqueous solution. The pK_a curve is obtained from Eq. (9) with $c = 0$, and includes therefore the electrostatic repulsion between ionized acid groups (see Fig. 3). Finally, in the dotted curve α is calculated from Eq. (9) with $c = 0.1$ M to show the effect of counterion binding to the ionized acid group. The calcium binding constant is $10^{pK_c} = 10$ M^{-1} and the electrostatic interaction energy is $u = 3kT$.

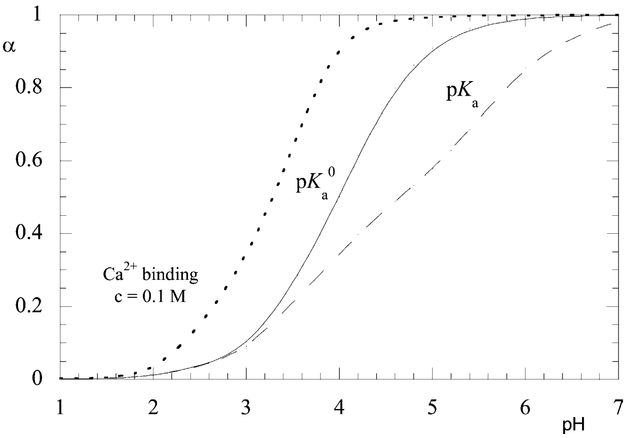

Fig. 6. The calculated fraction α of unprotonated polyacid vs. the solution pH when groups a and b are the same weak acid group in presence of counterion binding. Again, α is calculated from Eq. (3) for the free polyacid dissociation in aqueous solution in the pK_a^0 curve. The pK_a curve includes the effect of the electrostatic repulsion between ionized acid groups (α is calculated from Eq. (9) with $c = 0$). Finally, the dotted curve shows the effect of counterion binding to the ionized acid group (α is calculated from Eq. (9) with $c = 0.1$ M). The calcium binding constant is $10^{pK_c} = 10$ M^{-1} and the electrostatic interaction energy is $u = 3kT$ with $pK_a^0 = 4$.

Some ion exchange fibers of potential use in controlled drug delivery incorporate carboxylic acid groups and the effect of divalent ions on the release of model drugs is important [14,15,28]. The calcium binding to the ionized polyacid group is relatively strong, and can reverse the sign of the fixed charge attached to the polymer chains at high enough concentrations. (This effect has also been confirmed in synthetic nanopores that display some of the ionic transport characteristics of biological ion channels [29,30].) It has been shown that the binding interaction of calcium with some polyacrylic acid polymers is pH dependent and apparently related to an ionic interaction with the ionized carboxylate groups in the polymer [28]. The calcium binding appears to reduce the interaction between neighboring acid groups, and thus the apparent pK_a of the polyacrylic acid is significantly decreased in the presence of added calcium, approaching the intrinsic pK_a of monomeric acrylic acid (see in particular Table 2 of [28]).

The idealized molecular model of Fig. 3 together with the theoretical curves of Fig. 6 provide qualitative explanations for the above phenomena. Fig. 6 shows that the electrostatic repulsion between ionized acid groups (α calculated from Eq. (9) with $c = 0$, dashed curve) decreases the acidity of the ionizable group: the apparent pK_a increases respect to the case of the free polyacid in aqueous solution. On the contrary, addition of calcium followed by counterion binding to the ionized acid group changes the sign of this electrostatic interaction facilitating thus the ionization of the neighboring acid group (α calculated from Eq. (9) with $c = 0.1$ M, dotted curve). The model predicts that the apparent pK_a could be now even lower than pK_a^0 for high enough calcium concentrations because the attractive interaction between the negative (dissociated) and positive (bound to a divalent cation) acid groups stabilizes both deprotonated forms.

4. Conclusions

A simple molecular model based on Hill's theory for matching pairs of interacting sites on two large molecules has been used to estimate the pK_a shifts of a weak acid *a* in the vicinity of another ionizable group *b*. Three cases of great experimental relevance are considered for group *b*. In the first case, *b* is a strong basic group interacting electrostatically with the weak acid group *a*. In the second and third cases, groups *a* and *b* are the same weak acid, and the effects of hydrogen bonding interactions and divalent counterion binding on the effective pK_a of the polyacid are analyzed. The pK_a shifts are evaluated as a function of the interaction energy between the two relevant groups and the external salt concentration. It is shown that the theoretical results provide qualitative explanations for the pK_a shifts observed in experimental systems with weak polyacids (polyampholyte systems like gels and ion exchange membranes, polyelectrolyte multilayers and biological membranes). Future extensions of the model would be the inclusion of energy and entropy factors concerning the polyelectrolyte chains [26,27], the evaluation of the interaction energies as a function of the solvent and polyacid environments [19,20], and the estimation of the pH and salt concentration values in the polyelectrolyte system as a function of those in the external solution [2,22].

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