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Influence of Hofmeister Effects on Surface pH and Binding of Peptides to Membranes

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An understanding of local surface pH and binding of peptides to membranes is of interest for a number of biological processes. Ionic dispersion forces that give rise to Hofmeister effects have not previously been taken into account by theories. It is demonstrated that pH-changes near surfaces (e.g. membrane and mica) and binding of peptides to membranes depend on the specific ionic species. Near mica surfaces, the effect can be especially large: some anions, for example, Br^-, experience large attractive dispersion forces that can give rise to strong co-ion adsorption and enhanced pH-gradients. The concentration of hydronium ions at a model membrane surface is obtained from a modified nonlinear Poisson−Boltzmann equation that includes ionic dispersion potentials consistently. The fraction of ionizable surface groups is treated as a self-consistent functional of the electrostatic potential. We finally demonstrate that good agreement between theoretical and experimental binding energies of peptides to membranes requires ionic dispersion potentials that are consistent with our previous estimates based on surface tension of salt solutions.

I. Introduction

Electrostatics, screened by background salt solution, has an important role in biology, especially membrane biology.[1−3] For example, ionic strength and pH are thought to influence bacteria attachment to surfaces[4] and the invasive behavior of tumor cells.[5] It is known that the ionic environment near a biological cell surface often is very different from that of the bulk fluid.[1] It is the local surface pH, rather than bulk pH, that is relevant, for example, for membrane localized proteins such as rhodopsin.[6,7] pH near a surface depends on the pH of the reservoir, ionic strength, surface charge density, ion binding to ionizable groups, and valency of the background salt solution. Surface pH of some membranes can also be modified by phosphorylation.[6]

However, electrostatics is not the full story. It is often the case that dispersion forces on ions dominate, particularly at biological salt concentrations. With interacting membranes, such dispersion forces are included in Lifshitz theory through the dependence of bulk water refractive indices on salt concentration. But the usual DLVO decomposition of forces into electrostatic interactions, treated in a nonlinear theory, and dispersion forces treated in the (linear) Lifshitz theory is deficient. The theory is thermodynamically inconsistent and fails to deal with specific ion effects properly.[8−10] High-frequency correlations that give rise to ion specific dispersion effects are only weakly screened, and above 0.1 M salt can dominate electrostatic effects which are strongly screened in electrolyte solutions. The dispersion forces are dictated in part by the polarizabilities of the ions, which in turn are very ion specific. (It is important to point out that these ionic interaction potentials do not need to be "postulated". In fact, theory is thermodynamically inconsistent in their absence, and when they are included, Lifshitz theory follows after linearization[8]). We explore here how specific adsorption due to dispersion effects influences pH at membrane surfaces. Each species experiences different ionic dispersion potentials near an interface. These dispersion potentials influence both the self-consistent electrostatic potential and the pH-profile outside a membrane surface. Ion specific, or Hofmeister, effects[11,12] are common in biology. Examples abound: the surface tension of electrolytes,[13] forces between charged surfaces,[14,15] surface potentials,[16] ζ potentials of multilamellar vesicles,[17] pH values of buffer solutions,[18] bubble coalescence,[19] thermal stability,[20] and cutting efficiency[21] of peptide nucleic acid complexes all show marked specific ion effects. We have recently demonstrated that ionic dispersion potentials can explain ion specific effects that are found

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for the double-layer forces between charged surfaces across a salt solution,[9] and the surface tension of salt solutions,[8,10] and the ion specificity of micelles[22] and polyelectrolytes.[23] Dispersion forces have been neglected in the past, and it is only recently that their importance has been recognized.[8−10] Their omission of course is not the whole story. Other ion specific properties such as water structure, ion size, dielectric constant variation near the interface, and counterion and co-ion exclusion[24,25] are clearly also important, as may be the role of dissolved gas.[26] We focus here only on a demonstration of the qualitative effects arising from the previously neglected ionic dispersion potentials.

In this work we approximate pH by $-\log_{10}[H^+]$. In fact, pH depends on the activity coefficient,[18] rather than the molar concentration of hydronium ions ($[H^+]$). However, the purpose of this approximation is to highlight, with the simplest possible extension of existing theories, why the pH near membrane surfaces will be very ion specific. A more complete theory needs to acknowledge the fact that the activity coefficient of the bulk solution is also ion specific. Comparison of electrostatic theories with experimental activity coefficients, taking proper account of measured partial molar volumes, shows that the theory works more or less for alkali halides. The assumed "hard" hydrated radii of the primitive model that emerge do make sense. They are additive. However, they do not make sense for other ions such as NO_3^-, SO_4^{2-}, and Cs^+. The results for these ions are nonsensical because the hydrated radii that fit the measured activity coefficient over the entire concentration range are less than the bare ion radii. This can be accommodated by admitting an extra attractive ion specific potential.[27]

The paper is arranged as follows. The connection is made in section II between pH-changes near membrane surfaces and the charge regulated ion specific mean-field double-layer theory. It is an extension, to include specific ion effects, of previous work by Ninham and Parsegian[1] on the electrostatics outside membrane surfaces. Mean-field theories often describe membrane biology to a surprisingly good approximation. In section III we demonstrate with a few numerical examples that pH-gradients near membrane surfaces will have a large degree of ion specificity. The pH-microenvironment near a biological membrane is influenced by ionic dispersion potentials. The dispersion potential depends on the ionic excess polarizability but also on the dielectric properties of water and the membrane. Thus, we also demonstrate that otherwise similar membranes with different dielectric properties can have different pH-microenvironments. Our results should also have bearing for the understanding of chemical valves, that is, membranes where the permeability depends on pH and salt-concentration. We also note that measurements of pH with glass electrodes also involve interfaces. The origin of the measured ion specific pH[18] is not only changes in bulk activity but also ion specific changes in surface excess of the form predicted here. We demonstrate in section IV that there can be even stronger specific ion effects near, for example, mica surfaces. Attractive ionic dispersion potentials acting between the negatively charged mica surface and some anions may be strong enough to bind the anions to the interface. This co-ion adsorption gives rise to strongly enhanced pH-gradients near the interface. We discuss in section V how the modified Poisson−Boltzmann equation can also be used to calculate the binding energy of small basic peptides to acidic membranes. We demonstrate that good agreement between theoretical and experimental results[28] in fact requires that ionic dispersion forces are accounted for. The ionic dispersion potentials that can explain experimental data are furthermore consistent with previous estimates based on the surface tension of salt solutions. Finally, in section VI we end with a few concluding remarks.

II. Theory

Our model system consists of two identical membrane surfaces a distance $2L$ apart, interacting across a salt solution (a typical example in biological system is 0.156 M NaCl). This model system was chosen for both generality and computational convenience. At the moderately high (biological) salt concentrations that we are interested in, the surface hydronium concentration is only weakly influenced by the presence of the second surface. Both surfaces bear acidic ionizable surface groups with a surface density ρ_s. A fraction δ of these groups are dissociated,[1]

$$AH \rightarrow A^- + H^+ \tag{1}$$

Rather than stipulating a value for δ, it should be determined self-consistently.[1] The surface groups have an experimentally known effective dissociation constant,

$$Z = [H^+]_s \frac{\delta}{1-\delta} \tag{2}$$

and the surface concentration of hydronium ions follows a Boltzmann distribution,

$$[H^+]_s = [H^+]_r e^{-\beta[e\phi(s)+U_H(s)]} \tag{3}$$

where $[H^+]_r$ is the molar concentration of hydronium ions in the reservoir, e is the electric charge, $\phi(s)$ is the electrostatic potential at the surface, $\beta = 1/k_B T$, k_B is the Boltzmann constant, and T is temperature. In a general consideration, one must also take into account that the hydronium ions near an interface experience both image and ionic dispersion potentials (U_H). To focus on the influence of background salt, we neglect the influence of this interaction potential that acts on the hydronium ions. (For our purpose this can be viewed as a small shift of the effective bulk pH, $[H^+]_r e^{-\beta e\phi(s)+U_H(s)]} \rightarrow [H^+]_r$, which is of little relevance for the salt effects that we are focusing on here. The hydronium ion does not have any polarizable electrons. This means that the excess polarizability of a hydronium ion can be estimated from partial molar volume changes of water with added [HCl] and the polarizability of water.) To focus on the effects caused by ionic dispersion potentials, we furthermore neglect the differences in the ion radius, which we take to be 2 Å for all ions.

The expression for the surface charge ($\sigma = -e\delta\rho_s$) depends on the surface potential and must be determined

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self-consistently with the nonlinear Poisson−Boltzmann equation,

$$\frac{d^2\phi}{dx^2} = -e(c_+ - c_-)/(\epsilon_w\epsilon_0) \quad (4)$$

$$\frac{d\phi}{dx_s} = -\sigma/\epsilon_w\epsilon_0 \quad (5)$$

The Poisson−Boltzmann equation is solved numerically using the method of relaxation, with the above boundary condition on the surfaces and the vanishing of the electric field in the midplane between the two surfaces. The ion concentrations are given by

$$c_\pm = c_0 \exp[-\beta(\pm e\phi + U_\pm)] \quad (6)$$

Here c_0 is the bulk salt concentration and ϵ_w is the dielectric constant of water. The salt concentration is assumed to be larger than $[H^+]$ by many orders of magnitude. This is a very good approximation in the biological regime that we are interested in here, but it is less accurate at low salt concentrations. $U_\pm$ is the ionic interaction potential that receives contributions from the ionic dispersion potential,[9]

$$U_{dispersion}(x,2L) \approx \left[\frac{B_\pm}{x^3} + \frac{B_\pm}{(2L-x)^3}\right] \quad (7)$$

and from the image potential

$$U_{image}(\kappa,x,2L) \approx \frac{e^2(S_1+S_2)}{16\pi\epsilon_w\epsilon_0} \quad (8)$$

where

$$S_1 = -\ln[1-\Delta^2\exp(-4\kappa L)]/L \quad (9)$$

$$S_2 = \Delta^{-1}\sum_{p=1}^{\infty}\left\{\frac{e^{-2\kappa[2L(p-1)+x]}}{2L(p-1)+x} + \frac{e^{-2\kappa(2Lp-x)}}{2Lp-x}\right\} \quad (10)$$

Here $\Delta \equiv (\epsilon_w-\epsilon_m)/(\epsilon_w+\epsilon_m) \approx 1$, with ϵ_m being the dielectric constant of the membrane. The inverse Debye length is $\kappa_D = [(2\beta e^2 c_0)/(\epsilon_0\epsilon_w)]^{1/2}$.

The dispersion coefficients ($B_\pm$) can be calculated in a standard way as a sum over imaginary frequencies ($i\omega_n = i2\pi k_B T n/\hbar$, where $\hbar$ is Planck's constant):[8]

$$B_\pm = \sum_{n=0}^{\infty}\frac{(2-\delta_{n,0})\alpha^\pm(i\omega_n)[\epsilon_w(i\omega_n)-\epsilon_m(i\omega_n)]}{4\beta\epsilon_w(i\omega_n)[\epsilon_w(i\omega_n)+\epsilon_m(i\omega_n)]} \quad (11)$$

$$\alpha_\pm(i\omega_n) = \alpha_\pm(0)/(1+\omega_n^2/\omega_\pm^2) \quad (12)$$

We recently showed that the surface tensions of different salts could be accommodated when ionic dispersion potentials were accounted for.[10] The result was at high concentrations to some extent additive for the dispersion contributions, and it is not straightforward to obtain an unique set of dispersion coefficients. The increment of the refractive index of water when a salt solution is added is different for different salt solutions.[29] The refractive index of pure water is $n_w = 1.333$; when 1 g/L NaCl is added, the refractive index increase is $\delta n = 2 \times 10^{-4}$. The sum of static excess polarizabilities for Na^+ and Cl^- can then be estimated from the following approximation

$$\epsilon(0) \approx \epsilon_w(0) + 4\pi c_{ion}[\alpha_+(0)+\alpha_-(0)] \approx (n+\delta n)^2 \quad (13)$$

We find that the sum of static excess polarizability is approximately 4.1 Å^3. To find a simple estimate for the dispersion coefficients, we approximate the effective resonance frequency (ω_+) of Na^+ with a result found in free space[30] ($\omega_+ \approx 3.96$ Ry). If the entire refractive index increase came from sodium ions, the ionic dispersion coefficient near an air−water interface would be 32×10^{-50} N m^3. We expect Cl^- to be more polarizable than Na^+, but this should be of the right order of magnitude for the sum of ionic dispersion coefficients. In fact, this compares remarkably well with the value of 31×10^{-50} N m^3 for chloride that we found could accommodate nicely the surface tension changes of several different chloride salt solutions.[10] For bromide and potassium we assumed[10] that the values were $B_{Br^-} = 21 \times 10^{-50}$ N m^3 and $B_{K^+} = -5 \times 10^{-50}$ N m^3. Using the refractive index of KBr salt solutions, we find that the sum of static excess polarizability is around 5 Å^3. We will make two different estimates for KBr. We first use the same simple estimate as that for NaCl. With the effective resonance frequency of K^+ taken to be[30] 1.96 Ry, we find that the sum of dispersion coefficients should be around 25×10^{-50} N m^3. In the second estimate we use the B-values that we obtained from surface tension data and take the electron affinities to be the same for these two ions. Obviously, within this approximation, and using the B values given above, the separation of the sum of static polarizabilities becomes trivial. We find that $\alpha_- = 6.6$ Å^3 and $\alpha_+ = -1.6$ Å^3. Using the experimental dielectric function for water[29] and solving the expression for $B_\pm$ numerically at an air−water interface, we find that the resonance frequency is 2.23×10^{16} rad/s.

We can estimate B values at membrane−water interfaces using dielectric data for the membrane and water. A typical value for the dielectric constant for the interior of a membrane is around 2, but experiments suggest that the dielectric constant is in fact larger for the headgroups.[28] The ionization potential of the membrane will be around[31] $1-2 \times 10^{16}$ rad/s. Depending on the optical properties of water, membrane, and ion, the dispersion potential may be either attractive or repulsive. For cations near a membrane surface, $\pm 5 \times 10^{-50}$ N m^3 should be a reasonable upper estimate. For a mica−water interface, we use a model dielectric function for mica[32] and the second estimate for the excess polarizability of K^+ and Br^- to calculate the dispersion coefficients. We find that $B^{mica}_{Br^-} = -50 \times 10^{-50}$ N m^3 and $B^{mica}_{K^+} = 12 \times 10^{-50}$ N m^3. These values obviously only give an estimate, but it should be a reasonable one. Anions may in the same way experience large attractive forces near mercury surfaces and metallic electrodes.

III. Numerical Examples: Membranes

We have in the previous section explained why the ionic dispersion force depends on the dielectric properties of the membrane and on the ionic excess polarizability in water. We will now demonstrate with a few numerical examples that these specific salt effects have an important influence on surface pH and pH-profiles near a membrane

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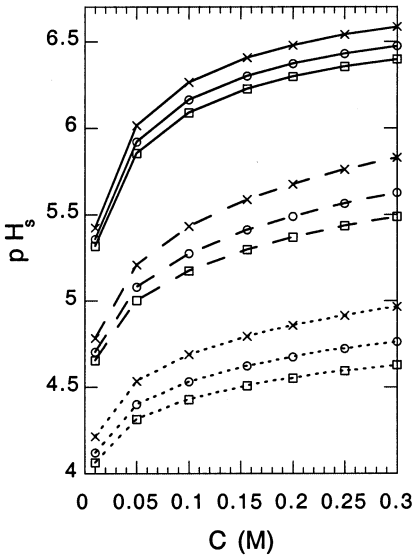

Figure 1. Calculated surface pH as a function of salt concentration. The three groups of curves correspond to a surface area per ionizable group of 20 (dotted lines), 100 (dashed lines), and 400 (solid lines) Å^2. The three curves in each curve group correspond to three different combinations of ionic dispersion coefficients: $B_- = 0$ in all three cases and $B_+ = 0$ (circle), 5 (square), and -5 (times sign) $\times 10^{-50}$ N m^3.

surface. We take the pH in the reservoir to be 7 and the dissociation constant for the surface groups to be to be $Z = 1.5 \times 10^{-5}$ M.

We first consider in Figure 1 a system consisting of two membrane surfaces 5 nm apart. Following Ninham and Parsegian,[1] we choose for ease of comparison the three groups of curves corresponding to a surface area per ionizable group of 20 (dotted lines), 100 (dashed lines), and 400 (solid lines) Å^2. The three curves in each curve group plot the surface pH as a function of concentration for three different combinations of ionic dispersion coefficients: $B_- = 0$ in all three cases and $B_+ = 0$ (circle), 5 (square), and -5 (times sign) $\times 10^{-50}$ N m^3. The increased change in surface pH at low concentrations reflects a reduced electrostatic shielding of the surface charge with decreasing salt concentration. At low enough concentrations the effect of ionic dispersion potentials becomes negligible. At the lowest concentration that we investigated (1 mM), the ion specific shift of surface pH was found to be substantially less than 1%. At biological concentrations the local surface pH depends not only on charges but also through the ionic dispersion on the actual ionic species. An attractive ionic dispersion potential acting on the cations will not only push these ions closer to the interface but also, via the self-consistent electric potential, influence the hydronium ion profile. The general behavior as a function of concentration is very similar for the different surface concentrations. These calculations predict ion specific changes in surface pH of the order of 0.1 at biological concentrations.

In Figure 2 we consider in more detail the pH-profile at a biological concentration (0.156 M, and a surface area per ionizable group of 400 Å^2). When two membrane surfaces come close enough together, the entire pH-profile becomes ion specific. One should be aware that the real pH profile also has a contribution from the interaction potential that acts on the hydronium ions (this corresponds to a separation dependent shift which is identical for all three curves).

The ionic dispersion coefficient will be different for different ions and also for different membranes. We

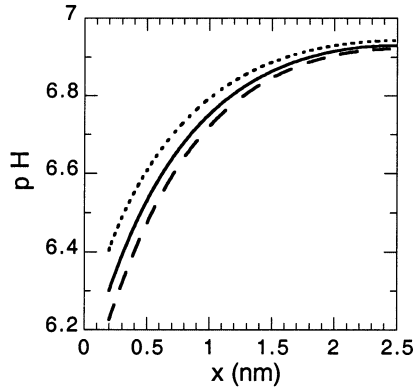

Figure 2. pH distribution outside a model membrane for different combinations of ionic dispersion potentials. The combinations of B_- and B_+ values are (in units of 10^{-50} N m^3) 0, 0 (solid), 0, 5 (dashed), and 0, -5 (dotted). The ion specific changes in this example may appear to be small, but one should keep in mind that small changes in surface pH can have an important and sometimes profound influence on biological processes.[5,6]

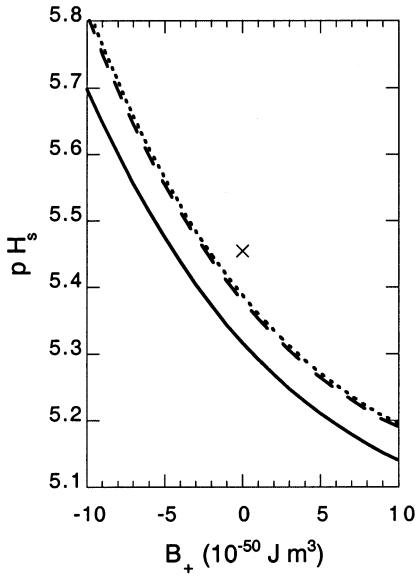

Figure 3. Calculated surface pH outside a model membrane (with 0.01 Å^{-2} ionizable groups) as a function of ionic dispersion coefficients (B_+) acting on the cations for three different dispersion forces acting on the anions: $B_- = 0$ (dotted line), -20 (dashed line), and -30 (solid line) $\times 10^{-50}$ N m^3, respectively. The times sign in the middle represents the Ninham−Parsegian result in the absence of interaction potentials.

therefore calculated the surface pH for different physically reasonable combinations of the ionic dispersion coefficients. We consider in Figure 3 two surfaces 2 nm apart, each with 0.01 Å^{-2} ionizable groups, and take the salt concentration to be 0.156 M. The calculated surface pH is shown as a function of B_+ for three different choices of B_-: 0 (dotted line), -20 (dashed line), and -30 (solid line) $\times 10^{-50}$ N m^3. Strong attractive ionic dispersion potentials that act on the anions can have a noticeable influence on the surface pH (here it is around 0.1). The dispersion forces that act on the cations have a larger influence on surface pH. The reason is simply that the anions are pushed away from the negatively charged interfaces by electrostatic forces. The anions may come closer to the interface, and therefore play a more important role, for systems with less ionizable surface groups. It may seem that the ion specific pH-shifts are quite small, but one should have in mind that even a small pH shift can have a profound

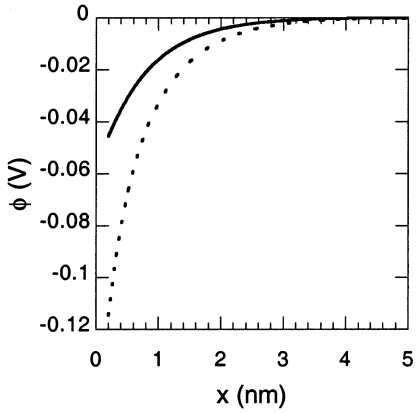

Figure 4. Electrostatic potential outside a mica surface for two different 0.156 M salt solutions. The solid (dotted) line represents an acetate-like (bromide-like) salt solution.

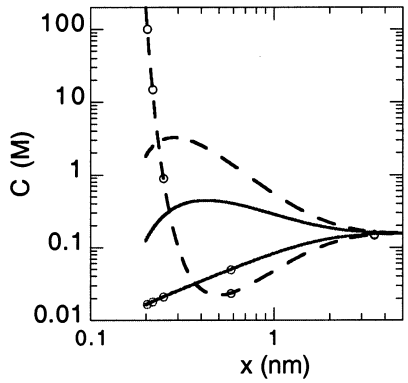

Figure 5. Concentration distributions outside a mica surface for an acetate-like salt (solid line) and for a bromide-like salt (dashed line). The co-ion (anion) distributions have been marked with circles.

influence on biological processes (the difference between the extracellular pH values of healthy cells and cancer cells is, for instance, only around 0.3, yet it is considered to be quite important[5]). The ion dependent pH shift should for example shift the rate constant in the active state equilibrium of rhodopsin on membrane surfaces. A lower surface pH favors MII formation, which is the state that activates the G protein.[6] We will come back in the next section to why anions can play a much more important role for the surface pH of other surfaces, for example, mica. The influence of having repulsive ionic dispersion potentials acting on the anions was in the present example found to be negligible. The difference between having $B_- = 20 \times 10^{-50}$ N m^3 and having no ionic dispersion acting on the anions was less than 0.1%. The times sign in the figure represents the result from a calculation made within the original Ninham−Parsegian theory, that is, when image and ionic dispersion interactions are neglected.[1]

IV. Numerical Examples: pH and Co-ion Adsorption on Mica

Ion specific surface pH is obviously not limited to membrane surfaces. It is much more general and important: the same phenomenon is for example expected for glass electrodes, metallic electrodes, and mica surfaces. Here, as an important example, we discuss why one should expect to find a very strong co-ion (anion) specificity for mica surfaces. Some anions, such as bromide, have a large excess polarizability. Others, such as CH_3COO^-, have approximately the same electron density as water and should have little excess polarizability.

We will in the following compare surface pH, electrostatic potentials, and ion distributions for two model salt solutions. The anions in model salt I do not experience any ionic dispersion potentials at all (acetate-like salt); the anions in model salt II experience strong attractive dispersion potentials ($B_- = -40 \times 10^{-50}$ N m^3) (bromide-like salt). The cations are the same for both salts and assumed to experience a repulsive ionic dispersion potential ($B_+ = 5 \times 10^{-50}$ N m^3). Our model system is a 0.156 M salt solution between two mica surfaces 10 nm apart. We take the pH in the reservoir to be 7, $Z = 1.5 \times 10^{-5}$ M, and a surface area per ionizable group of 400 Å^2. We find that the surface pH is around 6.2 for model salt I and 5.1 for model salt II. The electrostatic potential shown in Figure 4 also demonstrates a very large specific ion effect. As can be seen from the ion distributions, presented in Figure 5, large attractive ionic dispersion forces acting on anions can give rise to co-ion adsorption. There will in the same way be large attractive ionic dispersion forces near metallic electrodes that can give rise to this kind of very "specific adsorption".

V. Ion Specific Binding of Peptides to Membranes

We will now outline how one can extend the mean-field theory for the binding of small basic peptides to acidic membranes[28] to accommodate specific ion effects. For ease of comparison with Ben-Tal et al.,[28] we consider binding of pentalysine to vesicles containing 33% acidic phospholipids in a [KCl] molar salt solution. We will demonstrate that good agreement between theory and experiment can only be found if we include ionic dispersion potentials that agree well with our previous estimates.

The Gibbs binding free energy can be related to the molar partition coefficient (K) by[28]

$$\Delta G^\circ = -N_A k_B T \ln(K) \tag{14}$$

where N_A is Avogadros number. For low enough peptide concentrations, Ben-Tal et al.[28] demonstrated that the molar partition coefficient is directly proportional to the Gibbs surface excess of peptides,

$$K = A_L N_A \int_0^\infty dx\, [\exp(-\beta Ze\phi) - 1] \tag{15}$$

Here A_L is the area occupied by one lipid in the bilayer (68 Å^2), Z is the valency of the peptide (we use as an example pentalysine, i.e., $Z = 5$), and any influence from the peptides on the electrostatic potential is neglected.[28] Analogous to previous sections, we furthermore neglect image and dispersion interactions acting on the peptides. We solve the nonlinear modified Poisson−Boltzmann equation in the same self-consistent way as before, but with a new boundary condition on the surface. The surface charge is here taken to be[28]

$$\sigma = \frac{-e/S}{1 + K_{KL}[c^+]_s}. \tag{16}$$

For a 2:1 PC/PG bilayer the area per unit charge (S) is 204 Å^2, and the association constant of potassium ions with the acidic lipids ($K_{KL} = 0.3$ M^{-1}) was deduced from ζ-potential measurements.[28]

Figure 6 shows the binding energy of pentalysine to a 2:1 PC/PG bilayer as a function of concentration for four different combinations of ionic dispersion potentials acting on cations and anions. It is clear that the ionic dispersion potentials that act on anions only start to influence the

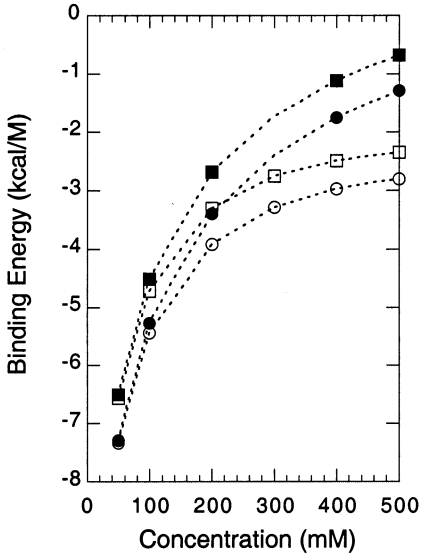

Figure 6. Calculated binding energy of pentalysine to 2:1 PC/PG bilayers as a function of molar concentration. Four different combinations of ionic dispersion potentials acting on cations and anions are considered (in units of 10^{-50} J m^3): −4, 0 (filled square); −2, 0 (filled circle); −4, −20 (open square); and −2, −20 (open circle). Image potentials are included in all cases.

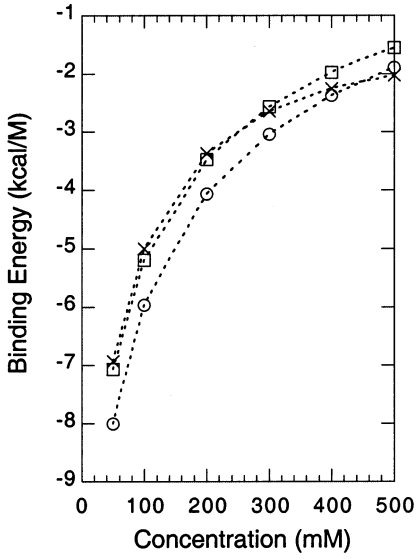

Figure 7. Calculated binding energy of pentalysine to bilayers as a function of molar concentration. We compare three different examples: Gouy−Chapman theory without interaction potentials (square); only image potentials included (circle); and our best fit to experiments, that we found taking $B_+ = -3 \times 10^{-50}$ J m^3 and $B_- = -17 \times 10^{-50}$ J m^3 (times sign).

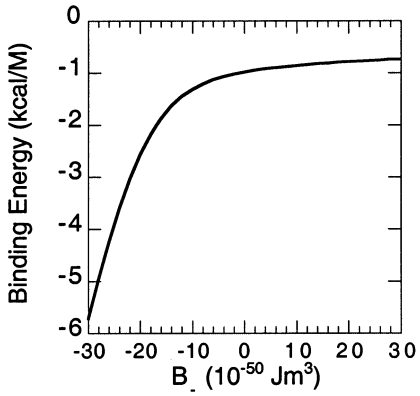

Figure 8. Calculated binding energy of pentalysine to bilayers as a function of anion dispersion coefficient. The concentration is 0.5 M and $B_+ = -3 \times 10^{-50}$ J m^3.

binding energy at biological and higher concentrations. Ionic dispersion potentials that act on cations influence the binding energy at lower concentration. We used that fact to find out what kind of values for the ionic dispersion potential could fit accurately the experimental binding energy found by Ben-Tal et al.[28] (cf. their Figure 6). They found that using a Gouy−Chapman theory (i.e. not including any interaction potentials) could give good agreement with experiments (except at the highest concentration where the errors were around 25%). However, as they noted, their model neglected image interactions. This means that the concentration of peptides close to the interface is overestimated. Nevertheless, the model gave for most concentrations good agreement with experiments. Ben-Tal et al. suggested that this implies that the model ignores some attractive interaction. It follows from comparison between experimental results at low concentrations and our Figure 6 that the ionic dispersion that acts on the cations must be between −2 and −4 × 10^{-50} J m^3. If we take the ionic dispersion potentials to be $B_{K^+} \approx -3 \times 10^{-50}$ J m^3 and $B_{Cl^-} \approx -17 \times 10^{-50}$ J m^3, good agreement with experiments follows. In Figure 7 we compare our result with the results when no interaction potentials are included and when only image potentials are included. We have used the ionic dispersion potentials as fitting parameters here to obtain good agreement with experiment, but what is remarkable is the very good agreement with our previous estimates of the ionic dispersion coefficients. Without these ionic dispersion potentials included, the agreement between theoretical and experimental binding energies is extremely poor (at worst more than 1 kcal/M difference).

We demonstrate in Figure 8 that the binding energy became highly anion specific at high concentrations. The binding energy is expected to be larger for highly polarizable anions,[12] such as nitrate, than for less polarizable anions, such as chloride. For other anions with very little excess polarizability (such as acetate) we expect even smaller binding energy. One should in this connection note that the biologically very important binding of ryanodine to heavy SR-vesicles (relevant for Ca^{2+} release channels which have a key role in biology[33−35]) follows exactly this kind of Hofmeister series.

VI. Conclusions

Ions in salt solutions experience ionic dispersion forces near interfaces. We have previously demonstrated that these forces have an important role behind the ion specific surface tension of salt solutions[10] and double-layer forces.[9] We predict here that these ionic dispersion forces will give rise to large specific ion effects for the way pH changes near interfaces. We have in particular investigated ion specific salt effects on surface pH outside biological membranes and mica surfaces. Due to ionic dispersion potentials, surface pH outside membranes depends on the choice of counterion, and to a smaller degree on the choice of co-ion. Near mica surfaces attractive ionic dispersion forces acting on anions can give rise to co-ion

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adsorption and a large degree of anion specificity for surface pH.

We have furthermore demonstrated that good agreement between theoretical and experimental binding energies of peptides to membranes requires that ionic dispersions are accounted for. The values for the ionic dispersion coefficients acting on K^+ and Cl^- that could accommodate the binding energy in the entire range of salt concentrations (50 mM to 0.5 M) were in good agreement with previous estimates based on surface tension data. Our results are also relevant for ion specific ryanodine binding to vesicles.[33] A further area where our work may be applied is to the interpretation of experiments involving aqueous electrolyte solutions in contact with mercury.[36] In these experiments, the surface excess as a function of applied voltage is measured, and very large specific ion effects occur. There is a strong correlation between the amount of so-called specific adsorption of anions[36] and their ionic polarizability. We have not investigated in detail these kinds of experiments here, but it is clear that dispersion forces should be responsible for some of the effects.

Our result also raise important questions on the origin of ion specific pH measurements. Clearly, the conventional theory that attributes this to changes in bulk activity does not give the entire answer. There will also be important, maybe even dominating, contributions from the ion specific surface excess of the form predicted here. This is a question that needs to be addressed soon.[37] Another important question that we will come back to is the origin of secondary hydration forces. Depending on glass properties, we might expect the ionic dispersion forces to change sign vis-à-vis mica. Secondary hydration forces have been found in force measurements between mica surfaces,[38] not between glass surfaces. As we have demonstrated, anions near mica surfaces may experience large enough attractive ionic dispersion forces to give rise to strong co-ion adsorption. This will clearly have a very important influence on the double-layer force. Near glass we expect anions to experience repulsive ionic dispersion forces which will have less effect on the DLVO force.

Computer simulations[28,39] can be extended to take ionic dispersion potentials into account. This may provide a more detailed molecular description of, for example, binding of peptides to membranes.

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