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Hofmeister effects in membrane biology: The role of ionic dispersion potentials

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Membrane biology is notorious for its remarkable, and often strong dependence on the supposedly irrelevant choice of ion pair of background salt solution. While experimentally well known, there has been no progress towards any real theoretical understanding until very recently. We have demonstrated that an important source behind these Hofmeister effects is the ionic excess polarizabilities of ions in solution. Near an interface an ion experiences not only an electrostatic potential, but also a highly specific ionic dispersion potential. At biological concentrations (around $0.1M$ and higher) when the electrostatic contribution is highly screened this ionic dispersion potential has a dominating influence. We present the result of model calculations for the interfacial tension and surface potential that demonstrates that inclusion of ionic dispersion potentials is an essential step towards predictive theories. Our results are compared with experimental surface and zeta potential measurements on phospholipid bilayers, zirconia, and cationic micelles.

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I. INTRODUCTION

Hofmeister, or specific ion, effects are as ubiquitous in biology and colloid science as they are ignored [1,2]. Examples abound, surface tension of electrolytes [3], interfacial work of adhesion at electrolyte-oil interfaces [4,5]; force measurements [6,7], zeta and surface potentials [8–14], pH measurements [15–17], ryanodine binding to calcium release channels [18]; cutting-efficiency and stability of DNA [19,20]; and formation of silicates [21]. We will demonstrate that a model originally proposed by Ninham and Yaminsky [1] offers an explanation for the ion specific surface and zeta potential of membranes, cationic micelles, and zirconia. We will also discuss how this model can accommodate the experimentally observed ion and alcohol specific oil-water interfacial tension, as well as leading to different perspectives on the origin of membrane folding.

The standard Gouy-Chapman mean-field theory [22–24], commonly and often successfully used in theoretical modeling in membrane biology and colloid science, rely on electrostatics, which in turn rely on the ionic charge. According to this theory all salt solutions with the same valency should be equivalent. Deviations from this theory (which occur commonly and are often very large) have been attributed to binding of unknown origin [8], sometimes associated with ion specific water structure effects (due to ions supposedly being either ‘‘structure breaking’’ or ‘‘structure creating’’ [25]). An important step towards a solution of the problem and predictive theories is to realize that the original double-layer theory of charged interfaces in salt solutions is thermodynamically inconsistent [1,26]. For consistency ionic dispersion potentials acting between ions and interface must be included in the theory. When this is done ion specific results emerge naturally [1,27,28]. An important question that remains is to what extent the inclusion of ionic dispersion potentials is sufficient to explain specific Hofmeister effects. Other ion specific properties like water structure [29], ion size, dielectric constant variation near the interface, solvation, electronegativity, counterion and co-ion exclusion [30,31] may clearly also be important, as may be the role of dissolved gas [32]. Ionic dispersion potentials have an important role in the ion specificity of surface tension [27,33], double-layer forces [28], ion binding to micelles [34], polyelectrolytes [35], and pH measurements with glass electrodes [17].

The ion specific double-layer theory is rehearsed in Sec. II. Ion specific oil-water interfacial tensions and other ion specific alcohol effects are considered in Sec. III. We discuss why the ionic dispersion potential near an oil-water interface, similar to the chemical potential of different n-alkanes, depend both for sign and magnitude on the chain length of different hydrocarbons. We show that large attractive ionic dispersion potentials acting on anions at biological concentrations result in negative interfacial tension changes. We briefly consider how these ion specific alcohol effects influence the self-assembly of silicates. We demonstrate in Sec. IV how a few experimentally measured ion specific surface and ζ potentials of cationic micelles, zirconia, and phospholipid membranes can be understood once ionic dispersion potentials are included in the theory. In Sec. V we summarize our results and discuss a mechanism in which the folding of membranes and proteins is a natural consequence of alcohol and Hofmeister effects.

II. ION SPECIFIC DOUBLE-LAYER THEORY

The model system that we consider is an aqueous solution of negatively charged monovalent anions and positively

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charged monovalent cations each with bulk concentration c_0 and charge e outside a charged impenetrable planar [1,27,28], or spherical [34], membrane surface. The self-consistent potential ϕ outside the charged surface is found by solving numerically (using the method of relaxation) the non-linear Poisson-Boltzmann equation,

$$\nabla^2\phi = -e(c_+ - c_-)/(\epsilon_w\epsilon_0), \tag{1}$$

with the ion concentrations given by

$$c_\pm = c_0 \exp(-\beta[\pm e\phi + U_\pm(r)]). \tag{2}$$

Here $\beta = 1/(k_B T)$, k_B is Boltzmann constant, T is temperature, and ϵ_w is the dielectric constant of water. Furthermore, $U_\pm(r)$ is the interaction potential experienced by the ions. In case of a planar surface the Laplace operator in the Poisson-Boltzmann equation is

$$\nabla^2\phi = d^2\phi/dx^2, \tag{3}$$

while for a spherical system it is

$$\nabla^2\phi = \frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{d\phi}{dr}\right). \tag{4}$$

The apparent worry about a mean-field theory of this kind to deal with electrostatics—a theory which ignores activity coefficients—is obviated by the fact that complete hypernetted chain (HNC) calculations [36] show that HNC and Poisson-Boltzmann give practically identical results for interfacial tension calculations at the air-water interface. In the present calculations we will assume that the surface charge σ is constant and uniformly distributed on the surface. This can be shown to be an excellent approximation [37]. The boundary conditions for the Poisson-Boltzmann equation for a planar surface are

$$\frac{d\phi}{dx}_{x=r_{ion}} = -\sigma/\epsilon_w\epsilon_0 \tag{5}$$

and

$$\frac{d\phi}{dx}_{\infty} = \phi(\infty) = 0, \tag{6}$$

while for a spherical surface the boundary condition at the surface is replaced with

$$(r_m + r_{ion})^2 \frac{d\phi}{dr}_{r=r_m+r_{ion}} = -Q_m/(4\pi\epsilon_0\epsilon_w). \tag{7}$$

Here r_m is the radius of the micelle and Q_m is the total charge on the micelle.

The interaction potential acting on ions near an interface will in general receive contributions from many different sources such as electrostatic, image, ionic dispersion potentials between ion and interface, and ion-ion interactions (for example, electrostatic, dispersion, and hard core). Here we neglect the effects of ion-ion interactions. For dissolved ions near a membrane-water interface the image potential is repulsive and screened:

$$U_{image}(x) \approx \frac{\Delta e^2}{16\pi\epsilon_w\epsilon_0 x}\exp(-2\kappa_D x), \tag{8}$$

where $\Delta \equiv (\epsilon_w - \epsilon_{oil})/(\epsilon_w + \epsilon_{oil}) \approx 1$. Here ϵ_{oil} is the dielectric constant of the oil (membrane). Since the dielectric constant of any oil is much smaller than it is for water, we can, as far as the image interaction is concerned, take it to be the same for all relevant oils ($\epsilon_{oil} \approx 2$). The inverse Debye length is $\kappa_D = \sqrt{(2\beta e^2 c_0)/(\epsilon_0\epsilon_w)}$. The image potential is independent of both the sign of the charge and the particular (monovalent) ionic species. The dispersion potential between an ion and a planar surface is approximated [1] with,

$$U_{dispersion}(x) \approx B/x^3, B \approx (n_w^2 - n_{oil}^2)\alpha^*(0)\hbar\omega_i/8. \tag{9}$$

Here, n_w (n_{oil}) is the refractive index of water (oil), $\hbar\omega_i$ is an effective electron affinity for the ion and $\alpha^*(0)$ is the static excess polarizability of the ion, in water. An approximate expression for the ionic dispersion potential near a spherical surface is given in our previous work on ion binding to micelles [34].

III. INTERFACIAL TENSION AND OTHER HOFMEISTER EFFECTS AT THE OIL-WATER INTERFACE

Hauxwell and Ottewill investigated the spreading of five *n*-alkanes on water [38]. They found that pentane, hexane, and heptane form stable wetting films while octane and dodecane do not. These hydrocarbons are very similar and have simple dielectric properties. Even though the differences in dielectric properties are small they have demonstrated to be sufficient to change the sign of the chemical potential [38,39]. The dielectric function at the relevant optical and ultraviolet frequencies are larger (smaller) for dodecane (pentane) than it is for water, explaining the change in sign. Near an oil-water interface the sign of the ionic dispersion potential in precisely the same way can be either positive or negative. Consider, for example, a highly polarizable anion such as bromide (with a large excess polarizability). Near an air-water (mica-water) interface the ionic dispersion potential will be large and repulsive (attractive). Near an oil-water interface on the other hand, the sign of the ionic dispersion potential changes sign, as for the chemical potential, proceeding from a short-chain to a long-chain hydrocarbon (while it is to oversimplify things to correlate the dielectric properties of oils with chain length, it functions as an useful rule of thumb). The effect of neutral salts on the solubility of proteins has been interpreted in terms of electrostatic (salting-in) and hydrophobic (salting-out) effects. An approximate expression for the solubility (ln[S]) in a salt solution was given by Melander and Horvath [40],

$$\ln(S) \approx \ln(S_0) - (\Delta G_{cav} + \Delta G_{e.s.})/(RT), \tag{10}$$

where $\ln(S_0)$ is the solubility of pure water, ΔG_{cav} is the Gibbs energy change for the formation of the cavity (which is approximately proportional to the interfacial tension), and $\Delta G_{e.s.}$ is the electrostatic energy between the solvent and solute. Water solubility is well known to follow a Hofmeister series that correlates with the corresponding series for the surface tension of salt solutions. It is for this and many other reasons clearly of interest to investigate the role of ionic dispersion potentials which underly the Hofmeister effects at an oil-water interface.

Aveyard and coworkers [4,5] demonstrated that the work of adhesion $[W(m)]$ of decanol, dodecane and other oils as a function of salt molality (m) could be described by

$$W(m)=W(0)+Am, \tag{11}$$

where A is a constant that depends on the choice of ion pair and oil. The magnitude of A typically follows a Hofmeister series, KCl$<$KBr$<$KI. This is the Hofmeister series found for the surface potential of micelles (which will be discussed briefly in the following section) and for the osmotic pressure measurements of Dubois *et al.* [6]. According to the Onsager-Samaris limiting law [41,27], all salts should have the same interfacial tension change with added salt irrespective of the choice of monovalent salt, and it should be almost identical for all kinds of oils. This is not what is seen experimentally. The interfacial tension change follows a Hofmeister series, and it can be either positive or negative. Aveyard *et al.* suggested that the origin of this Hofmeister series is due to the fact that the ions experience not only image and electrostatic forces, but also some additional force. We have recently demonstrated that a dominating contribution to this additional force is the ionic dispersion potential. When it is taken into account theoretical calculations give the right order of magnitude for the surface tension of air-water interface [27,33]. The interfacial tension at oil-salt solution interfaces and the corresponding ionic dispersion potentials obviously depend strongly on the choice of oil. While the ionic dispersion interaction is repulsive for highly polarizable anions near an air-salt solution interface, it can be either positive or negative near an oil-salt solution interface. The Gibbs interfacial tension increment of a salt solution is given by Ref. [27]

$$d\gamma/dc=-k_BT\int_0^\infty dx[c_+ + c_- - 2c_0]/c_0. \tag{12}$$

The numerically evaluated values for $d\gamma/dc(c)$ at an oil-water interface is shown in Fig. 1. In order to focus here on anion effects for three different oils we neglect the ionic dispersion potential acting on the cation. We consider three examples of ionic dispersion coefficients for the model anion ($B_-=10$ [dashed line], 0 [solid line], and -10×10^{-50} Jm^3 [dotted line]). Only at extremely diluted salt solutions do all three curves approach a common Onsager-Samaris limit. At biological and higher concentrations the sign and magnitude of the ionic dispersion potentials determine the surface tension increment. This demonstrates why the addition of salt in some cases can result in a decrease of the oil-water interfacial tension.

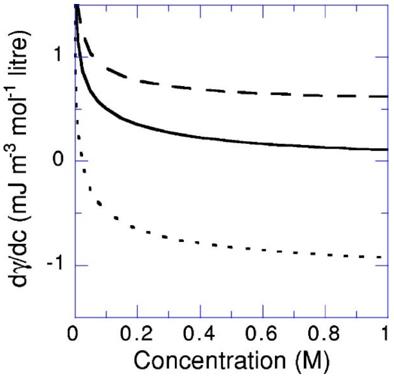

FIG. 1. $d\gamma/dc$ as a function of salt concentration for three different combinations of ionic dispersion coefficients acting on the ions ($B_+=0$ Jm^3, $B_-=10$ [dashed line], 0 [solid line], and -10×10^{-50} Jm^3 [dotted line]).

These ion specific alcohol effects have not only been observed for the interfacial tension of oil-water interfaces. They are presumably involved in many of the Hofmeister effects observed in membrane biology. They should be one important source behind the ion specific salting-in/salting-out effects observed for the solubility of proteins and other macromolecules. They should also have a quite important role in the formation of silica. Mesoporous silica is formed as a cooperative self-assembly of silicates and organic surfactant. The induction time for silicate formation in the alkaline route increases with the magnitude of the polarizability of the counterions in the salt solution (e.g., longer for bromide than for chloride) [21]. This ion specific result of ‘‘ion specific binding’’ is easy to understand, once ionic dispersion potentials are included in the formalism. The negative anions compete electrostatically with the negatively charged silicates. Bromide is more effective than chloride due to larger ionic dispersion potentials. More interesting for the present discussion is the effect of 1-alkanols as additives. Compared to the case without alcohol, the addition of short chain alcohols (e.g., ethanol or 1-propanol) decreases the induction time. One important reason for this must be that besides the electrostatic attraction on the counterions there will also be a repulsive ionic dispersion potential. The addition of longer chain alcohols (e.g., 1-butanol or 1-pentanol) has the opposite effect, increasing the induction time. Longer chain alcohols increase the adsorption of counterions which leads to less silicate adsorption and a longer induction time.

IV. ION SPECIFIC SURFACE POTENTIALS

McLaughlin and coworkers demonstrated that the surface potential of bilayer membranes not only depend strongly on the supposedly irrelevant choice of ion pair, especially on anions [9] but also on cations [8]. As should be evident from the discussion in the previous section it also depends on the choice of oil. Electrostatic properties of equally charged membranes can be very different since differences in the dielectric properties may cause a reversal of the sign of ionic dispersion potentials. McLaughlin *et al.* could relate their different results to a Hofmeister series. However, as they

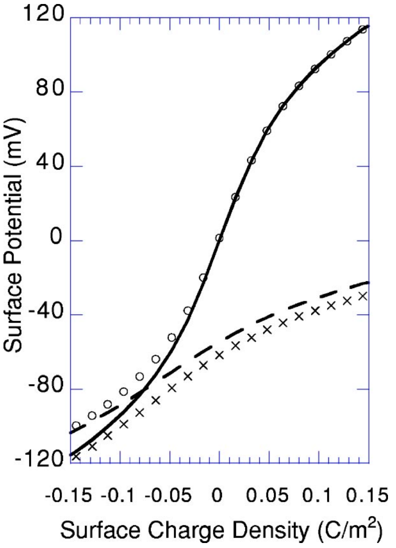

FIG. 2. Membrane surface potential as a function of surface charge density for four different combinations of ionic dispersion coefficients acting on the anions and cations (in units of 10^{-50} Jm^3): 0,0 (solid line); $-5,-30$ (dashed line); $-5,0$ (circles); $0,-30$ (crosses).

pointed out "the forces which cause chaotropic anions to adsorb to an air-water interface are not well understood" [9] and there is little consistency among various quantities that are related to "structure-making" and "structure-breaking" ions. Inclusion of the ionic dispersion potential is a vital step to understand the dependence on ion pair in membrane biology. When it is included we can begin to understand why an anion that is attracted to one surface may be repelled from a very similar surface. Lipid bilayers are important due to the fact that they are good model systems for biological membranes. One other appealing character that make lipid membranes suitable as model systems for investigation of Hofmeister effects is that different bilayers may have different surface charge density, including uncharged bilayers, and different optical properties (that give rise to different signs and magnitudes for the ionic dispersion potentials). We will illustrate the importance of including ionic dispersion potentials in this section with a few numerical examples, discussed in the light of experimental results.

The importance of short-ranged ionic dispersion potentials depend critically on the magnitude and sign of the surface charge density. Take for example the ionic dispersion potential acting on anions. It should always have a large effect on ion distributions and surface potentials near neutral and positively charged surfaces. However, for highly charged acidic surfaces, anions will be pushed away by strong electrostatic repulsion and it is then only at high salt concentrations (when the electrostatic potential is strongly screened) that an attractive ionic dispersion potential has a chance to compete. We show in Fig. 2 the surface potential versus the surface charge density for various $0.1M$ monovalent salts. The surface potential of an uncharged membrane ($\sigma = 0\,\mathrm{C/m^2}$), induced by unequal ionic dispersion potentials acting on anions and cations, can clearly be large for salt solutions with highly polarizable anions. We note that the

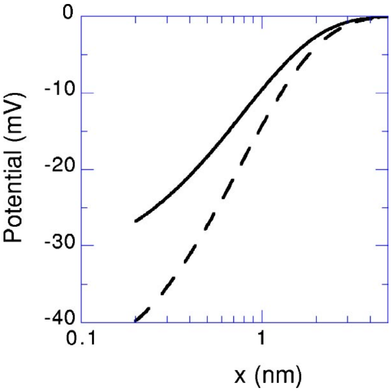

FIG. 3. The potential near an acidic membrane (with average unit charge area of 680 Å^2) in the presence of $0.156M$ salt solutions ($B_+=0$, $B_-=-20$ [dashed line], 0 [solid line] $\times 10^{-50}$ Jm^3).

nonzero surface potential of neutral bilayers measured with anionic fluorescent probes in the presence of KCl was attributed entirely to adsorption of the probe anions [24]. However, it is clear that there will in general also be contributions from background salt due to ionic dispersion potentials specific for each ionic species. Large attractive ionic dispersion potentials acting on the anions can even reverse the effective charge of the surface, and lead to co-ion adsorption. This kind of charge reversal has in fact been observed in experimental zeta potential measurements of TZ-0 zirconia [12]. The surface charge was modulated in that case by changing the *p*H. While neither the meaning of *p*H measurements [17] nor that of surface *p*H [42] is trivial (depending as it does on salt concentration, measurement technique, buffer, counterion, and notably also on co-ion) it is clear that one important effect of changing *p*H was to change the surface charge density. The result found by Franks *et al.* with Cl^- as a counterion is very similar to what we obtain for anions that experience small attractive (or repulsive) ionic dispersion potentials. For highly polarizable anions (which may have very large attractive ionic dispersion potentials), such as IO_3^-, they found a charge reversal of exactly the same form as the result presented in Fig. 2.

The phenomenological ion binding model used so widely in surfactant chemistry and with NMR to characterize binding to interfaces and proteins is precisely equivalent to a Poisson-Boltzmann description [43–45]. Measurement of binding of calcium to protein at air-water interface is different to binding to the same protein immersed in a membrane. This is accommodated when ionic dispersion potentials are included in the theory.

We next consider an acidic membrane (with an average area per unit charge of 680 Å^2) containing 10% acidic phospholipids (e.g., phosphatidylserine) and 90% charge neutral zwitterionic lipids (e.g., phosphatidylcholine). The calculated electrostatic potential and charge density in the presence of $0.156M$ salt solutions ($B_+=0$ Jm^3, $B_-=0$ [solid line], and $B_-=-20\times 10^{-50}$ Jm^3 [dashed line]) are presented in Figs. 3 and 4. These figures demonstrate that there can be co-ion adsorption on acidic membranes when the dielelectric properties of the membrane give rise to attractive ionic dispersion

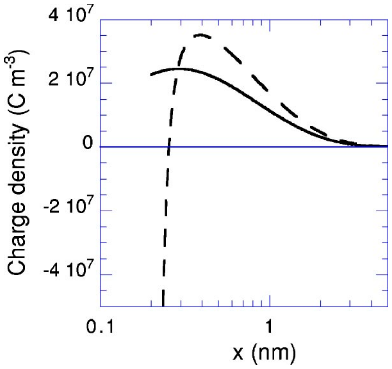

FIG. 4. The charge density distribution near an acidic membrane (with average unit charge area of 680 Å^2) in the presence of $0.156M$ salt solutions ($B_+=0$, $B_-=-20$ [dashed line], 0 [solid line] $\times 10^{-50}$ Jm^3).

potentials acting on the anions. In this instance, and in all other cases with high surface concentrations, it is essential to take co-ion and counterion exclusion effects into account.

Drummond *et al.* [10] demonstrated that the surface potential of cationic micelles depends on the choice of counterion in exactly the same way. In a previous paper we showed that highly specific ion binding follows when ionic dispersion potentials are included in the theoretical treatment [34,35]. There is more binding for highly polarizable ions such as bromide than it is for less polarizable ions. The surface potential outside a model cationic micelle (with head group area and micelle radius taken from Table 1 of Ref. [10]) as a function of salt concentration is shown for typical B values. As can be seen in Fig. 5 the experimental surface potentials are reasonably consistent with the theoretical results when the attractive ionic dispersion potential that acts on the anions is included ($B_+=0$ Jm^3, $B_{Cl}=-5$ [solid line], and $B_{Br}=-10\times 10^{-50}$ Jm^3 [dashed line]).

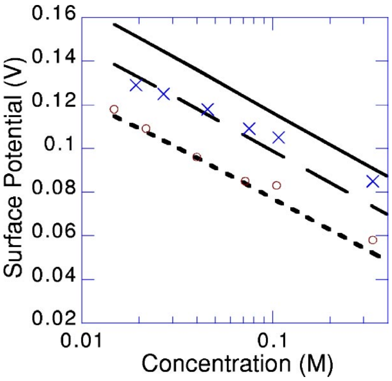

FIG. 5. Surface potential of a cationic micelle as a function of added salt concentration. The three curves correspond to the following combinations of ionic dispersion potentials acting on cations and anions (in units of 10^{-50} Jm^3): 0,0 (solid); 0,-5 (dashed), 0, -10 (dotted). The circles (crosses) are the experimental result for bromide (chloride).

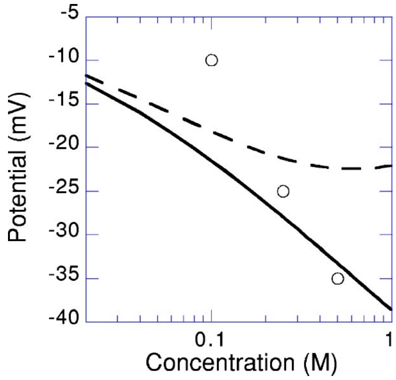

FIG. 6. Surface potential (solid line) and the potential 2 Å away from the interface (dashed line) of an uncharged membrane as a function of salt concentration ($B_+=-2$, $B_-=-20\times 10^{-50}$ Jm^3). The circles are the experimentally deduced surface potential of a black lipid membrane formed from a mixture of phosphatidylethanolamine and decane as a function of added [NaClO$_4$] [9].

The changes in conductance ($G\propto \exp[-\beta e\phi]$) of neutral black phospholipid membranes [9], and in the permeability of human red cells [9,46] with added salt, has been attributed to anion induced changes in the surface potential. These changes in conductance not only depended on the choice of salt, but also on the choice of membrane. While changes in permeability induced by ClO_4^- in membranes formed by neutral phospholipid membranes was found to be very large, the authors had no explanation for why the corresponding changes were not found for glycerol mono-oleate membranes [9]. We suggest that one obvious reason for these differences is that different oils have different dielectric properties. While the ionic interaction can be quite large and attractive near one oil-water interface, it can be much smaller and/or repulsive near another oil-water interface. It is then of some interest to investigate the electrostatic potential outside a charge neutral planar membrane in some more detail. Fig. 6 shows the surface potential, and the potential 2 Å further away from the interface, of an uncharged membrane in the presence of a typical model salt solution ($B_+=-2\times 10^{-50}$ Jm^3 and $B_-=-20\times 10^{-50}$ Jm^3). Due to screening there are obviously large differences (exactly as in the classical double-layer theory) between the surface potential and any experimentally observed potential measured outside the membrane surface (such as the ζ potential). We have for comparison included the surface potential that was experimentally deduced from conductance measurements of a zwitterionic lipid membrane in the presence of added NaClO$_4$ [9]. The anion induced changes observed by McLaughlin *et al.* [9] are consistent with the salt induced changes in the surface potential that we observe when attractive ionic dispersion potentials acting on the anions are taken into account.

V. CONCLUDING REMARKS

It is known that many biological processes across or at membrane surfaces depend sensitively on the choice of background salt. Our purpose here has been to demonstrate that many of these ion specific or Hofmeister effects can be understood once ionic dispersion potentials are taken into account. We recently demonstrated how these ionic dispersion potentials influence the binding of peptides to membranes [42]. An unanswered question is how proteins once they are bound to a membrane can be influenced differently by different salts solutions. A very important topic in membrane biology is to understand membrane assembly and dynamics. We propose that Hofmeister and alcohol effects may have a vital role. Within a membrane one has a mixture of lipids of different chain length and therefore different dielectric properties. This will undergo local phase separations within the membrane. So the ionic adsorption changes from place to place, potentially resulting in regions of variable stability, and thus activity of a protein embedded in, or bound to, the membrane. One important and related question is to what extent such regions of variable stability may be involved in inducing the correct folding of membranes.

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