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# *Communications to the Editor*

## Surface Titration: A Continuum Electrostatics Model

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This communication presents a computational study of a highly simplified model of a titrating docosyl amine monolayer at an air/water interface. The specific goal of the study is to reproduce experimentally measured p$K_a$ shifts associated with the formation of the monolayer. The calculations also demonstrate the strong dependence of the p$K_a$ shift on distance of the amine groups from the interface and the weak dependence of the p$K_a$ shift on the size and type of hydrophobic tailgroup. By comparing computation with experiment, an estimate of the amine−interface separation can be made. The dependence of the p$K_a$ shift on the ionic strength is calculated at this separation.

The experimental system on which this study is based consists of a self-assembled monolayer of docosyl amines ($CH_3(CH_2)_{21}NH_2$) at an air/water interface.[1] At 10 mM ionic strength, the docosyl amines form an ordered lattice with a density of 30 Å$^2$/molecule. A p$K_a$ of 9.9 ± 0.2 was then measured for the lattice. The p$K_a$ of a docosyl amine isolated in bulk solution is 10.6, giving a shift of −0.7 p$K_a$ unit between the isolated compound and the monolayer.

**Theory and Methods.** The simulations were performed using the UHBD program,[2] which calculates electrostatic potentials and energies using the nonlinear Poisson−Boltzmann equation. A single docosyl amine molecule was placed in a 5.5 × 5.5 × 120 Å$^3$ simulation box aligned perpendicularly to the interface. A grid spacing of 0.5 Å was used for the finite difference calculations. An all-atom model was used, with partial charges taken from the OPLS parameter set.[3] To represent an infinite monolayer, periodic boundary conditions were applied to the sides of the box. The air/water interface was modeled by choosing dielectric constants of 1 and 78 in the top and bottom halves of the box, respectively. A dielectric constant of 1 was also assigned to the docosyl amine monolayer. The Stern layer was set to zero for all calculations. An ionic strength of 10 mM was assumed for the water, except as noted below. The titrating headgroups of the docosyl amines were placed on or near the air/water interface.

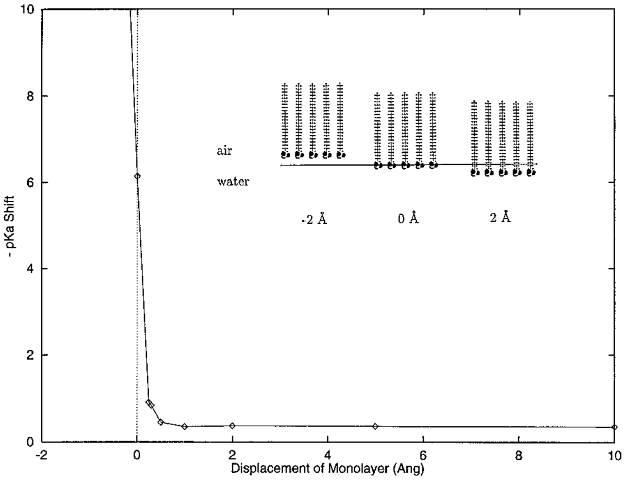

**Figure 1.** Dependence of the p$K_a$ shift on the displacement of the amine headgroups from the interface.

Since only electrostatic free energies are calculated in this model, determining the absolute p$K_a$ of the docosyl amine monolayer is impossible. It is, however, possible to calculate the shift in p$K_a$ as the molecule goes from an isolated state (in solvent) to a monolayer. To calculate this shift in p$K_a$, four quantities must be calculated: the energy of a charged docosyl amine monolayer, the energy of a neutral docosyl amine monolayer, the energy of an isolated charged docosyl amine, and the energy of an isolated neutral docosyl amine ($G^{+}_{\text{lattice}}$, $G^{0}_{\text{lattice}}$, $G^{+}_{\text{iso}}$, and $G^{0}_{\text{iso}}$, respectively). The p$K_a$ shift is then

$$\Delta \mathrm{p}K_a = -\frac{\Delta\Delta G}{k_B T \ln 10}$$

where $\Delta\Delta G = \Delta G^{\text{lattice}} - \Delta G^{\text{iso}}$, $\Delta G^{\text{lattice}} = G^{+}_{\text{lattice}} - G^{0}_{\text{lattice}}$, and $\Delta G^{\text{iso}} = G^{+}_{\text{iso}} - G^{0}_{\text{iso}}$.

**Results and Conclusions.** An initial test of the model involves determining whether the results are insensitive to the size of the unit cell. Calculations were performed on unit cells containing 2 × 2, 3 × 3, or 4 × 4 arrays of molecules (still with periodic boundary conditions). Since these setups represent the same monolayer as earlier but with a larger number of molecules in the actual computation, the energy should simply be 4, 9, or 16 times larger than the energy of a single molecule in the unit cell. When these runs (and others using a hexagonal lattice) were performed, the energies did, indeed, scale as the number of molecules in the unit cell. It is therefore safe to assume that $\Delta G^{\text{lattice}}$ calculated for a simulation containing a single molecule and periodic boundary conditions is equal to $\Delta G^{\text{lattice}}$ of a single molecule in the model of an infinite titrating monolayer.

When the nitrogen atoms of the monolayer headgroups are placed 0.25 Å on the water side of the interface, the shift in p$K_a$ is −0.91. A negative p$K_a$ shift is expected, since the nearby air phase increases the free energy of the charged monolayer, thus favoring a neutral monolayer. It is also encouraging that this shift is close to the value of −0.9 predicted by nonlinear Gouy−Chapman theory.[4]

To study the effects of the long hydrophobic tail on the p$K_a$ shift, similar calculations were performed on the docosyl amine headgroups alone. The observed p$K_a$ shift was −1.7, i.e., close to −0.91 for the docosyl amine molecules as a whole. This is not surprising since in this model the partial charges on the tailgroup atoms do not change as the molecule titrates, and therefore they do not make a strong contribution to the free energy difference. Experimentally, a similar effect was observed

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by Eisenthal et al. in their studies of docosyl amine[1] and *p*-hexadecylaniline[5] monolayers.

Certainly the most striking result of the study is the strong dependence of p$K_a$ shift on the location of the headgroups relative to the air/water interface. Figure 1 shows a plot of p$K_a$ shift versus the distance between the nitrogen atoms of the titrating headgroups and the interface. As the headgroups are shifted a few angstroms into the air (denoted by a negative separation), the p$K_a$ shift increases by several orders of magnitude. Conversely, as the headgroups become solvated, the curve rapidly levels off; the effect of the interface disappears at a separation of $+1$ Å. Peitzsch et al. also observed a strong dependence of the electrostatic potential on the separation of a charge layer from a dielectric interface in their continuum electrostatics calculations of a lipid membrane.[6]

The experimental p$K_a$ shift for the system modeled here is $-0.7$ (ref 1), corresponding to a 0.3 Å displacement of the headgroups into the aqueous phase of the model. Experimental verification of this displacement may be possible using neutron reflection detection or Brewster angle microscopy,[7−9] though these techniques are currently limited to about an angstrom or larger in resolution. Figure 2 plots the difference in energy between the charged and neutral monolayer versus ionic strength at this interface−monolayer separation. Significant destabilization of the monolayer is predicted at very small ionic strengths, but only minor increases in stability are predicted at higher ionic strengths.

It is important to note that the present model is very highly simplified. No disorder of the monolayer is allowed, the dielectric constant changes as a step function from 1 to 78, and the titration of the monolayer is assumed to occur as an all-or-nothing process. Despite these approximations, the p$K_a$ shift and the weak dependence of the shift are in reasonable accord with experiment. This suggests that the simple model described here is a useful starting point for the analysis of surface titration phenomena.

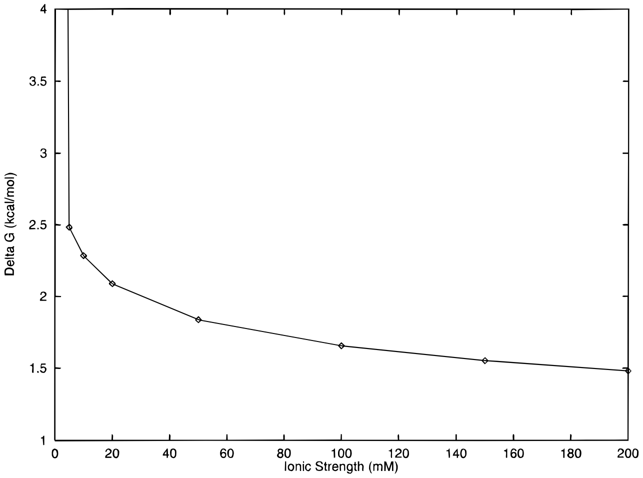

**Figure 2.** $\Delta G^{\text{lattice}}$ as a function of ionic strength.

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