Titration of Fatty Acids in Sugar-Derived (APG) Surfactants: A ^{13}C NMR Study of the Effect of Headgroup Size, Chain Length, and Concentration on Fatty Acid pK_a at a Nonionic Micellar Interface

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The pK_a of a ^{13}C-enriched fatty acid probe, tetradecanoic acid, was investigated in a variety of sugar-derived (APG) surfactants by using ^{13}C NMR to monitor the chemical environment of the probe during titration with base. There was an increase of approximately 2 pK_a units for the probe within the micellar systems compared to the value of acetic acid in water. Analysis shows that the interfacial environment of alkylglucoside surfactants is similar to, although slightly more polar than, that of ethylene glycol-derived (EO) nonionic surfactants, and there is no indication that the alkylglucoside surfactants are deprotonated at pH levels between 2 and 10. The average pK_a of the fatty acid probe in the APGs is measured to be 6.3, and it is argued that this value is an appropriate choice for pK_a^0, the intrinsic dissociation constant for an acid at a hydrophobic/hydrophilic interface, when calculating the surface potential of charged systems.

Introduction

The study of acid−base equilibria in micellar systems, particularly that of fatty acids, is of great interest because of its relevance to the understanding of mechanisms in biological membranes and cells[1−3] and in indicating properties—such as hydration[3] and thermodynamic stability[4,5]—of different colloidal systems. Minor pK_a shifts due to medium effects can modify reaction mechanisms and control chemical equilibria, and it is useful for synthetic chemists to understand how different types of colloidal systems may affect equilibria.[6−8] The way in which the lipid−water interfacial region of a micelle affects the ionization equilibrium (or pK_a) of a probe molecule is often discussed in terms of the polarity of the medium.[9,10] One can also extrapolate, from the direction and magnitude of a measured pK_a shift, whether a surfactant's behavior is cationic, anionic, or nonionic in solution because each class of surfactants has well-documented effects of the pK_a of various probe molecules.[4,8,9,11−16]

Alkylglucoside surfactants (APGs) are nonionic amphiphiles of interest as potential substitutes for petroleum-derived nonionic surfactants such as the common ethylene oxide-based surfactants (EOs).[17] They differ from EO surfactants in that the headgroups are made up of one or more glucose residues. The physical properties of an APG can be altered by changing the headgroup in a number of ways such as the linkage between the monosaccharide rings, the degree of ring opening, the number of monosaccharide rings in the headgroup, the type and degree of substitution on these residues, and the stereochemical linkage of the headgroup to the hydrocarbon tail.[18] Some of the current interest in alkylglucoside surfactants is due to the fact that they are categorized as "green chemicals:" in addition to being dermatologically safe, APGs are synthesized from renewable natural resources, glucose, and naturally occurring glycerol derivatives and break down readily in the environment.[17,19−21] Surfactant effects on acid−base equilibria are practically important, and it is thus of interest to continue characterizing the behavior of APG surfactants by examining the effect of the glucose-based headgroups on the pK_a of micellar-bound fatty acids as compared to the behavior of these probes in other surfactant systems.

For this study, a variety of alkylglucosides have been examined by varying both the number of glucose units in the headgroup and the alkyl chain lengths. Different surfactant concentrations are also examined to determine whether concentration affects the pK_a because there has been debate over whether alkylglucosides may in fact be nominally charged in solution, which can be resolved in part by examining the effect of concentration upon pK_a shift. Care was taken to follow the recommendations of El Seoud on how such experiments should be set up.[7] ^{13}C-enriched tetradecanoic (myristic) acid was used as a probe molecule because it is insoluble in water and can thus be assumed to locate at micellar lipid−water interfaces. ^{13}C NMR spectroscopy is the method of choice for these measurements because there are no problems with the measured property (the ratio of acid to anion in the sample) varying as a function of probe concentration in the micellar versus aqueous phase because the probe distribution is not expected to change with pH.[22,23]

Experimental Methods

Materials. The surfactants *n*-dodecyl β-D-maltotrioside (>97%) ($C_{12}G_3$), *n*-dodecyl β-D-maltoside (>99%) ($C_{12}G_2$), *n*-decyl-D-maltoside (>99%) ($C_{10}G_2$), and *n*-nonyl β-D-glucopyranoside (>99%) (C_9G_1) were from Anatrace and were used as received.

The prototropic molecule tetradecanoic (myristic) acid-1-^{13}C (>99.3 atom %, Isotec) was used for the NMR titrations. Deuterated acetone, CD_3COCD_3 (99.9 at. %, Aldrich) was used

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as an external reference and lock. Potassium hydroxide was made to varying concentrations by using aliquots, and deuterium chloride was used to adjust the pH for the NMR titrations.

For control experiments with glucose and acetic or hydrochloric acid, D-glucose monohydrate (>99%, Fluka) was used. Analytical grade (99.7%) acetic acid was from Scharlau Chemie SA (Barcelona, Spain), and hydrochloric acid (37%) was from Merck (Darmstadt, Germany). Potassium hydroxide was made up to varying concentrations with aliquots from BDH.

Titrations for the NMR studies were carried out at room temperature (23 ± 1 °C) in redistilled, CO_2-free deionized water.

pH Titration Experiments Using ^{13}C NMR. NMR samples were made by first dissolving labeled tetradecanoic acid in pure ethanol. The ethanol was then evaporated off, and the correct volume of surfactant solution was added, keeping the ratio of surfactant to probe molecule at 68:1, which gives approximately one probe per micelle, assuming spherical micelles, so as not to perturb the micellar structure. The samples were then briefly sonicated and left until the tetradecanoic acid in the NMR tube had fully dissolved.

Titrations of myristic acid in surfactant solutions were followed on a Varian Unity (Inova) spectrometer operating at 500 MHz for ^{1}H by using microliter amounts of base to adjust the pH without altering concentrations significantly. CD_3COCD_3 in a coaxial insert was both an external lock and a reference (δ_{CO} = 206.68 ppm). The pH was measured on a Fischer Accumet 925 pH/ion meter with an Aldrich combination glass/calomel electrode that fits the NMR tubes. The electrode was calibrated against three standard buffers (pH = 4, 7, and 10) to an accuracy of 99%, and the pH of the samples was checked before and after each NMR measurement. The electrode was rinsed thoroughly between each measurement with both ethanol and distilled water to prevent the build up of surfactant on the surfaces.

pK_a values were determined for the NMR titration experiments through a combination of the following equations:

$$HA \leftrightarrow H^+ + A^- \tag{1}$$

with

$$\delta_{obs} = \delta_0 X_0 + \delta_- X_- \tag{2}$$

where δ_i (i = obs, 0, and −) is the observed ^{13}C shift and the shifts for the protonated acid and the carboxylate ion, respectively, and X_0 and X_- are the mole fractions of the acid and the anion, respectively.[24] One can determine [A$^-$] and [HA] from the ^{13}C shifts

$$\frac{[A^-]}{[HA]+[A^-]} = \frac{\delta_{obs} - \delta_0}{\delta_- - \delta_0} \tag{3}$$

$$\frac{[HA]}{[HA]+[A^-]} = \frac{\delta_- - \delta_{obs}}{\delta_- - \delta_0} \tag{4}$$

and the titration curves are made using a nonlinear least-squares fit of the Henderson−Hasselbalch equation[25]

$$pH = pK_a + \log\frac{[A^-]}{[HA]} \tag{5}$$

where we assume that pH = −log a_H so that K_a is a mixed equilibrium constant made up of stoichiometric and thermodynamic binding constants.[4]

pH Titration Control Experiments. Titrations of an acetic acid/glucose/water solution were conducted with a PHM210 Meterlab standard pH meter (Radiometer). The electrode was calibrated with pH 4.0 and 7.0 buffer solutions to an accuracy of 96−98%. The samples were stirred during the titration, and the electrode was recalibrated afterward to check for instrument drift.

The pK_a of acetic acid in the glucose solution was obtained from the pH versus added amount of base using standard procedures. The experiment was twice repeated.

An additional control experiment was done to check whether the presence of glucose affected the accuracy of the pH meter by perturbing the liquid junction. For this test of the response of the glass electrode, we made a solution of 30 wt % glucose in water and added HCl so that its concentration was 3 mM in terms of the total solution volume. The measured pH was 2.48, which is reasonably close to the value of 2.52 for −log[H$^+$], which means that there will be an uncertainty of no more than 0.05 in our estimation of apparent pH. In fact, the value of 2.48 obtained is the value predicted in water solution if the activity coefficient is calculated on the basis of the Debye−Huckel approach

$$pH = -\log(\gamma[H^+]) = -\log(\gamma) - \log([H^+]) = \log(\gamma) + 2.52 = 2.48 \tag{6}$$

assuming a value of 0.94 for γ as obtained from the extended Debye-Huckel law. This control experiment shows that glucose does not significantly affect the liquid junction potential of the electrode.

Results and Discussion

A proper discussion of the results requires first a comment on the use of glass electrodes to measure the pH of micellar solutions. First, one must be aware of the possibility that surfactants, which are surface-active, can interfere with the pH measurement by forming a film on the surface of the electrode and/or perturbing the liquid junction potential.[8] Also, it has been argued that the observed pH does not necessarily correspond to either proton activity or concentration.[26] As noted above, we assume in this work that the pH measurements correspond to the activity of the hydronium ion in the micellar solution.

Effect of Glucose on pK_a. In the micellar solution, the probe resides at the hydrophobic/hydrophilic interface and so is situated in a region of high glucose concentration. To assess the influence of the glucose-rich environment, a control experiment was made with acetic acid (0.04 M) in 30 wt % aqueous glucose. Acetic acid is a suitable water-soluble substitute for myristic acid because the chain length of carboxylic acids does not significantly alter their pK_a and electronic effects are not felt beyond two or three carbons.[5] The pK_a was measured twice by plotting the volume of base added versus the measured pH. Glucose had a small effect on the observed pK_a of acetic acid, which was consistently decreased by 0.2 pK_a units from pK_a^w = 4.8, the literature value in water[4,5,10] (see Figure 1).

A control experiment was made to determine if the shift in pK_a was genuine or was due to interactions between the glass electrode and glucose. The measured pH of 3 mM HCl in 30 wt % aqueous glucose solution was the correct value, indicating that the response of the glass electrode and the availability of H$^+$ are not perturbed by glucose. Thus, the pK_a shift of acetic acid in a glucose solution must be a real effect. It is interesting that glucose slightly decreases pK_a, which is counterintuitive because organic solvents typically decrease the dissociation of

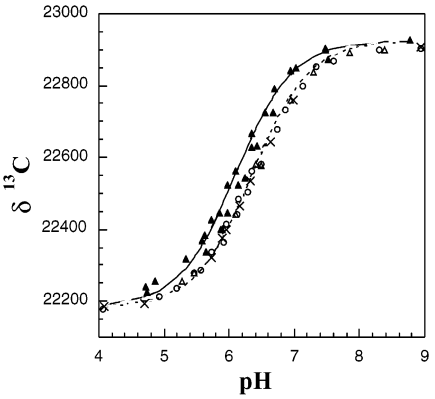

Figure 1. Effect of different alkylglucosides on the pK_a of myristic acid. The solid line is the prediction of eq 5 for pK_a = 6.1, and the dashed line is the prediction of eq 5 for pK_a = 6.35. (▲ = $C_{12}G_3$, various concentrations; ○ = $C_{12}G_2$, various concentrations; △ = $C_{10}G_2$, various concentrations; and × = C_9G_1, various concentrations.)

weak acids and the concentration of water is decreased by the large amount of glucose in the solution. These results indicate that there are specific interactions between acetic acid or acetate ion and glucose.

Effect of Alkylglucosides on pK_a. The effects of several alkylglucosides at various concentrations on the pK_a of myristic acid (see Figure 1) were studied to determine whether the number of glucose residues in the headgroups affected the estimated pK_a. Because $C_{12}G_1$ has a high lyotropic transition temperature (38 °C)[27] and goes almost directly into a miscibility gap region,[27,28] it was impossible to conduct experiments with it, and C_9G_1 was used as an equivalent one-glucose-residue surfactant because it is the longest chain length glucopyranoside that one can use without phase separation at concentrations above 1 wt %[29] and it has well-documented phase behavior.[17,18] To verify that changing the tail length would not substantially affect the ionization constant, a titration was made using $C_{10}G_2$. The results of the titration in $C_{10}G_2$, compared with that in $C_{12}G_2$ (see Figure 2), indicate that altering the chain length of the surfactant does not affect the environment of the fatty acid enough to shift the pK_a, despite greater differences between the chain lengths of the probe molecule and the surfactant. This result was expected because measurements reported in the literature indicate that a carboxylic acid headgroup is solubilized at the micellar interface, regardless of the fatty acid chain length.[4]

A striking observation from these experiments is that concentration does not affect the shift in pK_a of the fatty acid probe (see Table 1, Figure 2). A dependency of ΔpK_a^{obs} ($\Delta pK_a^{obs} = pK_a^{obs} - pK_a^{w}$) on the concentration would be expected if the surfactant headgroups were charged. According to the pseudophase ion-exchange model of micellar effects, ion selectivities depend on concentrations of ionic surfactants[12] or, in terms of electrostatics, the electrostatic potential at the charged interface where the probe resides.[4,30] The lack of concentration effects on the observed pK_a of fatty acids in these APG surfactant solutions demonstrates that they are indeed nonionic in character. This result is not surprising because pK_a values for simple mono- and disaccharides are in the range of 13.5−14,[31−33] so there should be little deprotonation in neutral aqueous solutions.

Although ΔpK_a^{obs} shows no dependence on surfactant chain length or concentration, there seems to be some slight effect of headgroup size. However, it is only for the $C_{12}G_3$ surfactant that there is a clear downward shift of approximately 0.15 pK_a units (see Figure 1 and Table 1). This result could be due to an increase in the effective concentration of the glucose residue at the interface where the probe headgroup resides or to the greater flexibility of the G_3 headgroup, which may favor specific interactions with the probe due to an increased ability to position itself relative to the probe. Although more work is required to verify this conclusion, the explanation is reasonable since a shift of similar magnitude was observed in the titration of acetic acid in glucose.

Hydration of Sugar Headgroups. One can also reason that interfaces of the sugar surfactant micelles are more polar than those of the EO surfactants because the pK_a values of myristic acid in solutions of the sugar surfactants are lower by 0.3 to 0.5 units than those in ethylene oxide-based nonionics (see Figure 3). Previous calculations have indicated that one can directly relate the hydration of a membrane to the degree of acid dissociation of the probes located in it.[34] Additionally, the observed pK_a of myristic acid responds uniquely to the solvent dielectric constant,[10] and thus it is common to use ΔpK_a^{obs} values as indicators of "effective" dielectric constants, ϵ_{eff}, of interfacial regions.[10] These estimated values of ϵ_{eff}, based upon Drummond's work,[10] are listed in Table 2 and are based upon a pK_a^{w} of 4.8. From these values, one can infer that the interfacial headgroup regions of sugar-derived nonionic surfactants are probably more hydrated than those of ethylene oxide-based nonionic surfactants on the basis of the higher effective dielectric constant ($\epsilon_{eff} \approx 35$ and 27, respectively) together with the smaller shift in pK_a observed for the APG surfactants.

Data from Sugar Surfactants as a Measure of the Intrinsic Interfacial Dissociation Constant pK_a^0. The ΔpK_a of a probe in ionic surfactants is often measured to calculate the electric potential at the interface (ϕ) using the equation

$$pK_a^{obs} = pK_a^0 - \frac{F\phi}{RT \ln 10} \qquad (7)$$

where pK_a^0 is the intrinsic dissociation constant, which should be the pK_a of the molecule at an interface without any electrostatic potential,[4,9,10] F is Faraday's constant, R is the universal gas constant, and T is the absolute temperature. The calculated value of ϕ then aids in understanding the colloidal stability of systems containing charged amphiphiles.

According to eq 6, the pK_a^{obs} of a probe should either be greater than or less than pK_a^0, depending on whether the interface is positively or negatively charged, and the size of the shift should be equal to either side of pK_a^0 as long as the concentration of surfactant is equivalent and the charge per surfactant is equal. However, if one compares the pK_a^{obs} to the pK_a of the probe in water, it is always greater than that of the probe in water regardless of the sign of the ionic surfactant (see Figure 3 and Table 2). This means that a large part of the shift seen in surfactants is due to the nonelectrostatic effects of an interface. In calculating ϕ from eq 6, the main problem is always that the value of the intrinsic interfacial dissociation constant pK_a^0 is uncertain. Clearly, it should be the acid constant in the absence of electrostatic interactions, and hence its determination is a difficult matter. Because of this problem, the most common approaches have been to use either the pK_a values obtained for the probe in water[9] or in a solution of nonionic (EO) surfactants.[9,35−37] For convenience, the two commonly used values of pK_a^0 are seen in Figure 3 as dashed lines.

The titration curves for a series of concentrations of anionic (SDS) and cationic (DoTAC) surfactants are plotted in Figure 3 alongside the curve for sugar-derived surfactants (APGs), EO

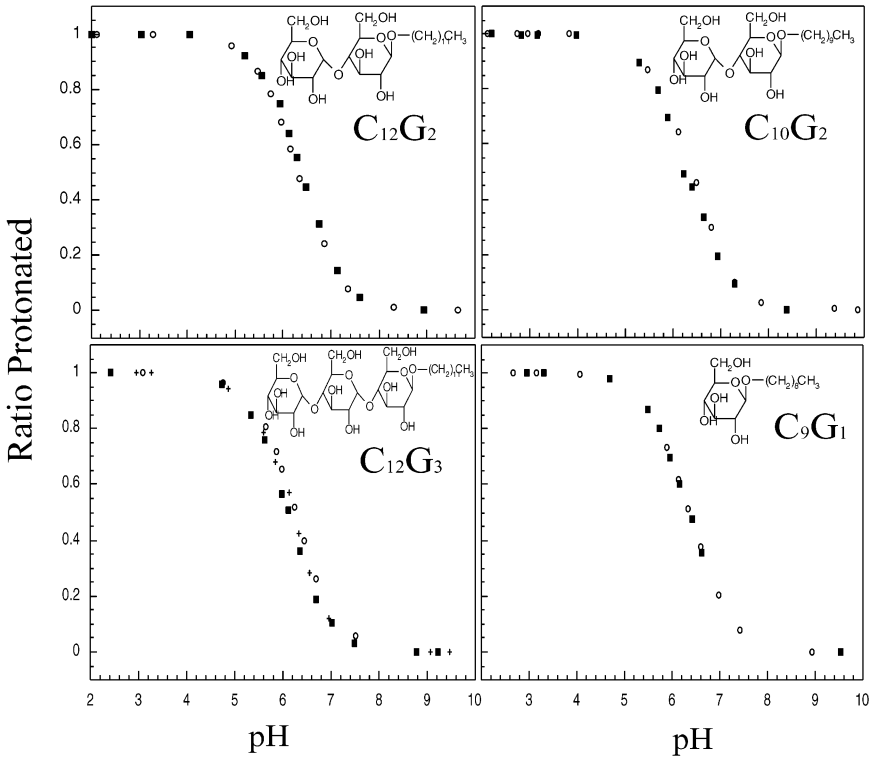

Figure 2. Deprotonation as a function of pH. ■ = 0.208 M, ○ = 0.138 M, and + = 0.107 M.

TABLE 1: Measured pK_a of Myristic Acid in Various Sugar Surfactants

	$C_{12}G_3$	$C_{12}G_2$	$C_{10}G_2$	C_9G_1	$C_{12}E_8$
.207 M	6.11 ± 0.01 (12.2 wt %)	6.39 ± 0.01 (9.6 wt %)	6.27 ± 0.03 (9.1 wt %)	6.35 ± 0.01 (6.0 wt %)	
.138 M	6.26 ± 0.01 (8.5 wt %)	6.31 ± 0.01 (6.6 wt %)	6.40 ± 0.02 (6.3 wt %)	6.36 ± 0.01 (4.1 wt %)	
.107 M	6.21 ± 0.02 (6.7 wt %)				
~9 wt %	6.3[b]	6.4[b]	6.3[b]		6.7[a]

[a] Value from measurements of da Silva, et al.[4] [b] Approximate pK_a values measured for concentrations of sugar surfactants nearest to 9 wt %, except for $C_{12}E_8$.

surfactants, and acetic acid in water. Immediately apparent is that because of their slightly lower ΔpK_a than that of the nonionic EO surfactants, the APG surfactants lie in a position almost precisely between the charged surfactants of opposite sign but equal concentrations (excluding the anomaly of the titration for SDS at 15 wt %) in the position where the true pK_a^0 should lie if eq 6 is correct. It is our conclusion, therefore, that the sugar-derived surfactants provide a reasonable value of the intrinsic dissociation constant, pK_a^0, for myristic acid, and we recommend that the pK_a values of APGs rather than EO surfactants be used as a reference pK_a^0 for accurate calculations of ϕ.

We note that the pK_a shift due to the presence of the hydrophobic/hydrophilic interface corresponds to roughly 1.5 pK units. In terms of electrostatics, this corresponds to the change in free energy in moving a charge from infinite distance to a certain distance from a dielectric discontinuity. We are currently computing such energy differences in different geometries. Preliminary results show that the magnitude of the effect can be accounted for.[38]

Conclusions

The estimated pK_a of myristic acid in several sugar-derived surfactants is approximately 6.3, consistently higher than for

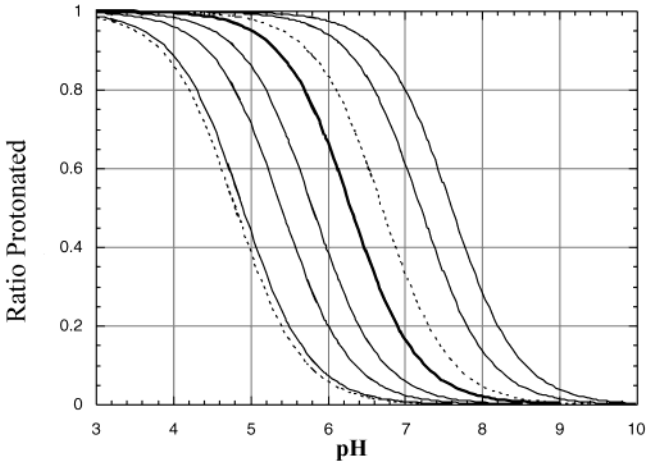

Figure 3. pK_a of myristic acid in water and various surfactant solutions. Left to right: acetic acid in H_2O (- -), DoTAC (5 wt %), DoTAC (10 wt %), DoTAC (15 wt %), APG (−), $C_{12}E_8$ (- -), SDS (15 wt % and 10 wt % on top of each other), and SDS 5 wt %. Values for DoTAC, $C_{12}E_8$, and SDS are from those reported in ref 4.

medium chain length carboxylic acids in water but lower than in EO-derived micelles. The magnitude of the pK_a shift does not clearly depend on the chain length of the surfactant, the number of glucose units in the headgroup, or the concentration of surfactant. On the basis of the independence of observed pK_a from surfactant concentration and the positions of the pK_a plots relative to those for other nonionic and cationic surfactants, one can also assume that sugar surfactants are nonionic in nature.

The results also indicate that sugar surfactants are better hydrated at the lipid−water interface than similar EO-based nonionic surfactants. Sugar-derived and EO-derived micelles differ in regard to their hydrogen-bonding interactions with water. There is extensive water content in the headgroups of both sets of micelles,[17,39,40] but the EO segments are hydrogen bond acceptors, and the sugar headgroups, with their hydroxyl

TABLE 2: ΔpK_a Values for Myristic Acid in Various Surfactants

surfactant	w_f[a]	c_{probe}	pK_a^{obs}	ΔpK_a^{obs}	ϵ_{eff}[c]
$C_{12}G_3$	.12	3	6.1	1.3	40
	.09	2	6.3	1.5	35
	.07	1.5	6.2	1.4	37
$C_{12}G_2$	.10	3	6.4	1.6	33
	.07	2	6.3	1.5	35
$C_{10}G_2$	.09	3	6.3	1.5	35
	.06	2	6.4	1.6	33
C_9G_1	.06	3	6.4	1.6	33
	.04	2	6.4	1.6	33
$C_{12}E_8$[b]	.09	2.3	6.6	1.9	27

[a] w_f = weight fraction of probe used. [b] Based on data acquired from ref 4. [c] Extrapolated from data reported in ref 10.

groups, are both acceptors and donors. This difference in the donor/acceptor balance allows the sugar headgroups, or their attached water molecules, to be much more effective than EO headgroups in hydrogen bonding to, and the stabilization of, carboxylate ions.

Finally, it is observed that the measured values for the pK_a of myristic acid in the sugar-derived surfactants provide an appropriate pK_a^0 value for use in eq 6 to calculate the electrostatic potential, ϕ, at charged interfaces.

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