Effect of Headgroup Size, Charge, and Solvent Structure on Polymer—Micelle Interactions, Studied by Molecular Dynamics Simulations

Barry Z. Shang, Zuowei Wang, and Ronald G. Larson*
Department of Chemical Engineering, University of Michigan, Ann Arbor, Michigan 48109-2136
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We performed atomistic molecular dynamics simulations of anionic and cationic micelles in the presence of poly(ethylene oxide) (PEO) to understand why nonionic water-soluble polymers such as PEO interact strongly with anionic micelles but only weakly with cationic micelles. Our micelles include sodium n-dodecyl sulfate (SDS), n-dodecyl trimethylammonium chloride (DTAC), n-dodecyl ammonium chloride (DAC), and micelles in which we artificially reverse the sign of partial charges in SDS and DTAC. We observe that the polymer interacts hydrophobically with anionic SDS but only weakly with cationic DTAC and DAC, in agreement with experiment. However, the polymer also interacts with the artificial anionic DTAC but fails to interact hydrophobically with the artificial cationic SDS, illustrating that large headgroup size does not explain the weak polymer interaction with cationic micelles. In addition, we observe through simulation that this preference for interaction with anionic micelles still exists in a dipolar “dumbbell” solvent, indicating that water structure and hydrogen bonding alone cannot explain this preferential interaction. Our simulations suggest that direct electrostatic interactions between the micelle and polymer explain the preference for interaction with anionic micelles, even though the polymer overall carries no net charge. This is possible given the asymmetric distribution of negative charges on smaller atoms and positive charges on larger units in the polymer chain.

1. Introduction

The existence of interaction between nonionic water-soluble polymers and micelles is often inferred experimentally from the appearance of a critical aggregation concentration (cac) lower than the critical micelle concentration (cmc) of the pure surfactant solution. However, it has been more difficult to obtain from experiments a clearer microscopic picture of the polymer—micelle complex. For example, while most experiments indicate the polymer is adsorbed onto the micelle surface, a few have suggested solubilization of the polymer into the micelle interior. Further, while some studies suggest that the driving force for association is a hydrophobic interaction between the polymer and micelle, others suggest it is an electrostatic attraction between the polymer and surfactant headgroups, possibly mediated by counterions or by partial protonation of polymer oxygens.

Recently, we performed atomistic molecular dynamics (MD) simulations to address these questions. While a number of previous simulation studies focused on isolated aqueous micelles, we simulated a sodium n-dodecyl sulfate (SDS) micelle interacting with poly(ethylene oxide) (PEO) polymers. We were thereby able to show that the polymer is adsorbed onto the hydrophobic regions of the micellar surface and weaves in between the surfactant headgroups, in agreement with the traditional “beaded-necklace” model of the polymer—micelle complex. In addition, we found that a strong driving force for association is a hydrophobic interaction between PEO and SDS that roughly 120 ethylene oxide monomers are required to saturate the SDS micelle surface, in excellent agreement with experiment.

However, important questions still remain. It is generally known that micelles formed from anionic surfactants, such as SDS, interact with hydrophilic polymers such as PEO and poly(vinyl pyrrolidone) (PVP), while cationic micelles, such as those formed from n-dodecyl trimethylammonium bromide (DTAB) and chloride (DTAC) surfactants, show limited or no interaction with hydrophilic polymers at room temperature. Similarly, nonionic and zwitterionic micelles, composed of surfactants such as poly(oxyethylene) monoalkyl ethers (C₉H₂₈O₇E₆) and n-octyl thioglucosides, show negligible interaction with hydrophilic polymers. The limited interaction of PEO with cationic surfactants has been attributed to the bulky size of the trimethylammonium (TMA) headgroup, the hydration shell overlap between the headgroups and polymer, and the electrostatic repulsions due to partial protonation of ether oxygens in the polymer segments.

Unfortunately, these traditional explanations are inconsistent with a wide range of experimental data. For example, arguments based on large headgroup size cannot explain (1) why nonionic water-soluble polymers such as PEO do not interact with cationic micelles with smaller headgroups, such as those of n-dodecyl ammonium chloride (DAC); (2) why bulky hydrophobic polymers such as ethyl(hydroxyethyl) cellulose do interact with micelles with large cationic headgroups; and (3) why the large headgroup size of anionic malonate surfactants does not prohibit PEO adsorption. Explanations based on the partial protonation of polymer ether oxygens also seem implausible given the low pKₐ (~3.5) of the ether oxygen. The most plausible explanation thus far seems to be that the differences in interactions between the hydration shells of the polymer and micelle account for the preference for polymers such as PEO to interact with anionic micelles. Since a water molecule possesses a partial positive charge on each hydrogen atom, it
could possibly act as a solvent bridge between two anionic headgroups but be unable to bridge between cationic headgroups. However, further evidence is needed to test this view. Questions that need to be addressed include the following: is water special in giving rise to this sign-dependent interaction? If not, then in what other types of solvent could this behavior occur? Finally, why does the sign of the micelle headgroup charge seem important in polymer–micelle interactions, even though the polymer overall carries no charge?

In this paper, we present MD simulations aimed at resolving these issues. Specifically, we investigate the effect of headgroup size, sign of headgroup charge, and solvent hydrogen bonding on polymer–micelle interaction. To do this, we simulate five types of micelles in the presence of PEO. These include SDS, DTAC, and DAC micelles and micelles in which we artificially reverse the sign of the partial charges of SDS and DTAC, to distinguish the effect of charge from that of headgroup size. Our results suggest that the lack of interaction of cationic micelles with PEO cannot be attributed to the large headgroup size that supposedly shields the polymer from the hydrophobic regions of the micelle surface. In fact, even though DTAC micelles possess large TMA headgroups, the micelle surface is still appreciably hydrophobic, and we find that replacing the positive charges with negative charges on the headgroup actually leads to PEO interaction, despite the large size of the headgroup.

In addition, we simulate micelles and polymers in a model dipolar “dumbbell” solvent to investigate the effects of water geometry and hydrogen bonding on polymer–micelle interaction. The dumbbell solvent is different from water in that it replaces the two positive fractional charges on the water hydrogen atoms with a single positive fractional charge on a fictional atom with the same size and magnitude of charge as the water oxygen. This creates a solvent with a symmetric charge distribution and also unable to form hydrogen bonds. We observe that even in this symmetric dumbbell solvent the PEO still interacts more strongly with the anionic micelle than a cationic one with the same headgroup size. The results suggest that rather than indirect water-mediated interactions it is the direct electrostatic interactions between the polymer and micelle that likely play a role in the differences in polymer behavior toward anionic and cationic micelles. We suggest that for anionic micelles an electrostatic attraction among the polymer carbons and micelle headgroups can assist the hydrophobic interaction in stabilizing the polymer at the micelle surface.

2. Methods

We have used the GROMACS 3.3.1 simulation engine41 and GROMOS 45a3 force field42 for all simulations. The initial coordinates for the surfactant molecules and polymer chain were generated from ProDRG,43 while trajectories were visualized with VMD 1.8.5.44

2.1. Simulations of Polymer-Free Micelles. First, we describe separate simulations of five different micelles without polymer. These include micelles composed of SDS, DTAC, and DAC surfactants, as shown in Scheme 1. In addition, we have simulated micelles composed of the charge inversions of SDS and DTAC, in which we switched the sign of the partial charges of each atom in the surfactant headgroup. Methyl groups on DTAC headgroups were modeled as united atoms, while hydrogen atoms on DAC headgroups were modeled explicitly. For all surfactants, hydrocarbon tail carbons were also modeled as united atoms. When appropriate, we will refer to anionic SDS as (−)SDS and cationic SDS as (+)SDS and likewise for DTAC.

### Table 1: Surfactant Partial Charge (e) Assignments

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<tr>
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<th>(+)SDS</th>
</tr>
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<table>
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<th>(−)DTAC</th>
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<td>all other atoms</td>
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</table>

<table>
<thead>
<tr>
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<th>(+)DAC</th>
</tr>
</thead>
<tbody>
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<td>Cl</td>
<td>−1</td>
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<tr>
<td>all other atoms</td>
<td>0</td>
</tr>
</tbody>
</table>

*Ref 19. †Ref 22.

Partial charge assignments for the headgroup atoms, given in Table 1, were taken from ref 19 for (−)SDS and ref 22 for (+)DTAC. For DAC, literature values were unavailable, and the partial charge assignments remained identical to those in (+)DTAC. However, we found that doubling the partial charge magnitudes of the hydrogen atoms in the DAC headgroup (while placing a compensating charge on the nitrogen atom) did not affect the qualitative results. Further, simulations of (−)SDS using the (−)DTAC partial charge distribution and simulations of (−)DTAC using alternative partial charges recommended in ref 45 yielded qualitatively similar results. This indicates that our conclusions are largely insensitive to the particular choice of partial charge assignments.

The (−)SDS micelle consists of 60 surfactant molecules, close to the experimental mean value of 63 at the cmc,46 and is consistent with values used in previous simulations.17–21,23 The (+)DTAC micelle contains 44 surfactant molecules, consistent with experimental values around 47 at the cmc.47 Aggregation numbers for DAC were not provided in the literature, and a value of 44 was chosen to match that of (+)DTAC. The (+)SDS and (−)DTAC micelles consist of 60 and 44 surfactant molecules, respectively, consistent with their oppositely charged counterparts. Although we have used different aggregation numbers for different micelles, our qualitative results are not dependent upon the aggregation number. For example, simulations of (−)SDS micelles with 44, rather than 60, surfactants...
and (+)DTAC micelles with 60, rather than 44, surfactants yielded qualitatively similar results in both cases.

System preparation details for the polymer-free (−)SDS micelle simulation are provided in ref 17, and analogous procedures were followed to prepare the other micelle simulations. In short, each micelle was initially centered in a truncated octahedron with a periodic image distance of 6.54 nm, yielding a total surfactant concentration of 0.46 M. The system was then solvated with SPC water molecules48 and enough counterions to keep the system electrically neutral. Ryckaert–Bellemans dihedral potentials49 were used to model torsional motion of the surfactant chains. Temperature and pressure control were applied isotropically at 300 K ($T_\tau = 0.1$ ps) and 1 bar ($P_\tau = 1.0$ ps) using the Berendsen weak-coupling method,50 where $T_\tau$ and $P_\tau$ are the temperature and pressure time constants, respectively. A cutoff scheme was used for short-range nonbonded interactions (van der Waals, 1.4 nm; real-space Coulomb, 0.9 nm), and electrostatics were computed using the Particle Mesh Ewald technique.51 For non-DAC simulations, a time step of 5 fs was used with a neighbor list update every five time steps. For DAC simulations, a time step of 2 fs was used to account for the presence of explicit hydrogen atoms. Bond lengths in surfactant molecules were constrained using LINCS,52 while water geometry was constrained using SETTLE.53 Energy minimization was performed before and after the addition of water and counterions to keep the maximum force on any atom below 2000 kJ mol$^{-1}$ nm$^{-1}$. Further position-restraint runs of duration 20 ps were employed by harmonically restraining the headgroup atoms with a force constant of 1000 kJ mol$^{-1}$ nm$^{-2}$ to allow water molecules to relax around the micelle. The full MD run lasted 6 ns, and trajectories were saved every 1 ps. The last 5 ns were used for analysis, during which the potential energy remained stable.

2.2. Simulation of Micelles with 40-Monomer PEO. To prepare the polymer–micelle systems, a 40-monomer PEO chain (Scheme 2) was added within 5 Å of the surface of each equilibrated micelle, yielding a total ethylene oxide concentration of 0.31 M. Any overlapping waters whose oxygens lay within 3 Å of any of the polymer atoms were then removed. In simulating PEO in water, we discovered earlier that the standard GROMOS 45a3 Lennard-Jones potentials for united atom carbons and oxygens produced a collapsed PEO chain, insoluble in water.17 The likely cause is that GROMOS forcefields are tuned for biological macromolecules where esters are more common than ether groups. To repair this, we adjusted the forcefield parameters for PEO using 1,2-dimethoxymethane (DME) as a model compound and matched its hydration enthalpy and conformational behavior (i.e., percentage of gauche O–C–C–O dihedrals) to the experimental values. The details of our model for PEO and its parameters are discussed in ref 17. The simulation conditions for the polymer–micelle systems were identical to those used in the polymer-free micelle simulations, with polymer atoms also harmonically restrained in the position-restraint equilibration runs. The equilibration of the system during the final MD run was monitored both through the Lennard-Jones (LJ) potential between the micelle and PEO, calculated as the sum of the LJ interactions between all micelle atoms and PEO atoms, and through the number of ethylene oxide monomers adsorbed over time. A monomer was consid-

<table>
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<th>TABLE 2: Dumbbell Solvent Parameters</th>
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<tr>
<td>parameter</td>
</tr>
<tr>
<td>atom type</td>
</tr>
<tr>
<td>bond length</td>
</tr>
<tr>
<td>Lennard-Jones $\sigma$</td>
</tr>
<tr>
<td>Lennard-Jones $\epsilon$</td>
</tr>
<tr>
<td>partial charges (e)</td>
</tr>
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</table>

ered adsorbed if its ether oxygen was within 5 Å of any micelle atom. The simulations were visually inspected to ensure that no adsorbed polymers were bridging periodic images of the micelle. After equilibration, each simulation was extended for at least an additional 10 ns for data collection.

A distance criterion of 5 Å for an adsorbed monomer is appropriate because it allows us to compare the extents of polymer–micelle interaction obtained in MD simulations with those obtained in experiments.3,9,39 In ref 9, Gao et al. used NMR paramagnetic relaxation measurements to obtain the number of associating monomers, which they defined to be those within the electric double layer of the micelle. In our earlier work,17 we found that for an SDS micelle the first two counterion shells extend to about 5 Å from the micelle surface. Further, in ref 8 and ref 39, the number of associating monomers was obtained through isothermal titration calorimetry, by measuring the increase in enthalpy as surfactant is gradually added to a polymer solution. The endothermic effect likely occurs as the adsorbing polymer displaces the first shell of hydration waters around the surfactants. In our simulations, this first shell lies within 5 Å from the micelle surface. Therefore, by considering those monomers within 5 Å of the micelle as adsorbed, we can appropriately compare the interaction strengths obtained from simulation with those from experiment.

2.3. Simulation of Micelles and PEO in Dumbbell Solvent. Our dumbbell solvent was created by connecting two SPC water oxygen atoms by a bond length of 1 Å. Partial charges on the atoms are $-0.82e$ and $0.82e$, respectively, which gives a dipole moment of 3.94 D, compared to 2.27 D for SPC water.54 We have used a larger dipole moment for the dumbbell solvent than exists in SPC water because simulations of micelles in a dipole solvent made to match the dipole moment of SPC water by reducing the partial charge magnitude to 0.47e resulted in breakup of the micelle. Therefore, we have chosen to use the original partial charge of the SPC oxygen for our dumbbell solvent model. The parameters for our dumbbell solvent model are given in Table 2.

Before simulating micelles and polymers in the dumbbell solvent, a cubic box with length of 4 nm containing pure dumbbell solvent was simulated for 1 ns, allowing the solvent to equilibrate. Temperature and pressure control parameters, as well as treatment of electrostatics and LJ interactions, were identical to those used in the micelle–polymer simulations. After equilibration, each micelle was then solvated with equilibrated boxes of the dumbbell solvent. System preparation after the addition of dumbbell solvent was analogous to the procedure used for the simulations using water as solvent. PEO was added by first placing the polymer within 5 Å of the surface of each equilibrated micelle and then removing any overlapping solvent atoms that lay within 3 Å of any PEO atom. The final MD run parameters were identical to those used for the simulations of micelles and polymers in water.

2.4. Simulation of Micelles with Multiple 20-Monomer PEO Chains. To study polymer–micelle behavior at higher levels of adsorption, we performed simulations of multiple 20-monomer PEO chains in the presence of (−)DTAC in both water.
and dumbbell solvent. Using larger numbers of shorter polymer chains allows us to mimic systems with longer PEO chains without having to greatly increase the system box size. For each concentration of polymer, three separate simulations were performed starting from different initial configurations of the polymer chains to obtain wider sampling of the adsorption behavior. Each system was arranged by initially centering an equilibrated micelle in a truncated octahedron with periodic image distance 6.54 nm and then randomly distributing polymer chains around the micelle, removing any overlapping solvent molecules. The number of chains was varied from 3 to 12, yielding ethylene oxide concentrations from 0.46 to 1.85 M. We note that the polymer and surfactant concentrations used in our simulation are at least an order of magnitude higher than those used in experiments. However, as we will discuss shortly, we believe these higher concentrations do not have any qualitative effect on our results and main conclusions.

The simulation conditions and equilibration monitoring were identical to those used for the simulations with a single 40-monomer PEO chain with a micelle. The simulations were visually inspected to ensure that no adsorbed polymers bridged periodic images of the micelle. After equilibration, each simulation was extended for at least an additional 10 ns for data collection. Details of the simulations are summarized in Table 3. A typical run of 20 ns took about 200 h on a dual quad-core AMD Opteron processor.

### 3. Results

First, we show that our simulations are consistent with experimental results. This provides us a foundation from which we can investigate further the molecular details that affect the association process. In addition, we use our MD simulations to investigate the shortcomings of traditional models of polymer–micelle interaction that cannot account for certain experimental observations, such as the lack of PEO interaction with cationic DAC micelles. From our simulations of (−) and (+)SDS, (+) and (−)DTAC, and DAC, along with PEO, we observe that the sign of the headgroup charge has a much larger effect than the headgroup size on polymer–micelle interactions. This means that the preference for PEO to interact with anionic micelles is likely due to either indirect solvent-mediated interactions or to direct electrostatic interactions between the polymer and micelle. We perform simulations in a dipolar dumbbell solvent to further probe the importance of these effects.

#### 3.1. Comparison of Simulation Results with Experiment

Experiments with many different surfactant micelles have confirmed that nonionic water-soluble polymers such as PEO interact with anionic micelles but not with cationic ones. For example, PEO interaction with the anionic micelle (−)SDS has been observed from surface tensiometry, NMR spectroscopy, light scattering, viscometry, conductometry, and isothermal titration calorimetry. PEO interactions with other anionic micelles with carboxylate and malonate headgroups have also been reported. Other experiments have shown that at room temperature PEO does not interact with cationic micelles, such as those with trimethylammonium (TMA). As described below, our simulations of interactions of PEO with (−)SDS, (+)DTAC, and DAC micelles agree with these experimental results.

#### Anionic (−)SDS Micelle

We have already reported in ref 17 simulations showing that PEO interacts strongly with the anionic (−)SDS micelle. In brief, the PEO wraps around the (−)SDS surface, weaving in between the sulfate headgroups and adsorbing selectively onto the hydrophobic regions of the micelle surface. On average, the PEO is located slightly beneath the headgroups at a position closest to that of the O₆ atom (see Scheme 1). We also quantified the degree of adsorption by defining an ethylene oxide monomer as adsorbed when its ether oxygen is within 5 Å of any micelle atom. Figure 1 shows the degree of PEO adsorption onto (−)SDS over time and indicates that the short 40-monomer chain adsorbs almost completely onto the surface. We have also performed simulations of different numbers of 20-monomer PEO chains interacting with the

#### TABLE 3: Overview of Polymer–Micelle Simulations

<table>
<thead>
<tr>
<th>Micelle type</th>
<th>Solvent type</th>
<th>n-mer PEO</th>
<th>[EO] (M)</th>
<th># surfactants</th>
<th>[Surfactant] (M)</th>
<th># solvent molecules</th>
<th>Equilibration time (ns)*</th>
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<tr>
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*Average values are given for simulations with 20-mer PEO chains. Full production runs add an additional 10 ns.
The extents of polymer–micelle interaction at both high and low PEO concentrations are in excellent agreement with those obtained from experiment. Gao et al. found that at low PEO concentrations roughly 90% of the monomers are associated with the micelle, while at high PEO concentrations about 114 monomers are required to saturate the micelle. Meanwhile, Bernazzani et al. and Dai et al. report that a PEO chain of molecular weight 4000 Da (≈91 monomers) is the optimum length to bind a 60-surfactant SDS micelle. The ability of our simulations to quantitatively reproduce experimental trends in degree of PEO adsorption also provides support for the accuracy of our PEO model.

**Cationic (+)DTAC and DAC Micelles.** Meanwhile, we observe little or no interaction of a 40-monomer PEO with the cationic micelles (+)DTAC and DAC. This is seen by plotting the number of adsorbed monomers over time, as shown in Figure 2 for (+)DTAC and DAC. For both micelles, we observe that PEO adsorption is either very weak or simply not present at all. The apparent interactions are largely the result of thermal fluctuations and the relatively high concentrations of both micelle and polymer used in the simulations relative to those in experiment. To confirm this, we also simulated systems with PEO initially placed inside the (+)DTAC and DAC micelles. Details of the preparation are analogous to those used for the PEO/(−)SDS system described in ref 17. We eventually observed rehydration of the PEO chains and dissociation from the micelles, confirming that PEO remains largely dissociated from the cationic micelles in the aqueous systems.

The weakness of PEO adsorption to both the large (+)DTAC and small cationic DAC headgroups indicates that surfactant headgroup size plays only a weak role in polymer adsorption, in contrast to the traditional view that it is the large headgroup size that is primarily responsible for preventing the PEO polymer from interacting with the hydrophobic regions of the micelle surface. Our simulations serve as a complement to experimental results which also undermine arguments based on headgroup size. Although our simulations show that PEO does seem to interact with DAC slightly more favorably than (+)DTAC, its interaction is still much weaker than its interaction with (−)SDS. According to arguments based on headgroup size, one would expect PEO to interact strongly with DAC micelles since the ammonium headgroup volume is even smaller than that of the sulfate headgroup.

**3.2. Simulations of Charge-Inverted Micelles with PEO.** The above discussion indicates that the headgroup size is not playing nearly as large a role as previously suggested and the sign of the headgroup charge is more important in modulating polymer–micelle interactions. It has in fact been previously argued that it is the positive charge of the cationic micelle that tends to prevent PEO adsorption. Such arguments typically hinge on the claim that the ether oxygens of PEO are partially protonated, and therefore, the electrostatic repulsion between the “partially positive” protonated ether oxygens and cationic headgroups prevents the polymer from adsorbing onto the micelle surface. However, the low pKₐ value (≈3.5) of the ether group indicates significant partial protonation is highly unlikely at the neutral pH conditions used in experiments. Furthermore, electrostatic repulsion obviously cannot explain why nonionic micelles also do not interact with PEO. Therefore, while the sign of the headgroup charge is important, prior arguments based on “charge repulsions” between the micelle and polymer seem to be misplaced. As we discuss below, our simulations suggest alternative mechanisms for electrostatic interactions in polymer–micelle behavior.

**Anionic (−)DTAC Micelle.** To study the influence of the sign of the headgroup charge on PEO adsorption, we simulated (−)DTAC micelles interacting with a 40-monomer PEO. These inverted partial charge assignments are given in Table 1. Our expectation is that if the sign of the headgroup charge is an important factor in determining polymer–micelle interaction then the anionic (−)DTAC micelle should adsorb PEO. This is exactly what we observe in our simulations. A typical snapshot is provided in Figure 3, which shows that the polymer adsorbs onto the hydrophobic regions of the micelle surface and weaves in between the headgroups, just as is observed for the anionic SDS micelle in ref 17. By computing radial distribution functions of the surfactant and polymer atoms to the micelle center-of-mass, shown in Figure 4, we find that on average an adsorbed oxygen is located slightly beneath the headgroup at a position closest to that of the C2 atom on (−)DTAC, labeled as the second carbon from the headgroup in Scheme 1. By computing changes in solvent-accessible surface areas of the micelle, we also observe that the polymer adsorbs selectively onto the hydrophobic regions of the micelle surface.
onto the (−)DTAC micelle surface over time, shown in Figure 6, we observe that roughly 90% of the monomers are adsorbed after 10 ns, similar to the case for adsorption onto (−)SDS.

The observation that (−)DTAC micelles adsorb PEO, while still possessing large TMA headgroups, further discredits the idea that the large headgroup size alone should prevent polymer adsorption.13,30,35 This is consistent with the experimental observation that PEO interacts with anionic malonate surfactants,40 which also possess large headgroups. In Figure 7, the radial distribution functions between headgroup nitrogen atoms from the polymer-free micelle simulations show that the headgroups of (−)DTAC are actually packed more closely than those in (+)DTAC. Even so, it is only the (−)DTAC micelle that adsorbs PEO. Therefore, the MD results dispel the traditional notion13,30,35 that there is insufficient space between the large TMA headgroups in (+)DTAC for polymer adsorption. Instead, factors other than steric repulsion between the headgroups and polymer must prevent PEO adsorption when the headgroups are cationic.

Cationic (+)SDS Micelle. In contrast to the PEO/(+)DTAC system, we observe significant polymer interaction with the (+)SDS micelle, as seen in Figure 8. However, the interaction in this case is electrostatic rather than hydrophobic, as the PEO segments wrap around the headgroup and adopt structures similar to those of crown-ethers, as seen in the snapshot in Figure 9. This structure is also reflected in radial distribution functions between the headgroup sulfur atoms and polymer atoms, as seen in Figure 10. The PEO oxygens are attracted
toward the (+)SDS headgroup, and the polymer atom peaks are well-defined, which is indicative of the local crown-ether structure. Near the (−)SDS headgroup, however, the PEO oxygens are repelled, and the polymer atom peaks are broader due to a less defined polymer structure around the headgroups.

The wrapping of PEO segments around the sulfate headgroups when they are made artificially cationic is not entirely surprising, given the ability of PEO and crown-ethers to coordinate with cations in aqueous solution.58,59 Placing a positive charge on the headgroup oxygens eliminates their ability to accept hydrogen bonds from water while introducing an electrostatic attraction with PEO oxygens. However, we observe that this attraction can be eliminated by either increasing the size of the sulfate “oxygens” or eliminating their Lennard-Jones (LJ) interaction parameters. This is consistent with the lack of headgroup complexation by PEO in (+)DTAC and DAC micelles in our simulations. Meanwhile, reducing the partial charge of the cationic sulfate “oxygens” to 0.25e still leads to crown-ether formation, suggesting that these structures mainly arise due to differences in LJ interactions of the PEO oxygens with the sulfate and methyl headgroups. The repulsive C12 parameter between the sulfate and PEO oxygens is more than three times lower than the C12 parameter between the methyl group and PEO oxygens, as shown in Table 4. For negatively charged sulfate oxygens, this weaker LJ repulsion is coupled to an electrostatic repulsion between the oxygens. However, once the sign of charge on the sulfate oxygen is switched, the weak LJ repulsion is now coupled to an electrostatic attraction, which creates a strong net attractive interaction between the oxygens allowing crown-ethers to form. In any case, although interaction is present in the (+)SDS system, the mode of interaction is different from that seen in anionic micelles. In general, we see that the hydrophobic mode of polymer–micelle interaction, which is of interest here, only occurs in systems with anionic micelles and that the interaction occurs regardless of headgroup size.

3.3. Effect of Micelle Hydrophobic Surface Area. The experimental and simulation results discussed above suggest that it is not merely the amount of available hydrophobic surface area on the micelle that modulates the strength of polymer adsorption. Indeed, as shown in Table 5, we find that (+)DTAC micelles actually have larger hydrocarbon–water surface areas than (−)DTAC micelles, yet only the (−)DTAC micelles adsorb PEO. Therefore, the lack of interaction of (+)DTAC with PEO observed in experiment cannot be attributed to any supposed lack of hydrocarbon–water interfaces on the cationic micelle surface, as had been previously suggested.13,30,35 Additionally, as seen in Table 5, the hydrocarbon–water surface area for (+)SDS is larger than that for (−)SDS, yet only (−)SDS associates hydrophobically with PEO. Therefore, the mere availability of hydrocarbon–water surface area on the micelle cannot be the sole factor in driving polymer adsorption. Our MD simulations suggest that additional forces, which depend upon the sign of the headgroup charge, also modulate the interaction.

3.4. Simulations of Micelles and PEO in Dumbbell Solvent. One possible explanation for the preferential interaction of PEO with anionic micelles is that the hydration environment around cationic headgroups is unfavorable to PEO.29 Water molecules orient differently around cationic and anionic micelles,20,22 and this could explain the preference for nonionic water-soluble polymers such as PEO to interact with anionic micelles. These hydration effects are known to be important in mediating the interactions among biological molecules and modulating the stability of proteins in water and cosolvents.60 Furthermore, the hydrogen-bond network in water also plays a role in explaining several observations regarding polymer–micelle interactions. For example, the interaction of PEO with cationic micelles at higher temperatures has been attributed to disruption of the polymer hydration shells.31 In addition, the counterion effect on polymer–micelle interaction appears to follow the Hofmeister series,61 indicating that hydrogen-bond structure around counterions may be important in modulating polymer–micelle interaction.1,32,33 Therefore, it is reasonable to suggest that hydration asymmetries may also play a role in explaining the asymmetric behavior of polymers such as PEO toward micelles with respect to the sign of headgroup charge.

A reasonable hypothesis is that the oxygen atoms on PEO and anionic sulfate headgroups are stabilized by water bridges formed through hydrogen bonding and that this structure assists PEO in adsorbing onto the micelle surface. Water bridges have been observed previously in simulations of lipid membranes62 and have been found to modulate the mechanical unfolding of proteins.63 For cationic micelles, this solvent bridge would no longer be present, and lacking this stabilization, PEO would rather remain completely hydrated than adsorbed at the micelle surface. In our simulations of the PEO/(−)SDS system, we analyze the existence of water bridges and define a hydrogen bond as any approach of a donor oxygen OW to within 3.2 Å of an acceptor OAC that also forms an H_W−O_W−O_A angle less than 30°. As seen in Figure 11, we do observe water bridge formation upon polymer adsorption onto the micelle, although only about 12% of the adsorbed PEO oxygens are bridged by water to an SDS oxygen. From this, it is difficult to conclude that these water bridges are actually playing a decisive role in stabilizing the polymer–micelle complex.

However, we can also test the importance of water bridges by performing simulations of (+) and (−)DTAC micelles and PEO in a dipolar dumbbell solvent, where hydrogen bonding is no longer present. We have focused on using the DTAC pair of micelles since for our simulations in water the differences in PEO behavior toward the (+) and (−)DTAC micelles are clearly distinguished. If water bridging via hydrogen bonding plays an important role in mediating the polymer–micelle interaction, then we would expect that in the dumbbell solvent the preference for PEO to interact with anionic micelles would disappear.

(+)DTAC and (−)DTAC Micelles in Dumbbell Solvent. We have performed simulations of (+)DTAC and (−)DTAC micelles in the presence of PEO with our dumbbell solvent. We monitor the extent of interaction by counting the number of monomers adsorbed over time. As seen in Figure 12, PEO still interacts more strongly with the anionic micelle. On average, about 25 ± 3 monomers are adsorbed onto the (−)DTAC micelle.
micelle in the dumbbell solvent, compared to 36\% in water. Thus, while some 90\% of the 40 PEO monomers adsorb to the micelle in water, around 62.5\% adsorb in the dumbbell solvent. This value remains roughly constant over a period of about 10 ns, indicating a stable interaction between the polymer and the micelle. Meanwhile, the number of adsorbed monomers on (+)DTAC fluctuates, with the polymer periodically desorbing, indicating only weak interaction between the polymer and micelle.

Interestingly, however, replacing water with the dumbbell solvent does tend to strengthen the PEO interaction with (+)DTAC slightly but weaken its interaction with (−)DTAC. This weakened interaction in the dumbbell solvent also occurs at higher PEO concentrations, as illustrated in Figure 13, which shows the adsorption behavior as the number of 20-monomer PEO chains is increased. For all concentrations of PEO, we see that polymer interaction with the micelle is weakest in the dumbbell solvent, suggesting that solvent interactions play a modest role in the sign-dependent behavior of PEO interaction with micelles.

We note that our production runs for these systems typically range from 20 to 30 ns, which seems rather short given that micelle structural rearrangement may occur upon polymer adsorption. To determine if our systems remain stable at longer times, we extended the production runs for systems with ten polymer chains and monitored the extent of polymer–micelle interaction, measured by the number of adsorbed monomers. We observe that this quantity reaches its “equilibrium” value within roughly 20 ns and remains stable up to 50 ns, with fluctuations typically around 10 monomers, as shown in Figure 14. The equilibration times in our simulations are on the order of nanoseconds largely due to the small system sizes used in the simulations and our choice of a preformed micelle as an initial condition.

In the dumbbell solvent, the polymer–micelle structure for (−)DTAC is similar to the one formed in water. As seen in

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### TABLE 4: Lennard-Jones (LJ) Interaction Parameters between PEO Oxygens and Headgroup Atoms and Existence of Crown-Ether Structures

<table>
<thead>
<tr>
<th>micelle</th>
<th>headgroup “atom”</th>
<th>C6 (kJ mol(^{-1}) nm(^6))</th>
<th>C12 (kJ mol(^{-1}) nm(^{12}))</th>
<th>crown-ethers?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)DTAC</td>
<td>methyl</td>
<td>0.00466</td>
<td>5.81e-06</td>
<td>no</td>
</tr>
<tr>
<td>DAC</td>
<td>nitrogen(^a)</td>
<td>0.00235</td>
<td>3.76e-06</td>
<td>no</td>
</tr>
<tr>
<td>(+)SDS</td>
<td>oxygen</td>
<td>0.00226</td>
<td>1.51e-06</td>
<td>yes</td>
</tr>
</tbody>
</table>

\(^a\) Hydrogen atoms on DAC headgroup have no LJ parameters.

### TABLE 5: Solvent-Accessible Surface Areas (nm\(^2\)) of Polymer-Free Micelles and Average Number of Monomers Adsorbed during Polymer–Micelle Simulations in Water

<table>
<thead>
<tr>
<th>hydrophobic</th>
<th>hydrophilic</th>
<th>total surface area</th>
<th># monomers adsorbed</th>
<th>adsorption mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>(−)DTAC</td>
<td>37.0</td>
<td>56.6</td>
<td>93.6</td>
<td>36 ± 2</td>
</tr>
<tr>
<td>(+)DTAC</td>
<td>43.1</td>
<td>62.8</td>
<td>105.9</td>
<td>0.3 ± 0.8</td>
</tr>
<tr>
<td>(−)SDS</td>
<td>50.2</td>
<td>54.5</td>
<td>104.7</td>
<td>35 ± 3</td>
</tr>
<tr>
<td>(+)SDS</td>
<td>54.0</td>
<td>60.5</td>
<td>114.5</td>
<td>38 ± 2</td>
</tr>
<tr>
<td>DAC</td>
<td>54.3</td>
<td>23.0</td>
<td>77.3</td>
<td>2 ± 3</td>
</tr>
</tbody>
</table>

---

Figure 11. Number of water bridges formed between (−)SDS and PEO. Black line indicates block average over a period of 1 ns.

Figure 12. Number of EO monomers adsorbed onto (+) and (−)DTAC micelles in dumbbell solvent.

Figure 13. Extent of polymer adsorption as a function of polymer concentration. Error bars represent standard deviations obtained from three independent simulations at each polymer concentration. Results for the (−)SDS/water system were taken from ref 17.

Figure 14. Number of EO monomers adsorbed onto micelles in systems with ten 20-mer PEO chains. Extended runs indicate polymer–micelle interaction is stable at longer time scales.
which modest adsorption occurs. This allows us to determine if there is any local effect of the cationic headgroups on the structure of nearby PEO atoms. As seen in Figure 17, we observe that the sign of headgroup charge does affect the local structure of polymer carbon and oxygen atoms around the headgroup. In addition, to stabilize a PEO segment near a cationic headgroup, it appears that the smaller oxygen atom must approach the headgroup more closely than the larger carbon (or methylene) unit near an anionic headgroup. This difference in structure suggests that direct electrostatic interactions between the polymer and micelle could influence their association behavior. Calculations of Coulomb interactions among atoms in (−)DTAC micelles and PEO indicate a slight electrostatic attraction, consistent with the ordering of polymer atoms shown in Figure 17.

4. Discussion

4.1. Limitations. System Size and Concentrations. Although our atomistic MD simulations provide detailed molecular insight into the structure of polymer−micelle complexes, they cannot validate experimental cmc’s and aggregation numbers since larger system sizes must be investigated to do so. Due to the high computational cost of simulating system sizes of tens of nanometers, we are limited to simulating one micelle in the presence of short-chain polymers. In addition, we have used a preformed micelle in the starting state for the simulation, and although it remains stable over the course of the simulation, it is unknown if the forcefields used in this study can reproduce experimental cmc’s and aggregation numbers, given an initial configuration farther from equilibrium. Although we cannot be sure that our MD simulations are able to reproduce such thermodynamic behavior, they nevertheless allow us to study the atomistic and molecular details of the polymer−micelle complex. This enables us to investigate the possible factors that explain why neutral polymers such as PEO prefer to interact with anionic micelles over cationic micelles.

Experimentally, the surfactant and polymer concentrations affect equilibrium micelle aggregation numbers and polymer−micelle interactions. In our simulations, these concentrations are at least an order of magnitude higher than the experimental concentrations. At such high concentrations in experiment, the micelles may be larger in size and exhibit polydispersity which cannot be captured by our simulations. When studying the interaction of PEO with cationic micelles (−)DTAC and DAC, the high concentrations used in the simulation give the polymer and micelle a relatively high probability to meet each other, which occasionally leads to weak adsorption of PEO onto the micelle surface but never any strong interactions between them, as seen in Figure 2. Thus, the relatively high concentrations of surfactant and polymer have no qualitative effect on our main conclusions. In addition, the ratio of polymer-to-surfactant concentrations is well within experimental limits, and we have shown that the stoichiometry of the PEOP/(−)SDS system is in quantitative agreement with experiment at the relative polymer-to-surfactant concentrations studied in our simulations.

Simulation Time Scales. Although we are unable to obtain true thermodynamic equilibrium from MD simulation, we believe that our variables of interest, mainly the numbers of interacting PEO monomers, are sufficiently equilibrated during the simulations. We have performed longer simulations to show that the observed extent of PEO interaction is robust at longer time scales, as seen in Figure 14. Similarly, time scales for polymer diffusion and adsorption onto the micelle are within

Figure 15. Radial distribution functions of selected (−)DTAC and PEO atoms relative to micelle center of mass (COM) in dumbbell solvent, averaged over the last 15 ns. Atom labels refer to those in Schemes 1 and 2.

Figure 16. Surface coverage of (−)DTAC micelle by PEO in dumbbell solvent.

Figure 17. Radial distribution functions between PEO atoms and methyl headgroup atoms for (a) (−)DTAC micelle in water, (b) (−)DTAC micelle in dumbbell solvent, and (c) (+)DTAC micelle in dumbbell solvent.
Thus, the preference for PEO to interact with anionic micelles is evidently mostly due to direct electrostatic interactions between the polymer and micelle. For anionic micelles, these electrostatic interactions seem to complement the adsorption of PEO onto the hydrophobic regions of the micelle surface. For cationic micelles, the electrostatic interactions seem to compete with the hydrophobic interactions that drive polymer adsorption onto the micelle surface. Such differences in interaction can exist even though the polymer is overall neutral since its atoms still carry partial charges. An extreme example of these electrostatic effects on polymer structure was shown for (−) and (+)SDS micelles in Figure 10, although they are also present for (+) and (−)DTAC micelles, as illustrated in Figure 17.

Therefore, a possible explanation of the preference for PEO to adsorb onto anionic micelles is an additional electrostatic attraction between the polymer carbons and headgroup atoms when the headgroup charge is negative. This electrostatic attraction would assist the strong hydrophobic interactions that stabilize polymer complexes with anionic micelles. Such a mechanism, however, would require that electrostatic interactions between the micelle and polymer be dominated by interactions between the headgroup and polymer carbons, rather than polymer oxygens, since the polymer is overall neutral. We suggest that this may be possible given the asymmetry in partial charge distribution of PEO. The placement of negative charges on the smaller oxygen atoms and positive charges on the larger carbon (or methylene) units may result in differences in polymer behavior toward anionic and cationic micelle surfaces, even though the polymer overall carries no net charge. Further simulations should investigate the extent to which the partial charge distribution on the polymer modulates polymer−micelle behavior.

5. Conclusion

From MD simulations, we have found that the sign of the headgroup charge itself dominates the preference for PEO to adsorb onto anionic micelles. As evidence for this, first we have reproduced the experimental observation that PEO interacts strongly with anionic SDS micelles but only weakly with cationic DTAC and DAC micelles. Then, by switching the sign of the headgroup charge on SDS and DTAC surfactants, we observed PEO interaction with the anionic (−)DTAC but a lack of hydrophobic interaction with the cationic (+)SDS micelle. These results suggest that the extent of PEO interaction correlates more strongly with the sign of the headgroup charge than the headgroup size, which provides further evidence against the traditional view that the large headgroup size on cationic micelles prevents polymer interaction.

We have observed that this preference for PEO adsorption onto anionic micelles also occurs, although to a somewhat weakened degree, in a symmetric dipolar dumbbell solvent, with a single positive fractional charge, as well as in water, with its two positive fractional charges on the hydrogen atoms. Therefore, it does not appear that the asymmetric geometry of water or any resulting solvent bridge formation plays a dominant role in the preferential interaction of PEO with anionic micelles. It appears instead that direct electrostatic interactions between the polymer and micelle are most responsible for the preference for interaction with anionic micelles. We suggest that the asymmetric distribution of negative charges on smaller atoms and positive charges on larger units in the PEO chain may allow the polymer to behave differently toward anionic and cationic micelles, even if the polymer is overall neutral.
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References and Notes

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