



Effect of diffuseness of micelle boundary on the solute distribution upon solubilization



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ABSTRACT

Micelle is a soft aggregate of surfactants, and its boundary with the aqueous region is diffuse. All-atom molecular dynamics simulation is conducted in the present work to elucidate the effect of diffuseness of the micelle–water boundary on the distribution of hydrophobic solute bound to micelle. A restraining potential is applied to the headgroup atoms in surfactant for controlling the diffuseness of the boundary, and it is found that when the boundary is sharper, the micelle has less homogeneous structure and binds the hydrophobic solute through less flat free-energy profile with respect to the binding depth.

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1. Introduction

Micelle is a self-organizing aggregate of amphiphilic surfactants in water. A major function of micelle is solubilization, the enhancement of the solubility of a solute that is insoluble or sparingly soluble in water. The extent of solubilization is typically expressed by viewing the micellar region as a ‘pseudophase’ [1]. The location of the micelle–water interface cannot be defined precisely at Å resolution, though. Water penetrates into a micelle, and the boundary is diffuse between the micellar and aqueous regions. The purpose of the present work is to examine the effect of boundary diffuseness on the solute distribution in micelle using molecular dynamics (MD) simulation.

The solubilization results from the contrast of the interactions among water, surfactants, and the solute to be bound into the micelle. An all-atom treatment is then necessary for quantitative description of a micellar solution. MD meets this necessity, and can determine the atomic distributions of water and of hydrophobic tail and hydrophilic headgroup of the surfactant under the used set of potential functions. When the micelle is small and spherical (on average), the headgroup occupies a diffuse region typically of several Å thickness [2–12]. The distribution of the headgroup at instantaneous (snapshot) configuration is not spherical, furthermore, and it becomes spherical only after the averaging over statistical ensemble and/or time.

An advantage of MD is that an arbitrary potential field can be exerted on a selected set of atoms. In the present work, we exploit this advantage to control the diffuseness of the boundary between the micellar and aqueous regions and see the effect of boundary diffuseness on the free energy of binding an organic solute into micelle. The basic idea is to apply a restraining potential on headgroup atoms. The radial distance of the headgroup atom from the micellar center is first averaged without any restraint, and the restraint is then introduced relative to the average distance. In this procedure, the force constant within the restraining potential controls the diffuseness of the radial distance of the headgroup from the micellar center; when the restraint is strong enough, the headgroup is kept at virtually constant distance and the micelle is spherical at any instant.

The focus of the present work is the free-energy profile of binding hydrophobic solute into a micelle of sodium dodecyl sulfate (SDS, $\text{CH}_3(\text{CH}_2)_{11}\text{OSO}_3^- \text{Na}^+$) in water. We examine the dependence of the free-energy profiles for methane and benzene on the extent of diffuseness of the micelle–water boundary, and find that the free-energy profile is more flat when the boundary is more diffuse. It should be noted that the headgroup plays a key role in determining the structure and function of a micelle. The present work is a model study, and aims at obtaining the general view on the effect of the spatial distribution of headgroup.

2. Methods

The SDS micelle was investigated in water both with and without solute. The solutes examined were methane and benzene. The force fields adopted were TIP3P for water (the CHARMM version

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with non-zero Lennard–Jones parameters on the hydrogen sites), CHARMM36 for SDS, and CHARMM22 for methane and benzene [13–15]. The aggregation number of the micelle was set to 60, a value close to the experiment [16], and a spherical micelle was generated with CHARMM–GUI Micelle Builder [17]. All the molecular dynamics (MD) simulations were conducted with NAMD2.9 in the isothermal–isobaric (*NPT*) ensemble at 25 °C and 1 atm [18]. The unit cell was cubic, and the periodic boundary condition was employed with the minimum image convention. 60 dodecyl sulfate anions, 60 sodium cations, and 10 000 water molecules were located in the unit cell, also with a single solute molecule when the micellar system is simulated with solute. In the following, the center of micelle refers to the center of mass of the 60 sulfur atoms.

The electrostatic interaction was handled by the smooth particle-mesh Ewald (PME) method with a real-space cutoff of 12 Å, a spline order of 6, a tolerance of 10^{-6} (inverse decay length of 0.258 \AA^{-1}), and a reciprocal-space mesh size of 75 for each of the *x*, *y*, and *z* directions [19]. The Lennard–Jones (LJ) interaction was truncated by applying the switching function in the range of 10–12 Å [20]. The truncation was done on atom–atom basis both for the real-space part of PME interaction and the LJ interaction, and the long-range correction of LJ interaction was not included. The Langevin dynamics was employed for temperature control at a damping coefficient of 1.0 ps^{-1} and was integrated with the Brünger–Brooks–Karplus algorithm at a time step of 2 fs [21]. The pressure was maintained by the Langevin piston Nosé–Hoover method with barostat oscillation and damping time constants of 200 and 100 fs, respectively [22,23]. The lengths of the bonds involving the hydrogen atom were fixed with SHAKE, and the water molecules were kept rigid with SETTLE [24,25]. Throughout the present work, the center of micelle was restrained to the center of the MD unit cell using a harmonic potential of $A s^2/2$, where *s* is the radial distance in Å between the micellar center and the center of the MD cell and $A = 1 \text{ kcal/mol/\AA}^2$. This restraint was employed only to prevent possible complications in handling the simulation data due to the periodic boundary condition, and does not affect the statistical quantities of interest. The MD length for the SDS system without solute was 10 ns with a sampling interval of 2 ps.

The diffuseness of the boundary between the micellar and aqueous regions was controlled by applying a restraining potential on each sulfur atom in the harmonic form of

$$\frac{k}{2}(r - r_0)^2, \quad (1)$$

where *r* is the radial distance of sulfur from the micellar center in Å and *k* is the force constant. r_0 is the average of *r* at $k = 0$ (no restraint) without solute and is equal to 19.1 Å. The controlling parameter for the diffuseness is *k*, and MD was conducted at $k = 0$ and at $k = 0.2$ and 1 kcal/mol/Å² with $r_0 = 19.1 \text{ \AA}$. We will see in Section 3 that the micellar center becomes less dense with non-zero *k*. To ‘refill’ the micellar center in the presence of restraint and examine the effect of r_0 at fixed *k*, additional analyses were done with a smaller r_0 of 17.0 Å at $k = 1 \text{ kcal/mol/\AA}^2$, and are presented in Appendix A.

When the SDS system was simulated without solute, the average size of cavity in micelle was also calculated for each set of *k* and r_0 at radial distances of $r = 0.2, 0.4, \dots, 30.0 \text{ \AA}$ from the center of micelle in the following manner. A reference point in the system was first set at the distance *r* from the micellar center listed above, and the cavity size was determined as the minimum of the distances between the reference point and the heavy (non-hydrogen) atoms in the system. At each distance *r* from the center of micelle, the reference point was sampled 100 times to random direction, and the cavity size was averaged over the directions and over the snapshot configurations of the SDS system without solute.

At each restraining condition of the diffuseness (each set of *k* and r_0 in Eq. (1); $k = 0$ corresponds to the system without restraint), the

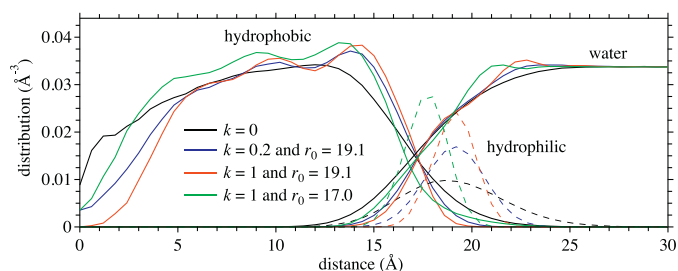


Figure 1. Densities of the hydrophobic tail (solid lines at smaller distances), the headgroup (dashed lines), and water (solid lines at larger distances) as functions of the radial distance from the micellar center at $k = 0$ (no restraint), $(k, r_0) = (0.2, 19.1)$, $(k, r_0) = (1, 19.1)$, and $(k, r_0) = (1, 17.0)$ in Eq. (1), where *k* and r_0 are expressed in the units of kcal/mol/Å² and Å, respectively. The density of the hydrophobic tail refers to the sum of the (number) densities of the carbon atoms of the dodecyl sulfate anion, and the density of the headgroup is the sum of the (number) densities of the sulfur and oxygen atoms. The water density is shown with respect to the center of mass of the water molecule.

SDS micelle with solute was simulated with the method of umbrella sampling. The umbrella potential was implemented as

$$\frac{K}{2}(R - R_c)^2, \quad (2)$$

where *R* is the radial distance of the solute center of mass from the micellar center in Å and 16 windows were prepared at $R_c = 0, 2, \dots, 30 \text{ \AA}$. At each R_c (and each set of *k* and r_0), two simulations were carried out to compute the potential of mean force between the solute and the micellar center and the average interaction energy of the solute with the other molecules. To compute the potential of mean force, *K* was set at 1 kcal/mol/Å² so that the distributions of *R* have widths of $\sim 2 \text{ \AA}$ and overlap sufficiently with those in the neighboring windows. The free-energy profile of binding the solute into the SDS micelle was then determined from the *R* distributions using WHAM (weighted histogram analysis method) [26,27]. When the average interaction energy of the solute was calculated, *K* was taken to be 250 kcal/mol/Å² to keep *R* close to R_c within $\sim 0.1 \text{ \AA}$. With this setup, the average interaction energy calculated is essentially the value for the solute with fixed distance R_c from the center of micelle. The MD length for each window of the umbrella sampling was 20 ns with a sampling interval of 2 ps.

3. Results and discussion

When *k* of Eq. (1) was increased to 0.2 and 1 kcal/mol/Å² at $r_0 = 19.1 \text{ \AA}$, the average of the radial distance of sulfur from the micellar center was found to stay at 19.1–19.2 Å in the absence of solute. This average is in correspondence to the value without restraint ($k = 0$), and the restraint at the fixed r_0 keeps the overall ‘size’ of micelle. In the present section, we focus on the effect of *k* at fixed $r_0 = 19.1 \text{ \AA}$. A supplementary treatment will be given in Appendix A for the variation of r_0 at fixed *k*.

Figure 1 shows the density profiles at each set of *k* and r_0 in Eq. (1) for the hydrophobic tail, the headgroup, and water in the micellar system without solute. Evidently, the restraint localizes the hydrophilic headgroup. Water penetrates less at larger *k*, furthermore, and the boundary is sharper between the micellar and aqueous regions. The extent of boundary sharpness/diffuseness may be quantified by the standard deviation of the distances of the sulfur atoms from the micellar center, and it was 2.7, 1.3, and 0.7 Å at $k = 0, 0.2$, and 1 kcal/mol/Å², respectively, without solute. In the central portion of the micelle, it is notable in Figure 1 that the density reduces with *k* at fixed r_0 . This means that the boundary diffuseness acts to ‘fill’ the micellar core with the hydrophobic tail. In the outer portion of hydrophobic-tail region and the aqueous region in the vicinity of the headgroup, fine structures develop

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