Graphical Abstract

Molecular Dynamics Simulation Study of Sodium Dodecyl Sulfate Micelle: Water Penetration and Sodium Dodecyl Sulfate Dissociation

Byeong Jae Chun,^{†,‡} Ji Il Choi,[‡] and Seung Soon Jang^{‡,*}

[†] School of Chemical & Biomolecular Engineering, Georgia Institute of Technology, 311 Ferst Drive NW, Atlanta, GA 30332-0100, USA

[‡] Computational NanoBio Technology Laboratory, School of Materials Science and Engineering, Georgia Institute of Technology, 771 Ferst Drive NW, Atlanta, GA 30332-0245, USA

* Corresponding author at: Computational NanoBio Technology Laboratory, School of Materials Science and Engineering, Georgia Institute of Technology, 771 Ferst Drive NW, Atlanta, GA 30332-0245, USA.
E-mail: SeungSoon.Jang@mse.gatech.edu

ABSTRACT

We investigate a micelle consisting of 60 sodium dodecyl sulfate (SDS) molecules in water phase using molecular dynamics simulation method. The dimension of the micelle is evaluated as ~ 16 Å and ~ 21 Å for the radius of gyration and geometric radius, respectively, which are well agreed with the previous studies. By calculating the formation energy, it is found that the stability of micelle is driven by the interaction of the micelle with water phase. Via Connolly surface analysis, it was found that ~ 58 % of the micelle surface is occupied by the hydrophobic alkyl tails. The conformation analysis shows that the individual SDS molecules are bent within the micelle and are not aligned radially from the center-of-mass of the micelle. However, it turns out that the micelle is well packed with a small free volume (0.35 % of the micelle volume) which does not allow the diffusion-in of water molecules. The PMF required to drag a water molecule from water phase to the center-of-mass of micelle is calculated as ~ 10 kcal/mol while the PMF for a SDS molecule to be dissociated from the micelle is ~ 13 kcal/mol, both of which demonstrate that the micellization is driven by minimizing unfavorable interaction of hydrophobic alkyl tail of SDS molecule with water phase.

Keywords: sodium dodecyl sulfate, micelle, molecular dynamics simulation, potential of mean force

1. Introduction

Researches on micelle have been mainly focused on the thermodynamic and structural properties at various conditions of micellization such as concentration and temperature [1-7]. Recently, the scope of the study has been expanded to synthesize various types of amphiphilic molecules in order to harness the properties of micelle for various applications utilizing the compartmentalization capability such as drug delivery [8-12], nano-reactor [13-16] and so on. For instance, O'Reilly and coworkers have successfully demonstrated that the polymeric micelle can have the high catalytic activity and specificity as frequently observed in enzymes of natural systems [14-16]. Following the compartmentalization in micelle, another point of interest is the transport of small molecules through the micelle, which is relevant for their storage and release in such compartment. In this context, it should be noted that the fundamental understanding of the relationship between the micelle structure and the small molecular transport through micelle is the most essential information for achieving micelle design for desirable performance for various applications.

In this study, we investigated the micellar structure and corresponding transport property in sodium dodecyl sulfate (SDS) micelle using molecular dynamics (MD) simulation method. Please note that SDS micelle has been selected as a model system because it is the most intensively-characterized micelle through experimental analysis [17-33] and simulation methods [34-45]. In experimental approaches, various techniques such as light scattering [18-21], fluorescence [24, 25], SAXS [17, 31] and SANS [23, 26, 27] have been used to characterize the size, shape, aggregation and charge of the SDS micelle at various conditions for concentration and temperature. Here it is noted that, despite great development in such experimental analysis, it is still challenging to attain molecular-level information of the internal structure of the SDS micelle experimentally.

In this context, the molecular dynamics (MD) simulation methods have been extensively used to provide such detailed structural information on the micelle in general [46-66] as well as the SDS micelle [34-45]. In 1990, Shelley and coworkers [34] reported the first large scale 182-picosecond MD simulation study on 42 monomer SDS micelle, in which they found that ~12 % of the sodium ions form contact ion pairs with the micelle. In 1995, Mackerell [35] simulated

91 SDS micelle comprised of 60 SDS molecules for 120 ps, reporting radial density profile,
92 conformations of SDS monomer, and the motion of micelle in addition to SDS monomers using
93 CHARMM [67] force field and TIP3P [68] water model. Bruce et al. [36, 37] also performed 5-
94 nanosecond all-atom MD simulations using AMBER [69] force field, reporting detailed
95 structural analyses such as radius of gyration, micellar size, carbon atom distribution,
96 eccentricity, accessible surface area and so on. Yoshii and coworkers investigated the free
97 energy of the SDS micelle as a function of the number of monomers using thermodynamic
98 integration method and MD simulation to analyze the free energy of the micelle as a function of
99 the monomer [38]. They presented that the free energy is minimized at 57 monomers, which
100 comparable to the experimental aggregation numbers (55-75) [22, 24, 26, 28, 30]. Jalili and
101 Akhavan [42] used a coarse-grained MD simulation method with MARTINI force field [70] to
102 investigate the structure of SDS micelle, showing that the coarse-grained MD simulation can
103 describe the SDS micelle accurately. From the recent study done by Tang et al. performing large-
104 scale MD simulation using various FFs for SDS micelle, it was reported that the united-atom FF
105 for sulfate head group does not capture realistic rod-like or cylindrical micelles at high
106 aggregation number (>300) while there is no significant difference at low aggregation numbers
107 (60 or 100).

108 In this study, we revisited SDS micelle to elucidate the internal and surface structure,
109 particularly focusing on the packing of alkyl tails in the micelle by analyzing the conformation of
110 the individual SDS molecules, the internal free volume, and surface occupation of sulfate groups
111 and alkyl tails. Although the SDS micellar structures such as micelle size, monomer
112 conformation have been characterized in previous studies [34, 35, 39], please note that those
113 results were attained from relatively short MD simulations running for a few nanosecond.
114 Therefore, it is still desirable to thoroughly scrutinize the various aspects of the micellar structure
115 based on the long production run of 20 ns, which will provide more reliable characterization of
116 the micellar structure. In addition, the structural integrity and molecular transport in the micelle
117 is evaluated by calculating the potential of mean force (PMF) via the steered molecular dynamics
118 (SMD) simulation method, which is the free energy change of the system as a function of the
119 molecular displacement along the designated path. We think that the present study can provide

computational procedure to investigate the relationship of the molecular transport through micelle with the micellar structure.

2. Models and Simulation Methods

The SDS molecules were simulated using a full-atomistic model (Figure 1) with Dreiding FF.[71] The atomic partial charges for SDS were calculated using Mulliken population[72] with B3LYP/6-31G** through a quantum chemistry package, Jaguar [73]. The detailed values of the partial charges for the SDS molecule are summarized in Table 1.

For this simulation study, the aggregation number is set as 60 that has been found in experiments [22, 24, 26, 28, 30], and used in simulation studies [35-39, 42, 45]. To build a SDS micelle in water phase, first, we arranged 60 lines radially to occupy the space equally (Figure 2a), and subsequently replace them by 60 SDS molecules (Figure 2b) in simulation box ($91.4 \times 91.4 \times 91.4 \text{ \AA}^3$). This SDS micelle was solvated by 24,650 water molecules, so that the total number of atoms in the system was 76,533. Water molecules were described by F3C model.[74] Since the effect of the amount of water content in the system was proven to be insignificant [45], the box size was determined to be large enough to avoid the influence of neighboring self-image through the periodic boundary conditions. The temperature was maintained at 300K using Nosé-Hoover thermostat [75, 76]. The particle-particle particle-mesh (PPPM) method was used for the long-range electrostatic interaction calculation [77]. The equation of motion was integrated using velocity-Verlet algorithm with a time step of 1 fs [78]. A periodic boundary condition was imposed in all directions. The LAMMPS (large-scale atomic/molecular massively parallel simulator) code developed by Sandia National Laboratories was employed to perform MD simulations [79]. To equilibrate the system, first, we ran annealing simulation to relax the system out of the local minima. Then, we ran 18 ns of NVT MD simulation to reach the equilibrium state. The actual data collection for statistical analysis, we ran another NPT MD simulation at 1 atm for 20 ns. To verify the equilibration of the system, the radius of gyration (R_g) of micelle was calculated using the following definition [80]:

$$R_g^2 = \sum_i \frac{m_i (\mathbf{r}_i - \mathbf{R}_c)^2}{M} \quad (1)$$

where m_i and $\mathbf{r}_i$ denote the mass and position of the i -th atom, respectively, and $\mathbf{R}_c$ and M denote the position of the center of mass of the micelle and the total mass of the micelle, respectively. The plot of R_g over simulation time (Figure 3) confirms that the micelle is equilibrated during 20 ns NPT MD simulation.

To investigate the molecular transport through the SDS micelle, SMD simulation was employed to displace a molecule along a designated path to calculate the PMF based on Jarzynski's equality [81] (Equation (2)) under the assumption that the molecular displacement proceeds through quasi-static state.

$$\langle e^{-W/kT} \rangle = e^{-\Delta F/kT} \quad (2)$$

where W and ΔF denote the work done through the displacement of molecule and the corresponding free energy difference, respectively, and k and T is the Boltzmann constant and absolute temperature, respectively. The PMF expresses the amount of work required for the molecular displacement, whose difference between its initial and final values is interpreted as the free energy change. Using such SMD simulation method, first, we obtained the PMF for a single water transport from the water phase to the core of SDS micelle. As shown in Figure 4a, the PMF was calculated through performing six independent SMD simulations. The initial positions of the water molecule in all cases were approximately 20 Å away from the surface of micelle. The steered molecular displacement was performed at 2.0×10^{-5} Å/fs with the spring constant of 200.0 kcal/mol/Å, which were determined after testing various conditions to achieve the converged PMF. Similarly, we performed SMD simulations to investigate the dissociation of a SDS molecule from the micelle using the same conditions mentioned above. For this purpose, we displaced a single SDS molecule from the equilibrated micelle to water phase as shown in Figure 4b. The simulation was independently repeated six times.

171

172 3. Results and Discussion

3.1. Structures and Energetics of SDS Micelle

A snapshot in Figure 2c shows one of the equilibrated micelle structures in which we find that the hydrophobic alkyl tails of SDS aggregate well and hydrophilic sulfate groups are located on the micelle surface. The radial density distribution analysis (Figure 5) also exhibits a consistent feature of the micelle structure in which the hydrophilic sulfate groups are associated with water phase whereas the hydrophobic hydrocarbons are aggregated in the micelle to reduce their undesirable interaction with water.

An interesting observation in Figures 2b and 2c is that the number of the sulfate group is not many enough to cover the entire surface of micelle, meaning that a significant portion of the surface would be occupied by hydrophobic alkyl tails. Indeed, the radial density profile in Figure 5 reveals that the alkyl tails contacts water phase directly to a certain extent. To characterize the micelle surface quantitatively, we performed the Connolly surface analysis with the probe radius of 1.4 Å. Through the equilibrium state of the simulation, the total surface area, hydrophilic surface area (occupied by sulfate groups), hydrophobic surface area (occupied by alkyl tails) were calculated as $9854.9 \pm 207.3 \text{ Å}^2$, $4176.9 \pm 31.2 \text{ Å}^2$, $5679.7 \pm 201.1 \text{ Å}^2$, respectively, indicating that ~58 % of the micelle surface is occupied by alkyl tails. Therefore, it is confirmed that the 60 sulfate groups do not cover the entire micelle surface, which allow the direct contact between water phase and hydrophobic alkyl tail phase of the micelle.

Next, the dimension of micelle was evaluated by the geometric radius (R) (Equation (3)) [36, 42, 80, 82] since the radius of gyration (R_g) does not necessarily represent the apparent size of micelle since it has been known that R_g is highly dependent on the mass distribution within the object. The geometric radius of micelle is frequently calculated from its correlation with R_g as defined in Equation (3):

$$R = \sqrt{\frac{5}{3}} R_g \quad (3)$$

The geometric radius is physically the radius of a sphere with a uniform density. From our simulations, the values of R_g and R for SDS micelle were calculated as ~16 Å and ~21 Å,

respectively (Table 3). Although the experimental value of R_g for SDS micelle has not been found in literature, our R_g value is in a good agreement with that obtained from other simulation study [35, 36, 42], while R value is also in accordance with the experimental value [31]. Please note that the micelle surface area calculated using the geometric radius (R) is $5661.9 \text{ \AA}^2$ that is $\sim 57.5 \%$ of the micelle surface calculated from the Connolly surface analysis. It is clearly due to the ruggedness of the micelle surface at molecular level.

We also analyzed the conformations of individual SDS molecules in the micelle. Previously, Shelley et al. [34] and MacKerell [35] reported the gauche population of alkyl tails for the micelle: 30 % and 20 %, respectively. Although the values were different in those two references, these two studies commonly observed the bent conformations. From our simulations, the gauche population is 15 %, which is less than those reported from the previous studies [34, 35]. However, it is also observed that the conformations of SDS molecules are significantly bent in equilibrium state as presented in Figure 6. In this analysis, we define two vectors and two angles. $\vec{r}_1$ is the vector from the center-of-mass (COM) of micelle to the head (sulfur, S in Figure 1) while $\vec{r}_2$ is the vector from the COM to the tail (carbon, C₁ in Figure 1). $\vec{r}_3$ is the tail-to-head vector of SDS. θ_1 is the angles between two segments (C₁-C₈ and C₈-S in Figure 1) in the alkyl tail and θ_2 is the angle between the tail-to-head vector and the COM-to-head vector ($\vec{r}_1$). Their measured values are summarized in Table 2.

From this analysis, it is found that the length of the COM-to-head vector ($\vec{r}_1$) is $\sim 20.1 \text{ \AA}$, which is consistent with the geometric radius of the micelle ($\sim 21 \text{ \AA}$ in Table 3). This seems to be reasonable since the outermost part of the SDS micelle consists of ionic sulfate groups. On the other hand, the analysis of the COM-to-tail vector ($\vec{r}_2$) resulted in an unexpected feature of the micelle: the alkyl tails are not necessarily pointing towards the COM of micelle. From the length of $\vec{r}_2$ ($\sim 11.4 \text{ \AA}$ in Table 2), it is thought that the alkyl tail is significantly bent as presented in Figure 6. The analysis of the angle θ_1 confirms the bent conformation of SDS molecule, which makes the tail-to-head vector ($\vec{r}_3$) deviate from the vector $\vec{r}_1$. Actually, we believe that this conformational analysis is consistent with the analysis of the micelle surface (Figure 2c). Under

the condition that the hydrophilic sulfate groups do not cover the micelle surface, the alkyl tails should form a condensed phase in the micelle by bending their conformations to minimize the direct contact with water phase. If the SDS molecules kept their straight conformation, the micelle would not retain a stable spherical shape.

To investigate the packing of alkyl tails in the micelle, we evaluated the free volume within the micelle using the free volume analysis in Cerius2 molecular modeling software [83] with the probe radius of 1.4 Å. As a result, the evaluated internal free volume is ~139 Å³ (Table 2) that is equivalent to the volume of sphere with a radius of ~ 3.2 Å. The measured free volume corresponds to ~0.35 % of the micelle volume with the geometric radius (Table 3). Please note that this amount of free volume is dispersed throughout the micelle during our simulations. Since two or three water molecules with the radius of 1.4 Å are barely accommodated in such free volume if the free volumes are gathered together, it seems that the SDS micelle has a well packed hydrophobic core. Indeed, during our simulation time (20ns), we have not seen even single water molecule in the micelle.

The evolution of the shape of micelle during the simulation was characterized by examining the eccentricity (e) (Figure 7) via the following definition [36]:

$$e = 1 - \frac{I_{\min}}{I_{\text{avg}}} \quad (5)$$

where $I_{\min}$ and I_{avg} are the minimum moment of inertia and the averaged moment of inertia along with the x , y , or z axis. The zero value of the eccentricity means that the micelle is a perfect sphere [36]. The averaged eccentricity of the simulated micelle was measured to be 0.057, indicating that the micelle has nearly spherical shape.

After 20 ns of the equilibration process, we obtained the formation energy ($\Delta E_{\text{Formation}}$) of SDS micelle (Figure 2c) was calculated by following equation:

$$\Delta E_{\text{Formation}} = E_{\text{system}} - n_{\text{SDS}} \times E_{\text{SDS}} - n_{\text{water}} \times E_{\text{water}} \quad (2)$$

where E_{system} , E_{SDS} , E_{water} , n_{SDS} and n_{water} denote the potential energies of total system, single SDS molecule, single water molecule, the number of SDS molecules, and the number of water

molecules in the system, respectively. The formation energies of the SDS micelle in vacuum and in water phase were calculated to be 7.07×10^3 kcal/mol and -222.88 kcal/mol, respectively. Considering that the formation energy is a measure of the stability of the system, such a highly positive formation energy of the micelle in vacuum means that the ordinary micelle structure consisting of hydrophobic core and hydrophilic shell is not energetically stable in vacuum, whereas the negative value of the formation energy in water phase indicates that the micelle in water phase is favorable. Therefore, it is clear that the micellization of SDS is not driven by the SDS-SDS interaction, but rather by the favorable water solvation of ionic head of SDS molecule.

3.2. Potential of Mean Force via Steered Molecular Dynamics Simulations

Water Permeation into Micelle. In order to assess the cohesiveness of the micelle core consisting of hydrophobic tails, the PMF was calculated by dragging a single water molecule into the core of SDS micelle from the surrounding water phase using SMD simulation method. The results of PMF calculation (Figure 8) demonstrates that the PMF increases as water molecule diffuses into the core of micelle. It is evident that the change of PMF has two distinct stages: stage 1 is the region from 0 Å to 16 Å and stage 2 is the region from 16 Å to 35 Å. First, while the water molecule is dragged towards the micelle in the stage 2, the PMF increases mildly by ~1 kcal/mol since the water molecule diffuses through water phase without significant resistance. However, as seen in the radial density profile (Figure 5), the water phase disappears at 13 Å ~ 20 Å from the COM of the micelle, in which the increase of PMF becomes more rapidly in the stage 1 due to the unfavorable interaction of the dragged water molecule with the hydrophobic alkyl tails in the micelle. Therefore, the overall PMF change is measured as ~10 kcal/mol. Since the PMF increases by ~1 kcal/mol in the stage 2, the PMF increment in the stage 1 is ~9 kcal/mol. According to the study done by Yoshii and his coworker [40], the free energy of water permeation into the hydrophobic core of SDS micelle was also calculated to be ~7 kcal/mol by the thermodynamic integration (TI) method, indicating that the magnitude of PMF change from SMD simulation is in a good agreement with the TI value although the theoretical

foundation of each method is different. From this investigation, it is concluded that water molecules would not be able to diffuse in and out of the SDS micelle core.

Dissociation of SDS from Micelle. The second set of SMD simulations was performed to calculate the PMF change to dissociate a single SDS molecule from the micelle. The PMF increment was approximately ~ 13 kcal/mol. It is clearly shown in Figure 9 that the PMF increased monotonously as the SDS molecule was pulled out of the micelle. The origin represents the initial position of the sulfate group of SDS. Considering the length of SDS molecule (~ 16 Å), the end of the alkyl tail would be almost dissociated from the micelle when the SDS is displaced from the initial position by ~ 15 Å. When the SDS molecule is pulled, the conformation is linear but becomes more folded when it is completely dissociated from the micelle. Therefore, it is thought that larger slope of PMF curve up to ~ 15 Å means that PMF is increased mainly due to the destabilizing dissociation of the alkyl tail from the SDS molecule.

Considering that the phase of the hydrophobic alkyl tail is immiscible with water phase, this result is consistent with that of the first set of SMD simulations for the water diffusion-in. Accordingly, it is concluded that the SDS molecule would not be dissociated from the micelle unless an external energy more than ~ 13 kcal/mol is applied for SDS micelles. Overall, the increase of PMF in the direction of pulling in both cases well demonstrates the strong segregation between hydrocarbon and water phases. Here, it should be noted that the steering rate (2.0×10^{-5} Å/fs) employed in our SMD simulation was determined to have no significant steering rate dependency in comparison with lower steering rate (1.0×10^{-5} Å/fs). Therefore, we believe that our SMD simulation condition would be able to produce approximate free energy difference efficiently although it should be admitted that the absolute quasistatic condition is not guaranteed.

4. Summary

A micelle consisting of 60 SDS molecules was investigated using molecular dynamics simulation method to elucidate the structure and stability in the presence of water phase. The formation energy of micelle was calculated as 7.07×10^3 kcal/mol and -222.88 kcal/mol in vacuum and water phase, respectively, which means that the stability of SDS micelle is achieved

in water phase. The dimension was evaluated as ~ 16 Å and ~ 21 Å for radius of gyration and geometric radius, respectively, which are well agreed with the previous studies. Via Connolly surface analysis, it was found that $\sim 58\%$ of the micelle surface is occupied by the hydrophobic alkyl tails of SDS molecules.

By analyzing the conformations of SDS molecules in the micelle, it was found that the tail-to-head vectors of SDS molecules have $\sim 68^\circ$ in average from the radial direction, indicating that the SDS molecules have significantly bent conformation. However, it was also found from the free volume analysis that the SDS micelle has a well-packed structure with a free volume of ~ 139 Å³ that is $\sim 0.35\%$ of the micelle volume.

As a measure of the micelle stability in water phase, we performed SMD simulations in attempt to evaluate the PMF for the water diffusion into the center of micelle, resulting in ~ 10 kcal/mol. This result is due to the unfavorable interaction between water molecule and hydrophobic alkyl tails in the core of micelle. We also performed another set of SMD simulations to evaluate the PMF related to the molecular dissociation of a SDS molecule from the micelle. The magnitude of PMF change was ~ 13 kcal/mol. We think that such positive PMF change is caused by the undesirable interaction between the hydrophobic alkyl tail of the surfactant and water phase. Overall, the PMF analysis via two sets of SMD simulations demonstrates that the micellization is driven by minimizing the undesirable interaction of hydrophobic alkyl tail of SDS molecule with water phase.

Acknowledgments

This research was supported by the Department of Energy (DE-FG02-03ER15459). We also acknowledge that this research used resources of the Keeneland Computing Facility at the Georgia Institute of Technology, supported by the National Science Foundation under Contract OCI-0910735.

References

- [1] L.M. Prince, Microemulsions versus micelles, *J. Colloid Interf. Sci.*, 52 (1975) 182-188.
- [2] J.N. Israelachvili, D.J. Mitchell, B.W. Ninham, Theory of self-assembly of hydrocarbon amphiphiles into micelles and bilayers, *J. Chem. Soc. Farad. Trans. 2*, 72 (1976) 1525-1568.
- [3] C. Tanford, in: K. Mittal (Ed.) *Micellization, Solubilization and Microemulsions*, Plenum Press, New York, 1977.
- [4] C. Tanford, *The Hydrophobic Effect*, Wiley, New York, 1980.
- [5] R.J. Hunter, *Foundations of Colloid Science*, Clarendon Press, Oxford, 1986.
- [6] P.C. Hiemenz, *Principles of Colloid and Surface Chemistry*, 2 ed., Marcell Dekker, INC., New York, 1986.
- [7] D. Langevin, Micelles and Microemulsions, *Ann. Rev. Phys. Chem.*, 43 (1992) 341-369.
- [8] A. Lavasanifar, J. Samuel, G.S. Kwon, Poly(ethylene oxide)-block-poly(L-amino acid) micelles for drug delivery, *Adv. Drug Deliver. Rev.*, 54 (2002) 169-190.
- [9] H. Zhang, O. Annunziata, Diffusion of an ionic drug in micellar aqueous solutions, *Langmuir*, 25 (2009) 3425-3434.
- [10] L. Vuković, F.A. Khatib, S.P. Drake, A. Madriaga, K.S. Brandenburg, P. Král, H. Onyuksel, Structure and Dynamics of Highly PEG-ylated Sterically Stabilized Micelles in Aqueous Media, *J. Am. Chem. Soc.*, 133 (2011) 13481-13488.
- [11] A.H. Gröschel, F.H. Schacher, H. Schmalz, O.V. Borisov, E.B. Zhulina, A. Walther, A.H.E. Müller, Precise hierarchical self-assembly of multicompartment micelles, *Nat. Comm.*, 3 (2012) 710-710.
- [12] X.D. Guo, Y. Qian, C.Y. Zhang, S.Y. Nie, L.J. Zhang, Can drug molecules diffuse into the core of micelles?, *Soft Matter*, 8 (2012) 9989-9989.
- [13] Y. Liu, Y. Wang, Y. Wang, J. Lu, V. Piñón, M. Weck, Shell cross-linked micelle-based nanoreactors for the substrate-selective hydrolytic kinetic resolution of epoxides, *J. Am. Chem. Soc.*, 133 (2011) 14260-14263.
- [14] P. Cotanda, R.K. O'Reilly, Molecular recognition driven catalysis using polymeric nanoreactors, *Chem. Comm.*, 48 (2012) 10280-10282.
- [15] P. Cotanda, A. Lu, J.P. Patterson, N. Petzetakis, R.K. O'Reilly, Functionalized Organocatalytic Nanoreactors: Hydrophobic Pockets for Acylation Reactions in Water, *Macromolecules*, 45 (2012) 2377-2384.
- [16] A. Lu, R.K. O'Reilly, Advances in nanoreactor technology using polymeric nanostructures, *Curr. Opin. Biotech.*, 24 (2013) 639-645.

367 [17] F. Reiss-Husson, V. Luzzati, STRUCTURE OF MICELLAR SOLUTIONS OF SOME
 368 AMPHIPHILIC COMPOUNDS IN PURE WATER AS DETERMINED BY ABSOLUTE
 369 SMALL-ANGLE X-RAY SCATTERING TECHNIQUES, *J. Phys. Chem.*, 68 (1964) 3504-3511.

370 [18] N.A. Mazer, G.B. Benedek, M.C. Carey, INVESTIGATION OF MICELLAR PHASE OF
 371 SODIUM DODECYL-SULFATE IN AQUEOUS SODIUM-CHLORIDE SOLUTIONS USING
 372 QUASI-ELASTIC LIGHT-SCATTERING SPECTROSCOPY, *J. Phys. Chem.*, 80 (1976) 1075-
 373 1085.

374 [19] C.Y. Young, P.J. Missel, N.A. Mazer, G.B. Benedek, M.C. Carey, DEDUCTION OF
 375 MICELLAR SHAPE FROM ANGULAR DISSYMMETRY MEASUREMENTS OF LIGHT
 376 SCATTERED FROM AQUEOUS SODIUM DODECYL-SULFATE SOLUTIONS AT HIGH
 377 SODIUM-CHLORIDE CONCENTRATIONS, *J. Phys. Chem.*, 82 (1978) 1375-1378.

378 [20] A. Rohde, E. Sackmann, QUASI-ELASTIC LIGHT-SCATTERING-STUDIES OF
 379 MICELLAR SODIUM DODECYL-SULFATE SOLUTIONS AT THE LOW
 380 CONCENTRATION LIMIT, *J. Colloid Interf. Sci.*, 70 (1979) 494-505.

381 [21] P.J. Missel, N.A. Mazer, G.B. Benedek, C.Y. Young, M.C. Carey, THERMODYNAMIC
 382 ANALYSIS OF THE GROWTH OF SODIUM DODECYL-SULFATE MICELLES, *J. Phys.*
 383 *Chem.*, 84 (1980) 1044-1057.

384 [22] S. Ikeda, S. Ozeki, S. Hayashi, SIZE AND SHAPE OF CHARGED MICELLES OF IONIC
 385 SURFACTANTS IN AQUEOUS SALT-SOLUTIONS, *Biophys. Chem.*, 11 (1980) 417-423.

386 [23] J.B. Hayter, J. Penfold, SELF-CONSISTENT STRUCTURAL AND DYNAMIC STUDY
 387 OF CONCENTRATED MICELLE SOLUTIONS, *Journal of the Chemical Society-Faraday*
 388 *Transactions I*, 77 (1981) 1851-1863.

389 [24] P. Lianos, R. Zana, FLUORESCENCE PROBE STUDIES OF THE EFFECT OF
 390 CONCENTRATION ON THE STATE OF AGGREGATION OF SURFACTANTS IN
 391 AQUEOUS-SOLUTION, *J. Colloid Interf. Sci.*, 84 (1981) 100-107.

392 [25] P. Lianos, J. Lang, C. Strazielle, R. Zana, FLUORESCENCE PROBE STUDY OF OIL-IN-
 393 WATER MICRO-EMULSIONS .1. EFFECT OF PENTANOL AND DODECANE OR
 394 TOLUENE ON SOME PROPERTIES OF SODIUM DODECYL-SULFATE MICELLES, *J.*
 395 *Phys. Chem.*, 86 (1982) 1019-1025.

396 [26] J.B. Hayter, J. Penfold, DETERMINATION OF MICELLE STRUCTURE AND CHARGE
 397 BY NEUTRON SMALL-ANGLE SCATTERING, *Colloid Polym. Sci.*, 261 (1983) 1022-1030.

398 [27] D. Bendedouch, S.H. Chen, W.C. Koehler, STRUCTURE OF IONIC MICELLES FROM
 399 SMALL-ANGLE NEUTRON-SCATTERING, *J. Phys. Chem.*, 87 (1983) 153-159.

400 [28] Y. Croonen, E. Gelade, M. Vanderzegel, M. Vanderauweraer, H. Vandendriessche, F.C.
 401 Deschryver, M. Almgren, INFLUENCE OF SALT, DETERGENT CONCENTRATION, AND
 402 TEMPERATURE ON THE FLUORESCENCE QUENCHING OF 1-METHYLPYRENE IN
 403 SODIUM DODECYL-SULFATE WITH META-DICYANOBENZENE, *J. Phys. Chem.*, 87
 404 (1983) 1426-1431.

405 [29] J.M. Chen, T.M. Su, C.Y. Mou, Size of sodium dodecyl sulfate micelle in concentrated salt
406 solutions, *J. Phys. Chem.*, 90 (1986) 2418-2421.

407 [30] R. Nagarajan, E. Ruckenstein, THEORY OF SURFACTANT SELF-ASSEMBLY - A
408 PREDICTIVE MOLECULAR THERMODYNAMIC APPROACH, *Langmuir*, 7 (1991) 2934-
409 2969.

410 [31] R. Itri, L.Q. Amaral, DISTANCE DISTRIBUTION FUNCTION OF SODIUM DODECYL
411 SULFATE MICELLES BY X-RAY SCATTERING, *J. Phys. Chem.*, 95 (1991) 423-427.

412 [32] Y. Moroi, N. Yoshida, A New Approach to Micellization Parameters: Its Application to
413 Sodium Dodecyl Sulfate Micelle, *Langmuir*, 13 (1997) 3909-3912.

414 [33] H. Shirota, Y. Tamoto, H. Segawa, Dynamic Fluorescence Probing of the
415 Microenvironment of Sodium Dodecyl Sulfate Micelle Solutions: Surfactant Concentration
416 Dependence and Solvent Isotope Effect, *J. Phys. Chem. C*, 108 (2004) 3244-3252.

417 [34] J. Shelley, K. Watanabe, M.L. Klein, SIMULATION OF A SODIUM DODECYL-
418 SULFATE MICELLE IN AQUEOUS-SOLUTION, *Int. J. Quantum Chem.*, (1990) 103-117.

419 [35] A.D. Mackerell, Molecular Dynamics Simulation Analysis of a Sodium Dodecyl Sulfate
420 Micelle in Aqueous Solution : Decreased Fluidity of the Micelle Hydrocarbon Interior, *J. Phys.*
421 *Chem.*, 99 (1995) 1846-1855.

422 [36] C.D. Bruce, M.L. Berkowitz, L. Perera, M.D.E. Forbes, C. Hill, N. Carolina, Molecular
423 Dynamics Simulation of Sodium Dodecyl Sulfate Micelle in Water : Micellar Structural
424 Characteristics and Counterion Distribution, *J. Phys. Chem. B*, 106 (2002) 3788-3793.

425 [37] C.D. Bruce, S. Senapati, M.L. Berkowitz, L. Perera, M.D.E. Forbes, C. Hill, N. Carolina,
426 Molecular Dynamics Simulations of Sodium Dodecyl Sulfate Micelle in Water : The Behavior of
427 Water, *J. Phys. Chem. B*, 106 (2002) 10902-10907.

428 [38] N. Yoshii, K. Iwahashi, S. Okazaki, A molecular dynamics study of free energy of micelle
429 formation for sodium dodecyl sulfate in water and its size distribution, *J. Chem. Phys.*, 124 (2006)
430 -.

431 [39] N. Yoshii, S. Okazaki, A molecular dynamics study of structure and dynamics of surfactant
432 molecules in SDS spherical micelle, *Cond. Matt. Phys.*, 10 (2007) 573-578.

433 [40] N. Yoshii, S. Okazaki, Free energy of water permeation into hydrophobic core of sodium
434 dodecyl sulfate micelle by molecular dynamics calculation, *J. Chem. Phys.*, 126 (2007) 096101-
435 096101.

436 [41] B.Z. Shang, Z. Wang, R.G. Larson, Molecular dynamics simulation of interactions between
437 a sodium dodecyl sulfate micelle and a poly(ethylene oxide) polymer, *J. Phys. Chem. B*, 112
438 (2008) 2888-2900.

439 [42] S. Jalili, M. Akhavan, A coarse-grained molecular dynamics simulation of a sodium dodecyl
440 sulfate micelle in aqueous solution, *Colloid. Surface. A: Physicochem. Eng. Asp.*, 352 (2009) 99-
441 102.

442 [43] F. Palazzesi, M. Calvaresi, F. Zerbetto, A molecular dynamics investigation of structure and
443 dynamics of SDS and SDBS micelles, *Soft Matter*, 7 (2011) 9148-9148.

444 [44] S. Storm, S. Jakobtorweihen, I. Smirnova, A.Z. Panagiotopoulos, Molecular dynamics
445 simulation of SDS and CTAB micellization and prediction of partition equilibria with
446 COSMOmic, *Langmuir*, 29 (2013) 11582-11592.

447 [45] X. Tang, P.H. Koenig, R.G. Larson, Molecular dynamics simulations of sodium dodecyl
448 sulfate micelles in water-the effect of the force field, *J. Phys. Chem. B*, 118 (2014) 3864-3880.

449 [46] T. Bast, R. Hentschke, Molecular Dynamics Simulation of a Micellar System, *J. Mol.*
450 *Model.*, 2 (1996) 330-340.

451 [47] S.J. Marrink, D.P. Tieleman, A.E. Mark, Molecular Dynamics Simulation of the Kinetics of
452 Spontaneous Micelle Formation, *J. Phys. Chem. B*, 104 (2000) 12165-12173.

453 [48] P. Ferrara, J. Apostolakis, A. Caflisch, Evaluation of a fast implicit solvent model for
454 molecular dynamics simulations, *Proteins*, 46 (2002) 24-33.

455 [49] S. Abel, F. Sterpone, S. Bandyopadhyay, M. Marchi, Molecular Modeling and Simulations
456 of AOT–Water Reverse Micelles in Isooctane: Structural and Dynamic Properties, *J. Phys.*
457 *Chem. B*, 108 (2004) 19458-19466.

458 [50] A.F.d. Moura, L.C.G. Freitas, Molecular Dynamics simulation of the sodium octanoate
459 micelle in aqueous solution: comparison of force field parameters and molecular topology effects
460 on the micellar structure, *Braz. J. Phys.*, 34 (2004) 64-72.

461 [51] P. Konidala, L. He, B. Niemeyer, Molecular dynamics characterization of n-octyl-beta-D-
462 glucopyranoside micelle structure in aqueous solution, *J. Mol. Graph. Model.*, 25 (2006) 77-86.

463 [52] M.H.H. Pomata, D. Laria, M.S. Skaf, M.D. Elola, Molecular dynamics simulations of AOT-
464 water/formamide reverse micelles: structural and dynamical properties, *J. Chem. Phys.*, 129
465 (2008) 244503-244503.

466 [53] X. Li, I.V. Pivkin, H. Liang, G.E. Karniadakis, Shape Transformations of Membrane
467 Vesicles from Amphiphilic Triblock Copolymers: A Dissipative Particle Dynamics Simulation
468 Study, *Macromolecules*, 42 (2009) 3195-3200.

469 [54] H. Kuramochi, Y. Andoh, N. Yoshii, S. Okazaki, All-atom molecular dynamics study of a
470 spherical micelle composed of N-acetylated poly(ethylene glycol)-poly(gamma-benzyl L-
471 glutamate) block copolymers: a potential carrier of drug delivery systems for cancer, *J. Phys.*
472 *Chem. B*, 113 (2009) 15181-15188.

473 [55] A. Amani, P. York, H. de Waard, J. Anwar, Molecular dynamics simulation of a
474 polysorbate 80 micelle in water, *Soft Matter*, 7 (2011) 2900-2900.

475 [56] O.-S. Lee, S.I. Stupp, G.C. Schatz, Atomistic molecular dynamics simulations of peptide
476 amphiphile self-assembly into cylindrical nanofibers, *J. Am. Chem. Soc.*, 133 (2011) 3677-3683.

477 [57] V. Barone, M. Casarin, D. Forrer, S. Monti, G. Prampolini, Molecular Dynamics
478 Simulations of the Self-Assembly of Tetraphenylporphyrin-Based Monolayers and Bilayers at a
479 Silver Interface, *J. Phys. Chem. C*, 115 (2011) 18434-18444.

480 [58] Y. Wang, J.a. Wallace, P.H. Koenig, J.K. Shen, Molecular dynamics simulations of ionic
 481 and nonionic surfactant micelles with a generalized Born implicit-solvent model, *J. Comput.*
 482 *Chem.*, 32 (2011) 2348-2358.

483 [59] R.A. Karjiban, M. Basri, M.B.A. Rahman, A.B. Salleh, Molecular dynamics simulation of
 484 palmitate ester self-assembly with diclofenac, *Int. J. Mol. Sci.*, 13 (2012) 9572-9583.

485 [60] S. Abel, F.-Y. Dupradeau, M. Marchi, Molecular Dynamics Simulations of a Characteristic
 486 DPC Micelle in Water, *J. Chem. Theory Comput.*, 8 (2012) 4610-4623.

487 [61] B. Guchhait, R. Biswas, P.K. Ghorai, Solute and solvent dynamics in confined equal-sized
 488 aqueous environments of charged and neutral reverse micelles: a combined dynamic
 489 fluorescence and all-atom molecular dynamics simulation study, *J. Phys. Chem. B*, 117 (2013)
 490 3345-3361.

491 [62] N. Thota, Z. Luo, Z. Hu, J. Jiang, Self-assembly of amphiphilic peptide (AF)6H5K15:
 492 coarse-grained molecular dynamics simulation, *J. Phys. Chem. B*, 117 (2013) 9690-9698.

493 [63] T. Ingram, S. Storm, L. Kloss, T. Mehling, S. Jakobtorweihen, I. Smirnova, Prediction of
 494 micelle/water and liposome/water partition coefficients based on molecular dynamics
 495 simulations, COSMO-RS, and COSMOmic, *Langmuir*, 29 (2013) 3527-3537.

496 [64] K. Bernardino, A.F. de Moura, Aggregation thermodynamics of sodium octanoate micelles
 497 studied by means of molecular dynamics simulations, *J. Phys. Chem. B*, 117 (2013) 7324-7334.

498 [65] S.M. Loverde, Molecular Simulation of the Transport of Drugs across Model Membranes, *J.*
 499 *Phys. Chem. Lett.*, 5 (2014) 1659-1665.

500 [66] S. Emamyari, H. Fazli, pH-dependent self-assembly of EAK16 peptides in the presence of a
 501 hydrophobic surface: Coarse-grained molecular dynamics simulation, *Soft Matter*, 10 (2014)
 502 4248-4257.

503 [67] B.R. Brooks, R.E. Bruccoleri, B.D. Olafson, D.J. States, S. Swaminathan, M. Karplus,
 504 CHARMM - A PROGRAM FOR MACROMOLECULAR ENERGY, MINIMIZATION, AND
 505 DYNAMICS CALCULATIONS, *J. Comput. Chem.*, 4 (1983) 187-217.

506 [68] W.L. Jorgensen, J. Chandrasekhar, J.D. Madura, R.W. Impey, M.L. Klein, COMPARISON
 507 OF SIMPLE POTENTIAL FUNCTIONS FOR SIMULATING LIQUID WATER, *J. Chem.*
 508 *Phys.*, 79 (1983) 926-935.

509 [69] D.A.P. Case, D. A.; Caldwell, J. W.; Cheatham, T. E., III; Ross, W. S.; Simmerling, C. L.;
 510 Darden, T. A.; Merz, K. M.; Stanton, R. V.; Cheng, A. L.; Vincent, J. J.; Crowley, M.; Tsui, V.;
 511 Radmer, R. J.; Duan, Y.; Pitera, J.; Massova, I.; Seibel, G. L.; Singh, U. C.; Weiner, P. K.;
 512 Kollman, P. A., AMBER 6, UniVersity of California, San Francisco, 1999.

513 [70] S.J. Marrink, H.J. Risselada, S. Yefimov, D.P. Tieleman, A.H. de Vries, The MARTINI
 514 force field: Coarse grained model for biomolecular simulations, *J. Phys. Chem. B*, 111 (2007)
 515 7812-7824.

516 [71] S.L. Mayo, B.D. Olafson, W.A. Goddard, DREIDING: a generic force field for molecular
 517 simulations, *J. Phys. Chem.*, 94 (1990) 8897-8909.

- [72] R.S. Mulliken, Electronic Population Analysis on LCAO–MO Molecular Wave Functions. I, J. Chem. Phys., 23 (1955) 1833-1840.
- [73] A.D. Bochevarov, E. Harder, T.F. Hughes, J.R. Greenwood, D.A. Braden, D.M. Philipp, D. Rinaldo, M.D. Halls, J. Zhang, R.A. Friesner, Jaguar: A high-performance quantum chemistry software program with strengths in life and materials sciences, Int. J. Quantum Chem., 113 (2013) 2110-2142.
- [74] M. Levitt, M. Hirshberg, R. Sharon, K.E. Laidig, V. Daggett, Calibration and Testing of a Water Model for Simulation of the Molecular Dynamics of Proteins and Nucleic Acids in Solution, J. Phys. Chem. B, 101 (1997) 5051-5061.
- [75] S. Nosé, A unified formulation of the constant temperature molecular dynamics methods, J. Chem. Phys., 81 (1984) 511-519.
- [76] W.G. Hoover, Canonical dynamics: Equilibrium phase-space distributions, Phys. Rev. A, 31 (1985) 1695-1697.
- [77] R.W. Hockney, J.W. Eastwood, Computer Simulation Using Particles, Taylor & Francis, Inc.1988.
- [78] W.C. Swope, H.C. Andersen, P.H. Berens, K.R. Wilson, A computer simulation method for the calculation of equilibrium constants for the formation of physical clusters of molecules: Application to small water clusters, J. Chem. Phys., 76 (1982) 637-649.
- [79] S. Plimpton, Fast Parallel Algorithms for Short-Range Molecular Dynamics, J. Comput. Phys., 117 (1995) 1-19.
- [80] M.Y. Lobanov, N.S. Bogatyreva, O.V. Galzitskaya, Radius of gyration as an indicator of protein structure compactness, Mol. Biol., 42 (2008) 623-628.
- [81] S. Park, K. Schulten, Calculating potentials of mean force from steered molecular dynamics simulations, J. Chem. Phys., 120 (2004) 5946-5961.
- [82] S. Bogusz, R.M. Venable, R.W. Pastor, Molecular dynamics simulations of octyl glucoside micelles: Structural properties, J. Phys. Chem. B, 104 (2000) 5462-5470.
- [83] Cerius2 Modeling Environment, Release 4.0, Accelrys Inc., San Diego, 1999.

Table 1. Atomic partial charges for the surfactant molecule. The carbon number and oxygen number correspond to the model in Figure 1.

Hydrocarbon												
Carbon Number	1	2	3	4	5	6	7	8	9	10	11	12
C	-0.3165	-0.1720	-0.1641	-0.1726	-0.1727	-0.1724	-0.1716	-0.1716	-0.1706	-0.1664	-0.1948	0.0879
H ₁	0.0994	0.0889	0.0849	0.0849	0.0845	0.0878	0.0828	0.0816	0.0683	0.0759	0.0864	0.0812
H ₂	0.0931	0.0900	0.0836	0.0869	0.0823	0.0838	0.0784	0.0921	0.0803	0.0129	0.0561	0.0821
H ₃	0.0986											
Sodium Sulfate												
S	1.2073	O ₁	-0.5796	O ₂	-0.6160	O ₃	-0.6137	O ₄	-0.5810	Na		1.000

Table 2. Results of geometry analysis. The symbols are corresponding to Figure 7.

$ \vec{r}_1 $	$ \vec{r}_2 $	θ_1	θ_2	Free Volume
$20.12 \pm 2.25 \text{ \AA}$	$11.41 \pm 4.43 \text{ \AA}$	$146.73 \pm 22.64^\circ$	$67.60 \pm 3.83^\circ$	$138.98 \pm 40.98 \text{ \AA}^3$

Table 3. Dimension of simulated micelle in comparison with experimental data

		Radius of Gyration ($\text{\AA}$)	Geometric Radius of Micelle ($\text{\AA}$)
Simulation	Our work	16.4 ± 0.04	21.2 ± 0.05
	MacKerell[35]	16.02 ± 0.06	N/A
	Bruce et al.[36]	16.2 ± 0.12	20.9 ± 0.15
	Jalili et al.[42]	15.7 ± 0.2	20.3 ± 0.3
Experiment	Itri et al.[31]	N/A	22.0-22.3

Figure 1. Chemical structure of sodium dodecyl sulfate surfactant. C₁ has three explicit hydrogens and the rest of the carbons from C₂ through C₁₂ have two explicit hydrogens although those hydrogens are omitted.

Figure 2. Scheme of constructing a 60 SDS micelle structure. (a) shows the skeleton of 60 SDS molecules equally occupying the space, (b) exhibits the structure of prefixed micelle whose monomers are placed on the blue rods, and (c) is the micelle structure after NPT MD simulation. The white, red, yellow, gray, and purple colored beads denote hydrogen, oxygen, sulfur, carbon, and sodium atoms, respectively. Water molecules in (b) and (c) are omitted.

Figure 3. Change in radius of gyration of SDS micelle over 20 ns of NPT MD simulation.

(a)

(b)

Figure 4. SMD simulations to calculate potential of mean force: (a) a water molecule is displaced from water phase to the center-of-mass of the micelle; (b) a SDS molecule is displace from the micelle to water phase. Arrows indicate the direction of the molecular displacement.

Figure 5. Radial density distribution from the center of micelle. The black, red, and blue colors denote the density of hydrocarbon, sulfate group, and water, respectively.

Figure 6. Geometry analysis of SDS molecule. The grey, yellow, and red colors denote carbon, sulfur, and oxygen, respectively. Hydrogens are omitted.

Figure 7. Change of Eccentricity of the micelle over the last 1 ns of the simulation

Figure 8. Change of potential of mean force as a function of the distance of water molecule from the center-of-mass of the micelle. Red colored curve denotes the PMF averaged over six simulated values displayed by light blue color.

Figure 9. Change of potential of mean force as a function of the distance of a SDS molecule from micelle. The origin represents the initial position of sulfate group of SDS molecule. Red colored curve denotes the PMF averaged over six simulated values displayed by light blue color.

Table of Content Image