Molecular dynamics simulations of the effects of sodium dodecyl sulfate on lipid bilayer*

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Molecular dynamics simulations have been performed on the fully hydrated lipid bilayer with different concentrations of sodium dodecyl sulfate (SDS). SDS can readily penetrate into the membrane. The insertion of SDS causes a decrease in the bilayer area and increases in the bilayer thickness and lipid tail order, when the fraction of SDS is less than 28%. Through calculating the binding energy, we confirm that the presence of SDS strengthens the interactions among the DPPC lipids, while SDS molecules act as intermedia. Both the strong hydrophilic interactions between sulfate and phosphocholine groups and the hydrophobic interactions between SDS and DPPC hydrocarbon chains contribute to the tight packing and ordered alignment of the lipids. These results are in good agreement with the experimental observations and provide atomic level information that complements the experiments.

Keywords: surfactant, sodium dodecyl sulfate, lipid bilayer, molecular dynamics simulations

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1. Introduction

Surfactants are the main components of detergents, which are widely used in cleaning products and inevitably released in the natural water. Biological membranes act as barriers between the inside and outside of a cell, and as matrices to support membrane proteins. The use of detergents leads to the frequent contact of surfactants with cell membranes. Therefore, it is fundamentally essential to understand the interactions between surfactants and cell membranes.

On the other hand, surfactants are also important reagents in membrane biochemistry. For example, surfactants can be used in cell lysis and membrane protein extraction.[1–4] Researchers pay more attention to the structure, the hydration force, and the partition of the surfactants–membrane mixture.[5,7,8] Klose and co-workers have published a series of papers on the structural and hydration properties of the mixed bilayers containing phospholipids and nonionic surfactants, using x-ray, deuterium NMR, and neutron diffraction. They explored in detail the effects of surfactants on the membrane structure with varied surfactant concentrations. They found that the presence of surfactants at low concentration in the membrane tightens the membrane packing, resulting in the decrease of the area per lipid.[8]

Molecular dynamics (MD) simulations have become an important alternative method that complements experimental studies in recent years.[9–11] Since the development of the accurate force fields of phospholipids, MD simulations have been extensively employed to elucidate the partitioning of small molecules in the biological membrane and the effects of small molecules on the membrane structure.[12–17] In the previous studies, we have investigated nitrogen partitioning into lipid membrane and the effects of noble gases on the membrane structure to explain the molecular mechanism of anesthesia,[18,19] using MD simulations. We have also simulated the translocation of graphene and its oxide across a lipid bilayer.[20] These simulations exhibit great potential for the study of membrane–foreign molecules interactions. However, there are few MD reports related to the interactions between surfactants and cell membranes. The latest literature was published in 2001 by Bandyopadhyay *et al.* and Schneider *et al.*[21,22] Their results showed that the presence of the surfactant causes a decrease in the area per lipid and an increase in the lipid tail order. It should be noted that their conclusions are dependent on the initial conditions, in which the surfactants are artificially embedded in the membrane.

In this paper, we performed MD simulations to investigate the permeation of sodium dodecyl sulfate (SDS) in a model membrane (dipalmitoylphosphatidylcholine, DPPC bilayer) and the effects of SDS on the membrane with different concentrations. The paper is organized as follows. In Section 2, details of the simulations are presented. The results concerning the preferable location of SDS in the membrane and the biophysical changes of the bilayer induced by SDS therein are given and discussed in Section 3. Finally, in Sec-

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tion 4, the main conclusions of this study and the future work are summarized.

2. Methods

The lipid bilayer was composed of 128 DPPC lipids and 5000 water molecules, which was fully hydrated for about 40 water molecules per DPPC lipid. This initial structure was developed by Tieleman.[23] The membrane contained different numbers of SDS, corresponding to the different concentrations, namely, 1.5 mol%, 12 mol%, 21 mol%, 28 mol%, and 44 mol%. Here, mol% was defined as the number of SDS divided by the sum of SDS and DPPC. The simulation has also been done for the pure, SDS free bilayer as control. The force field parameters for the DPPC lipids and SDS were created by Berger *et al.* and Sammalkorpi *et al.*, respectively.[24,25] Both parameters were realized by the united atom model (i.e., hydrogen atoms on alkyl groups were reduced, see Fig. 1), which was compatible with the GROMOS 53a6 force field.[26]

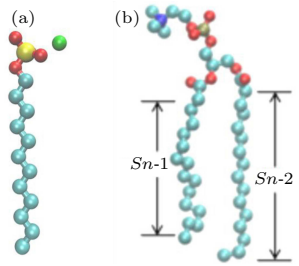


Fig. 1. (color online) Atomic structures of (A) SDS and (B) DPPC lipid. Color scheme: cyan (C), red (O), blue (N), yellow (S), tan (P), and green (Na).

All MD simulations were conducted under the isothermal–isobaric (*NPT*) ensemble using the Gromacs 4.5.5 package.[27,28] Periodic boundary conditions were employed in all directions. The Lennard–Jones interactions were treated with smooth cutoff at a distance of 12 Å, whereas the particle-mesh Ewald method was adopted to calculate the long-range electrostatic interactions.[29,30] Water was represented by the SPC model.[31] The pressure was controlled semi-isotropically by a Berendsen barostat[32] and the temperature was kept stable at 323 K using the V-rescale thermostat.[33] Bond lengths within SDS/DPPC and water molecules were constrained by the LINCS and the SETTLE algorithms,[34,35] respectively.

The binding energy of one DPPC lipid in the hydrated bilayer was computed from the potential of mean force (PMF) using umbrella sampling. First, we performed the steered MD simulation to pull one DPPC out and far away from the bilayer. Then, 30 windows were generated along the z axis (i.e., the membrane normal). The z coordinates of COM distance between the lipid and membrane in each window differed by about 0.1 nm. The COM distance between SDS and DPPC was restrained by a harmonic force constant of 1000 kJ·mol^{-1}·nm^{-2}. Each window was equilibrated for 5 ns and a production run of 5 ns was continued for sampling. Eventually, the PMF profile was reconstructed by the weighted histogram analysis method (WHAM)[36] using 'g_wham' program.[37]

3. Results and discussion

3.1. The preferable location of SDS in the membrane

To find the preferable location of SDS in the membrane, we first put only one SDS in the water and one in the bilayer center (see Fig. 2(a)). Figure 2 shows the initial and the final structures and the time evolution of the z coordinates of their COMs. During the first 55 ns, the outer SDS just moved randomly in the water. However, at $t \sim 55.68$ ns, the outer SDS rapidly penetrated into the bilayer and then stayed therein for the rest of the simulation. Meanwhile, the inner SDS inserted itself into another leaflet quickly and remained there till the end of the simulation. Due to the hydrophobic interactions between the dodecyl chain and the lipid tails and the electrostatic attractions among their polar headgroups, the orientation of SDS was that its hydrophobic chain was immersed in and parallel to the lipid tails, and its sulfate group was at the hydrophilic interface between water and lipid headgroups. The mass density profile (see Fig. 3) showed clearly that the preferable locations of SDS were symmetric. Interestingly, it was found that the profiles of SDS and DPPC were alike, since their atomic structures were similar, which both consisted of polar headgroups and long hydrophobic tails.

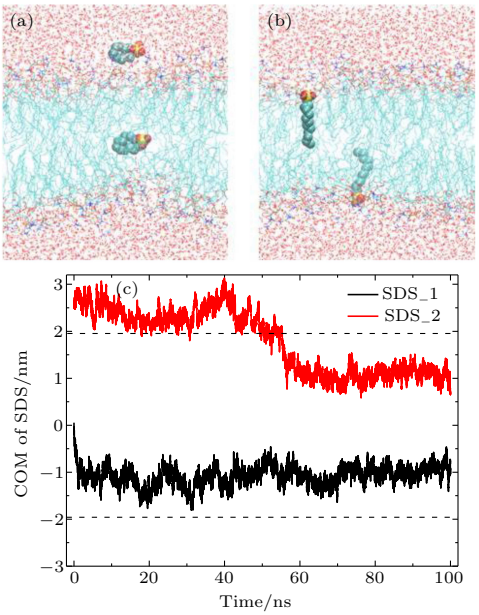


Fig. 2. (color online) Trajectory of SDS molecules entering the lipid bilayer. (a) The initial configuration. (b) The final snapshot. (c) Time evolution of COM of SDS, where the center of the bilayer is set as $z = 0$ nm, and the two dashed lines represent the interfaces between water and membrane.

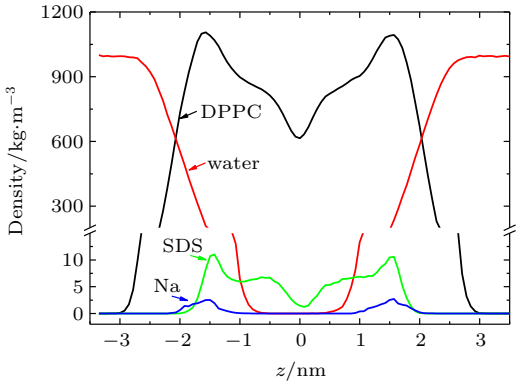


Fig. 3. (color online) Mass density profile of the system. The center of the lipid bilayer is fixed at $z = 0$ nm.

3.2. Effects of SDS on membrane structure

To explore the effects of SDS on the lipid bilayer, we constructed five independent systems, in which the concentrations of SDS were 0 mol% (the pure bilayer system as control), 12 mol%, 21 mol%, 28 mol%, and 44 mol%, respectively. Taking 21 mol% system as an example to illustrate the distribution of SDS in the membrane (see Fig. 4), we observed that all SDS randomly penetrated into the two leaflets (Fig. 4(b)), which were initially embedded in the bilayer center (Fig. 4(a)). The mass density profile of SDS showed that they were distributed almost evenly in the two leaflets. There were 18 SDS molecules in the upper leaflet and 16 SDS molecules in the lower leaflet.

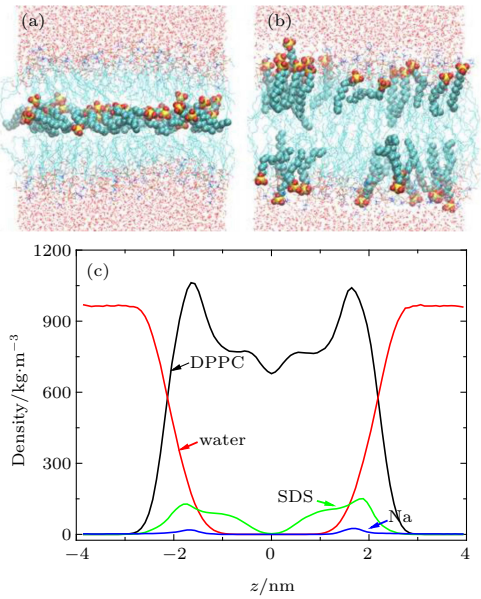


Fig. 4. (color online) The dynamic process of SDS with high concentration. (a) The initial structure, (b) the final snapshot, (c) the mass density profile of the system.

The effects of SDS on the lipid bilayer can be more quantitatively elucidated by the biophysical properties of the membrane, including bilayer area, thickness, volume, and lipid tail order. The bilayer area was defined as the area of the *xy* plane of the simulation box containing 64 DPPC lipids and inserted SDS, as shown in Fig. 5(a). Unexpectedly, it was found that the bilayer area decreased with increasing SDS concentration when the fraction of SDS was less than 28%. In contrast, the

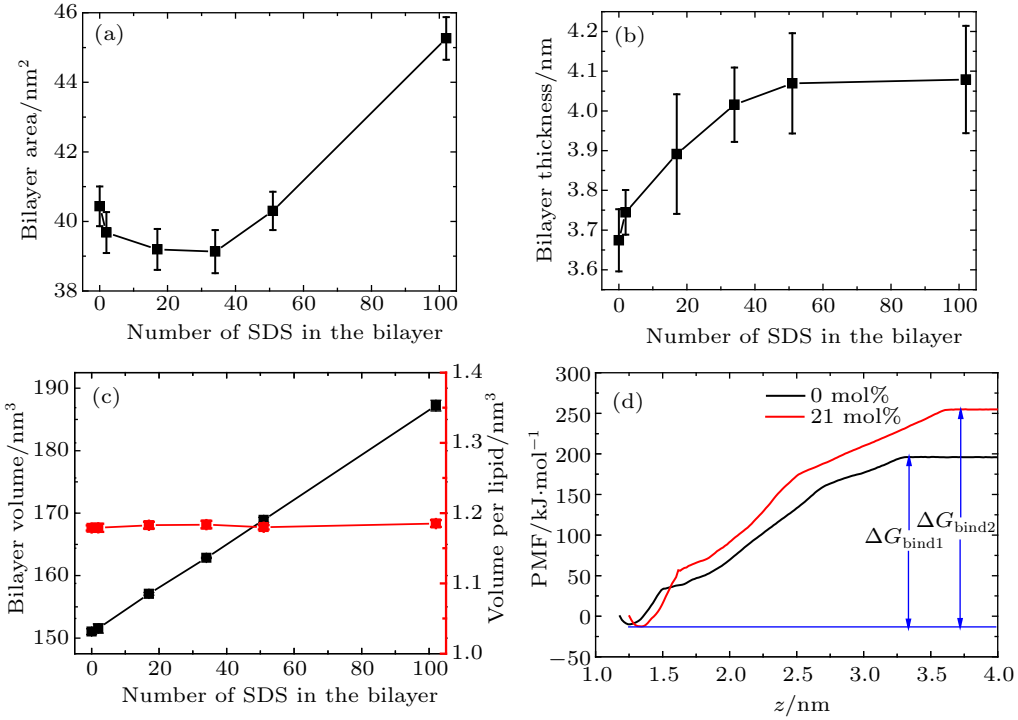


Fig. 5. (color online) The biophysical properties of DPPC bilayer at different SDS concentrations: (a) bilayer area, (b) bilayer thickness, (c) bilayer volume and volume per lipid, (d) PMF profile for the binding energy of one DPPC in the bilayer with or without SDS.

bilayer thickness rose gradually (see Fig. 5(b)). For example, the bilayer area and thickness of pure membrane were 40.43 nm^2 and 3.674 nm, respectively. However, the bilayer area fell to 39.13 nm^2 and the thickness climbed to 4.016 nm when the membrane contained 21 mol% SDS.

The two phenomena indicated that SDS enhanced the interactions among DPPC lipids and lipids aligned more tightly. To confirm this speculation, we calculated the binding energy of one DPPC lipid in the bilayer with or without SDS, as shown in Fig. 5(d). We observed that the binding energy of DPPC with 21 mol% SDS (ΔG_{bind2}) reached 275 kJ/mol, while that of neat membrane (ΔG_{bind1}) was about 200 kJ/mol. Obviously, the presence of SDS in the membrane enhanced the interactions among the DPPC lipids.

Taking the decrease of the bilayer area and the increase of the thickness together into consideration, we found that the bilayer volume still scaled proportionally with the SDS concentration, as shown in Fig. 5(c). To clarify whether the increased volume was attributed to the insertion of SDS, we calculated the volume per lipid (see Fig. 5(c), red line), and the results showed that the volume per lipid almost remained constant near 1.2 nm^3 except for negligible fluctuations, implying that the presence of SDS caused the linear rise of the bilayer volume.

When the fraction of SDS was more than 28 mol%, the bilayer area rose quickly, since the bilayer thickness reached almost a converged value. As shown in Fig. 5(a), the bilayer area was 40.3 nm^2 at 28 mol%. It climbed to 45.3 nm^2 at 44 mol%. Correspondingly, the bilayer volume increased linearly from 168.9 nm^3 to 187.2 nm^3, while the bilayer thickness was 4.07 nm and 4.08 nm at the two concentrations, which had no significant changes.

The bilayer area and thickness are mainly determined by the lipid tail order. The intervention of SDS in the membrane has substantial effects on the ordering of the lipid tails. Figure 6 shows the two lipid tail (*Sn*-1 and *Sn*-2) deuterium order parameters of the six systems. The deuterium order was defined by

$$S_{\text{CD}} = \left\langle \frac{3}{2}\cos^2\theta - \frac{1}{2} \right\rangle,$$

where θ is the relative angle between the CD bond vector and the bilayer normal, and the brackets denote averaging over the molecules and simulation time. The order parameter provided a quantitative measure of the alignment of the lipid tails. In general, S_{CD} with SDS was bigger than that of the purely hydrated membrane system. Interestingly, it was found that the lipid tail order was enhanced gradually with the increasing concentration of SDS. That is, the insertion of SDS made lipids more ordered, leading to the decrease in the bilayer area and increase in the bilayer thickness, which was in agreement with the experimental observations.[8] The increasing deuterium order parameters further proved that the presence of SDS tightened the membrane packing.

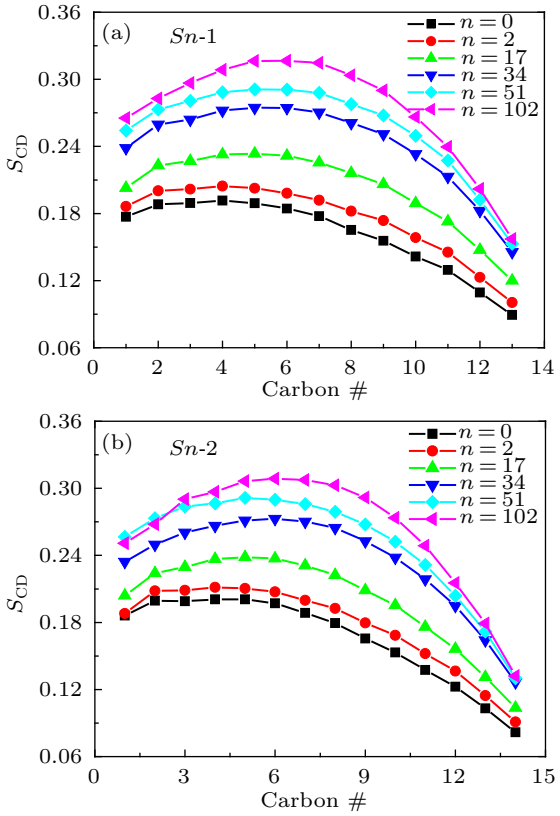


Fig. 6. (color online) Deuterium order parameters for (a) *Sn*-1 and (b) *Sn*-2.

4. Conclusion

In summary, using MD simulations, we have studied the penetration of SDS in the DPPC bilayer and the effects of SDS on the membrane structure with five different concentrations (1.5 mol%, 12 mol%, 21 mol%, 28 mol%, and 44 mol%), as well as the pure membrane for reference. SDS can readily penetrate into the membrane with its hydrocarbon chain parallel to the lipid tails, since both SDS and DPPC are amphiphiles. The insertion of SDS enhances the interactions among the lipids, leading to a decrease in the bilayer area and an increase in the bilayer thickness, when the SDS concentration is less than 28 mol%. This is confirmed by PMF profile and lipid tail order calculations. Different from the bilayer area and thickness, the bilayer volume is proportional to the SDS concentration, and the presence of SDS in the membrane causes the increasing bilayer volume.

However, it should be pointed out that we have investigated the direct interactions between SDS and DPPC bilayer, ignoring other important factors, such as pH, temperature, and ion concentration. Further simulations should take these factors into consideration, since they can affect the biophysical properties of the cell membranes.

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