Self-Assembly of Aldehyde Lipids in Water

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Abstract. Lipid based self-assembled structures has been applied for drug delivery systems. It is well known that lipid self-assembled structures depend on the chemical structures of lipids, however the self-assembled structures of oxidized lipids with asymmetrical structures remain unclear. In this study, 1-palmitoyl-2-(9-oxo-nonanoyl)-*sn*-glycero-3-phosphocholine (9-al) was used to investigate its self-assembly structure. The molecular dynamics (MD) simulation was performed with the system consisting of 128 lipids and 8,960 simple point charge (SPC) water molecules. Initially, all lipids and water molecules were randomly generated in the simulation box, then molecular trajectories were integrated and collected over microsecond times. The results showed that the equilibrium self-assembled structures of 9-al lipid preferred to form a micelle structure. We analyzed the lipid's angle distribution and the lipid's chain length to determine the lipid geometry. The results are in agreement with the previous MD simulation (Boonnoy, P.; *et al.* J. Phys. Chem. Lett. 2015, 6, 4884– 4888) that showed the deformation of aldehyde lipid bilayer into micelle structure due to their shorter and highly mobile of aldehyde functional group in oxidized chain.

1. Introduction

Oxidized lipids are the products of an oxidative attack on the unsaturated lipids acyl chains by free radicals (OH^-, O^{2-}, etc.)[1]. There are two major oxidized lipids species such as hydroxyl- or hydroperoxy-dieonyl PCs and truncated chains of PCs with aldehyde or carboxylic groups [2]. The previous experimental and computational studies have shown that the presence of oxidized lipid in cell membrane affect the biophysical properties of cell membrane and can lead to pore formation and lipid bilayer disintegration especially in case of the presence of high concentration of oxidized lipid with an aldehyde functional group [3,4]. In the previous study of Boonnoy *et al.* [5] have shown that the presence of 75% and 100% of aldehyde lipid in 1-palmitoyl-2-linoleoyl-sn-glycero-3-phosphatidylcholine (PLPC) lipid

bilayer lead to the lipid bilayer deformation into micelle. One possible explanation it that since the geometry of aldehyde lipid is a truncated cone the asymmetrical structure of aldehyde lipid and the extended structure of the oxidized chain. However the self-aggregation of aldehyde lipid remain unresolved. In this work, the self-assembly structure of aldehyde lipid starting from random configuration was investigated by using molecular dynamics simulations. The lipid self-assembly processes and the lipid geometry were analyzed and discussed.

2. Method

Molecular dynamics (MD) simulation of lipid self-assembly were performed using GROMACS 5.1.1 package [6]. 9-al lipid (1-palmitoyl-2-(9-oxo-nonanoyl)-*sn*-glycero-3-phosphocholine), an asymmetrical oxidized lipid structure with an aldehyde functional group in the oxidized chain (see figure 1(A) for the molecular structure) was used to study the self-assembled structures starting from random configuration to equilibrium structures. The united atom force-field parameters of 9-al lipid were taken from previous studies [5,7,8]. The system consists of 128 9-al lipid molecules and 8,960 simple point charge (SPC) water [9]. The initial structure of the system was generated using gmx insert-molecules tool that is provided in the GROMACS package by which all lipid and water molecules were randomly placed in the simulation box as shown in figure 1(B). After energy minimization process using a steeped descent algorithm, MD simulations were run for 1 microseconds with a time step of 2 fs. Periodic boundary condition were applied in all xyz directions and the neighbor list was updated for every time step. The simulation was run under the constant of particle number, pressure and temperature (NPT ensemble). A constant isotropic pressure coupling was controlled using the Parrinello-Rahman algorithm at 1 bar with a time constant of 3.0 ps and the compressibility of 4.5 x 10^{-5} bar^{-1} [10]. A constant temperature at 298 K was controlled using velocity rescaling algorithm [11] with a time constant of 0.1 ps. A cut-off of 1.0 nm was used for the long-range neighbor list of electrostatic and Van der Waals interactions. The Particle-mesh Ewald (PME) method was applied to calculate long-rang electrostatic interactions with the PME grid of 0.12 nm in the reciprocal-apace interactions and cubic interpolation. All bond lengths were constrained using the LINCS algorithm [12].The Visual Molecular Dynamics (VMD) software was used for molecular visualization [13].

3. Results and Discussions

In this section, we discuss the self-assembly of 9-al in water. Figure 1(A) shows the molecular structure of the aldehyde lipids in which an portion of lipid tail contains an oxygen atom. Figure 1(B-D) show the mechanism of 9-al self-assembly in water. The snapshots were taken at simulation times (B) t = 0 ns, (C) t = 214 ns, and (D) t = 1000 ns. The process start with all lipids and water were randomly dispersed in the simulation box. The self-assemble lipids quickly form to small clusters by which the polar lipid head group are in contact with water and the lipid tail tend to stay together. Then the small clusters gradually merge into the large clusters. Finally, the final structure of 9-al lipids are stable to form micelle structure. As the snapshot, we found the 9-al lipids bend the polar lipid tails in contact with water, therefore the average geometries of 9al-lipids is conical leading to form micelle structure.

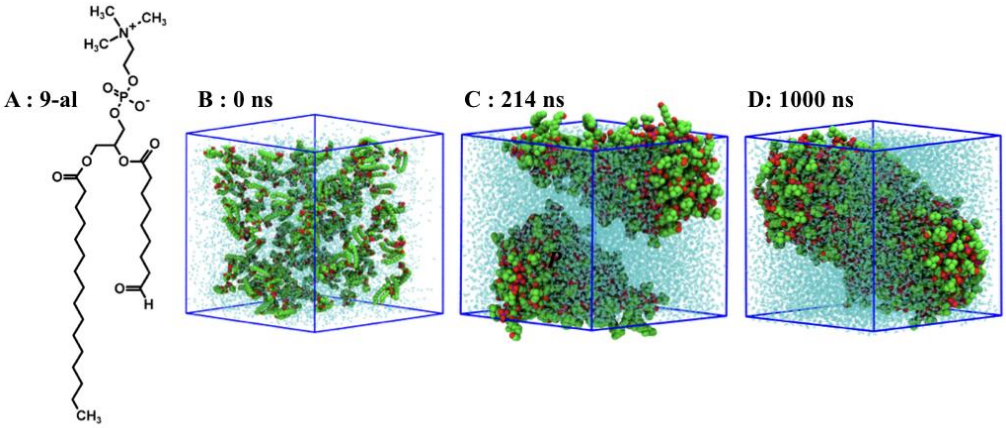

Figure 1. (A) Molecular structure of 9-al lipid (1-palmitoyl-2-(9-oxo-nonanoyl)-*sn*-glycero-3-phosphocholine). (B-D) The illustrations of self-aggregation of 9-al lipids in water. (B) The initial configuration of a simulated system. (C) Lipid gradually incorporates by bend the polar head contact with water. (D) 9-al lipids form the micelle structure. 9-al lipids are shown in green spheres, with phosphorus atom as purple spheres. Oxygen atoms are shown in red. Water is shown in light blue region.

Based on the final structure of lipid self-assembly, the shape of individual lipids were analyzed to explain how lipids prefer to form those structures. First, the distances between the phosphate atom in lipid headgroup and the last atom in the *sn-1* and *sn-2* chains (as defined l_1 and l_2, respectively) were calculated to characterized the tail lengths. In addition, the separation between the *sn-1* and *sn-2* chains was characterized by the distance between the last atoms in lipid tails, l_3. The results in Table 1 show that the l_1, l_2 and l_3. The ratio l_1:l_2 is greater than 1 due to the truncated lipids in the *sn-2* and the ratio l_2:l_3 is 0.65. The previous work of Boonnoy *et al.* [5] also showed that the ratio l_2:l_3 of the aldehyde lipids were significantly smaller than 1. Finally, the interior angles θ_A, θ_C were analyzed to determine the lipid geometry. The interior angles θ_A is averaged the angle between vectors of the head group to the last atom in the *sn-1* and *sn-2* chains. The interior angles θ_C is the angle between l_1 and l_3. As the figure 2 shown the angle distribution of θ_A and θ_C for 9-al lipids. The $\langle\theta_A\rangle$ and $\langle\theta_C\rangle$ of 9-al are were found at 74±2° and 37±1°, respectively. These results were in agreement with the previous study [5].

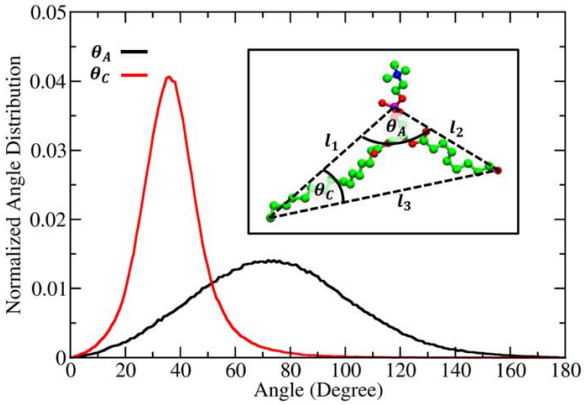

Figure 2. Angle distribution of θ_A and θ_C for 9-al cylindrical micelle. The definition of angle θ_A, θ_C, l_1, l_2 and l_3 are shown in the inset.

Table 1. The average angle θ_A , θ_C and the lengths of lipid chain ($l_1, l_2, and\ l_3$). See also figure 2.

	θ_A (degree)	θ_C (degree)	l_1 (nm)	l_2 (nm)	l_3 (nm)	$l_1 : l_2$	$l_2 : l_3$
9-al	74±2	37±1	1.91±0.01	1.27±0.01	1.95±0.03	1.50	0.65
9-al[a]	74±2	37±1	1.86±0.16	1.26±0.01	1.93±0.04	1.48	0.65

[a]Data were taken from a previous study by Boonnoy *et al.* [5]

Definition of angle and length. The interior angles of aldehyde lipid tails are represented by θ_A , θ_C . l_1 and l_2 are represent the lengths of the *sn-1* and *sn-2* lipid tails, respectively, and l_3 is the distance between the end of lipid tails.

4. Conclusion

MD simulation of aldehyde lipid self-assembly were performed to ensure that the lipid geometry play an essential role in the self-aggregation structure. The results showed that 9-al lipid spontaneously form stable cylindrical micelle structure similarly to the previous computer simulation [5]. The analysis of structural properties are in good agreement for all different initial configurations. Our results confirmed that the presence of aldehyde lipid can strongly modify membrane structure. An asymmetrical structures and the extended of aldehyde functional group in the oxidized chain can lead to form the micelle structure.

5. References

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