

Lipid-Carbon Nanotube Self-Assembly in Aqueous Solution

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One major drawback associated with single-walled carbon nanotubes (SWNTs) in the liquid phase is their hydrophobicity-induced aggregation, which prevents utilization of the unique physical and chemical properties of single SWNTs. Recently it has been found that lysophospholipids, or single-tailed phospholipids can readily form supramolecular complexes with SWNTs^{1,2} in large quantity, and the resultant SWNT solubility is superior to that provided by nucleic acids, proteins, and surfactants such as sodium dodecyl sulfate.² Using transmission electron microscopy (TEM), lysophospholipids were observed forming striations on SWNTs in a vacuum.^{1,2} Although the morphology of the striations seemingly favors the hemimicellar model,³ serious doubts remain about the arrangement of individual lipids within the striations. Here we present an *in silico* study of the binding of zwitterionic lysophosphatidylcholine, or LPC (18-carbon chain), to an (18,0) SWNT (diameter, 1.4 nm; length, 11.8 nm). We present compelling evidence that the binding of lipid surfactants to cylindrical nanostructures in the liquid phase does not obey any of the three popular models, that is, hemimicelles,³ cylindrical surfactant encapsulation,⁴ and random adsorption.⁵ Understanding the workings of lipid amphiphile-SWNT binding will facilitate research on improving nanomaterial solubility and biocompatibility, design of new nanostructures and molecular complexes for supramolecular chemistry,⁶ biosensing, drug delivery, and will enable an accurate characterization of nanotoxicity.

We performed classical molecular dynamics (MD) simulations to elucidate the binding of LPC on an SWNT. The simulation system consists of the SWNT fixed at the center of the simulation box, 76 LPC molecules, and 13395 water molecules. Initially, the dimensions of the simulation box were set at $6.5 \times 6.5 \times 12.0$ nm³, and the LPC molecules were distributed roughly uniformly within the box. The Gromacs force field was used, and the simulations were performed in NPT ensemble ($T = 300$ K, $P = 1$ bar) by using the Gromacs package.⁷ The electrostatic interactions were computed using the particle mesh Ewald method with an FFT grid spacing of 0.11 nm and a real space cutoff of 1.1 nm.⁸ The simulations ran for 24 ns (for details on the simulations see Supporting Information).

Figure 1 shows the number of lipid molecules adsorbed on the SWNT as a function of time. A lipid molecule was assumed to be adsorbed on the SWNT surface if at least three of its atoms were in contact with the SWNT surface or if the molecule was in contact with other lipid molecules that were adsorbed on the SWNT. Two atoms were assumed to be in contact if their distance $r_{ij} < R_i + R_j + 0.1$ nm, where R_i and R_j are the *van der Waals* radii of the two atoms, respectively. It was observed that the adsorption occurred quickly at the beginning ($t < 1.5$ ns) probably because of the close proximity of some of the lipids to the SWNT surface. Visualization of the simulation trajectories indicated that some of the lipid molecules simultaneously formed clusters in bulk. These processes

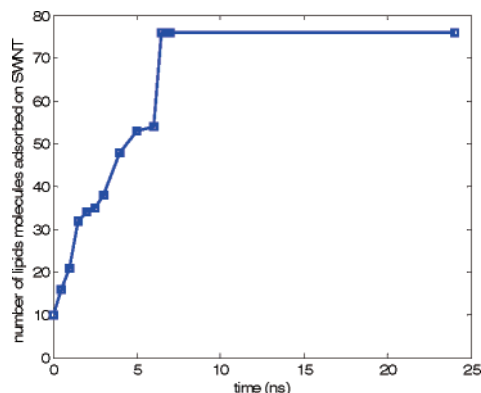


Figure 1. Variation of the number of lipid molecules adsorbed on the SWNT as a function of time.

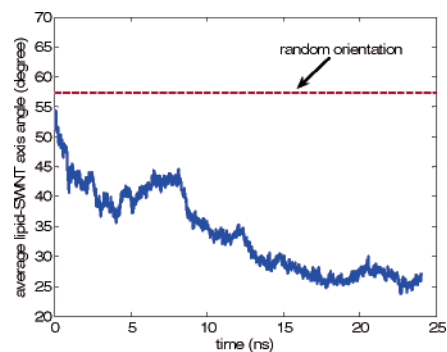


Figure 2. Evolution of the lipid-SWNT axis angle (in blue) as defined in the text. The dashed line (in red) denotes the average angle if lipids are randomly oriented with respect to the SWNT axis ($\theta_{\text{avg}} = \int_0^{\pi/2} \theta \sin \theta \, d\theta = 1.0 = 57.3^\circ$).

were followed by a gradual adsorption of both free lipid molecules and lipid clusters from the solution onto the SWNT. The significant jump of the number of adsorbed lipids (from 54 to 76) in Figure 1 at $t \approx 6.3$ ns corresponds to the adsorption of a large lipid cluster consisting of 22 lipid molecules onto the SWNT surface. After that phase, there were no free lipids or lipid clusters in the solution, and the adsorbed lipids remained bound on the SWNT surface. To quantify the lipid orientation, we computed the average orientation of lipid molecules θ_{lipid} with respect to the SWNT axis. Here θ_{lipid} is defined as the angle between the lipid vector \vec{v}_{lipid} and SWNT axis vector \vec{v}_{SWNT} :

$$\theta_{\text{lipid}} = \arccos \frac{|\vec{v}_{\text{lipid}} \cdot \vec{v}_{\text{SWNT}}|}{|\vec{v}_{\text{lipid}}| |\vec{v}_{\text{SWNT}}|}$$

where \vec{v}_{lipid} is defined as the vector originating from the last atom of the lipid tail to the center-of-mass of the lipid headgroup. Figure 2 shows the evolution of the average lipid orientation with respect to the SWNT axis. Initially, θ_{lipid} assumes the value of 51.2° ,

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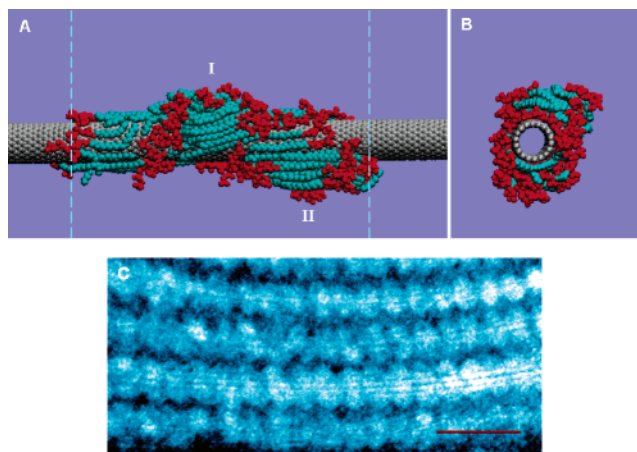


Figure 3. Self-assembly of LPC and an SWNT. (A) Front view of the simulation system configuration at $t = 24$ ns. The lipid bump I is formed from the gradual adsorption of lipids from the bulk, while the lipid bump II is formed from the adsorption of a lipid cluster in the bulk. The lipid headgroups and the tails are illustrated in red and cyan and the SWNT in gray, respectively. The dashed lines in panel A denote the periodic boundaries of the simulation box (~ 12 nm). Panel B shows the side view of the SWNT-LPC simulation system (water not shown). Image was rendered by using VMD. C. TEM (Hitachi 7600, stained with uranyl acetate)⁹ image of SWNT-LPC assemblies display a striation periodicity of ~ 4.5 nm; scale bar, 15 nm.

indicating that the adsorbed lipid molecules were approximately randomly oriented on the SWNT. As the simulations proceed, θ_{lipid} gradually decreases indicating that the lipids became more aligned with the SWNT axis. For $t > 15$ ns, the variations of θ_{lipid} become very small, and reach 27.1° at $t = 24$ ns. Such a small value of θ_{lipid} suggests that, at equilibrium, the lipids were predominately aligned along the SWNT axis, in contrast to that depicted by the “cylindrical surfactant encapsulation”⁴ or the “random adsorption”⁵ models. We noted that the aligning process was much slower compared to the adsorption of lipids from the solution to the SWNT surface. Specifically, all the lipid molecules adsorbed onto the SWNT within 7 ns, while it took approximately 15 ns for the lipids to relax toward the final configuration.

Figure 3a presents a side view of the simulation system at $t = 24$ ns, with large fractions of the lipids organized into “crests” that wrapped the SWNT spirally. The periodicity of the wrapping along the tube axis is ~ 4.5 nm, in good agreement with our TEM study of SWNT-LPC self-assembly (Figure 3C).⁹ Although these MD results seem to be in line with the hypothesis³ that surfactants form hemimicelles on nanotubes, there are fundamental differences. Instead of stemming out of a central corelike surfactants in a micelle,³ the “crests” in our simulations actually consist of several lipid layers (see Figure 3B) shifted along the tube axis and packed in parallel and antiparallel directions. The lipid tails are shielded by their headgroups at the outer rims of the “crests,” resulting in good SWNT solubility.

The binding pattern shown in Figure 3A is attributed to the hydrophobic and *van der Waals* interactions between the SWNT and the lipids and the large curvature of the SWNT. Specifically, in the beginning of the binding process when the lipid coverage of the SWNT surface was low, lipids were readily adsorbed on the SWNT surface and the motion of the lipid headgroups in the water

was retarded. This allowed for other lipids to bind onto the SWNT surface near the preadsorbed lipids, leading to the binding pattern shown in Figure 3A. Since it would leave large tube surface areas exposed to the water if lipids wrapped around the circumference of the SWNT, the lipids instead are generally aligned with the tube axis to maximize their contact with parallel lipids and with the hydrophobic SWNT surface. Obviously the cylindrical encapsulation model and the random adsorption model cannot explain the striations observed in the TEM experiments. The hemimicellar model requires lipid micelles first to break from the middle and then to assemble in tandem onto an SWNT. In comparison our illustrated mechanism agrees with the TEM experiments^{1,2} and is sterically and energetically favorable for the self-assembly of amphiphiles and cylindrical nanostructures.

Additional simulations were performed with the same system except that 152 LPC molecules were used (see Figure 1 in Supporting Information) to investigate the effect of the number of lipid molecules on the binding mode. Consistent results, that is, the general orientations of the lipids aligning along the SWNT axis and the ~ 4.5 nm periodicity of the lipid “crests”, were obtained. Adsorption and desorption were observed for several LPC molecules during the 20 ns simulation. Our results provide useful insight on the binding mechanism of amphiphiles and one-dimensional nanostructures. This knowledge may facilitate the bottom-up design of supramolecular assembly, nanotechnology, nanotoxicology, and gene and drug delivery.

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Supporting Information Available: Simulation details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) Pristine SWNTs were synthesized using the arc-deposition method. The average diameter of the SWNTs was approximately 1.4 nm measured by Raman spectroscopy and the average molecular weight of the SWNTs was 1×10^6 Dalton estimated from TEM. LPC was purchased from Avanti Lipids. SWNTs of 1 mg were placed in Eppendorf tubes containing LPC of 4 mg in 10 mL phosphate buffered saline (PBS, pH = 7.4) solution. The Eppendorf tube was probe sonicated for 15 min at room temperature and centrifuged for 3 min at 6177g RCF at tip to remove catalysts and amorphous carbon. The solution was placed on a holey carbon grid for 1 min, and the excess was drawn off with filter paper. The grid was negatively stained with a 2% uranyl acetate solution for 1 min. Images were recorded at a magnification of 600000 \times with a Hitachi 7600 transmission electron microscope at 100 kV.

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