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Peptide encapsulation regulated by the geometry of carbon nanotubes

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ABSTRACT

In this work the encapsulation of an α-helical peptide in single carbon nanotubes (CNTs) with similar diameter and length but different geometry (armchair and zigzag) was investigated through molecular dynamics simulations and free energy calculations. Our simulation results showed that *in vacuo* it makes no evident difference whether the investigated peptide is encapsulated in armchair or zigzag CNTs; however, in aqueous solution the armchair CNT encapsulates the peptide remarkably easier than the zigzag CNT does. A detailed analysis revealed that the equilibrium conformation of the water molecules inside the CNTs with varying geometry mediates the peptide encapsulation. It suggests that the water molecules play an important role in regulating behaviors of biomolecules in bio-systems. Then the impact of the CNT geometry on the conformational changes of the confined peptide was studied. Analyses of secondary structures showed the α-helix of the peptide could be better maintained in the zigzag CNT.

1. Introduction

The properties and applications of hybrid organic–inorganic nanomaterial have aroused great expectation of broad importance for future advancements in nanotechnology. In particular, the biomolecule-CNT complex that consists of single-walled CNTs (SWNTs) wrapped and/or filled with self-assembled bio-macromolecules continues to attract scientific attention. It has shown a wide range of interesting features with potential applications in CNT solubilization [1], single-molecule manipulation [2], biosensors [3], and biomedical devices [4], in which a few work have been reported by our group [5–9]. Meanwhile, these applications of SWNTs require their efficient dispersions based on geometry and diameter within cellular environment; separating and dispersing SWNTs, as well as the further detection of the CNTs with different geometry and/or diameters are therefore of importance [10].

To realize these applications, a detailed understanding of the fundamental molecular properties and interactions of the bio-nano complex is needed, which determines the potential applications of nanomaterial in biological settings. When concerning the interactions between CNTs and biomacromolecules, one should also pay attention to the role of the solvent molecules that extensively exist in the bio-nano systems. Currently the dynamic mechanism of water-CNT systems has been extensively investigated by both experiments [11,12] and simulations [13,14]. For example, Kolesnikov and co-workers [15] investigated the dynamic behaviors of water molecules in CNTs through both molecular dynamics (MD) simulation and neutron scattering techniques. Hummer and co-workers [16,17] reported a one-dimensionally ordered chain of water molecules confined in SWNTs. Alexiadis and co-workers [18,19] studied the density of water in CNTs with various diameters and different geometry. Huang and co-workers [20] revealed the distribution patterns of water inside and outside single-walled carbon nanotubes, suggesting that the water molecules tend to adsorb around the center of a hexagon formed by carbon atoms. Recently, our group reported the effects of geometry and diameter of CNTs on the water diffusion and conduction through MD simulations and quantum mechanics (QM) calculations [21,22]. In these works we have observed the significantly different potential energy surfaces of water molecules in armchair and zigzag CNTs, and confirmed that the minima of potential energy surfaces are at the center of a hexagon formed by carbon atoms and the maxima of potential energy are around the carbon atoms, which is consistent with the previous report [20]. More comprehensive understanding of the interactions between water and CNTs can be found in a review report [23].

Although the effects of geometry of CNTs on the dynamics of small molecules have been widely investigated experimentally and theoretically, the problem became more complicated when macromolecules were incorporated. Currently few works reported the

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impact of CNT topologies on the dynamics of macromolecules. Al-Haik and co-workers [24] investigated the binding affinity between polyethylene and CNTs with different geometry through MD simulations. In their work the CNTs with smaller chiral angles were observed to achieve higher adhesion energy, and tend to have smaller diameter and greater length. Zheng and co-workers [25] selected several CNTs with different geometry but similar diameters and lengths to investigate the interfacial binding of polymer-CNT composites, and the armchair CNT was considered to be optimal. However, the influence of the CNT geometry on the biomacromolecules in aqueous solution has not been reported so far, and the mechanism behind it remains obscure.

In this study an α-helical peptide was selected as a model molecule to investigate encapsulation behaviors of the biomacromolecules in SWNTs with similar diameters and lengths but different geometries through MD simulations and free energy calculations. We here try to focus on the different encapsulation processes of the peptide in the SWNT with two distinct structures, armchair and zigzag, to elucidate the effects of the tube geometry and the remarkable role of the solvent. The effects of tube length and diameter on the encapsulation of peptide molecule are not involved in this work, which have been investigated and reported by our group [6,7].

2. Modeling and simulation details

An α-helical peptide was taken as the model peptide from the Protein Data Bank (PDB), entry code 2OVN [26], with a sequence of NYHLENEVARLKKLCGE. According to the size of the model molecule, two types of uncapped SWNTs with similar tube length and diameter were selected: an armchair (14, 14) CNT and a zigzag (24, 0) CNT, with the tube diameter of 1.88 nm and 1.90 nm, and the tube length of 4.76 nm and 4.54 nm, respectively. The peptide was placed close to the entrance of each type of the nanotube, and was aligned along the tube axis. Then each peptide-CNT complex was immersed in a rectangular periodic box of TIP3P [27] water molecules (or in a rectangular periodic box of vacuum), in which the shortest distances between the complex surface and the box walls are larger than 1.0 nm.

In this work, all simulations were performed in the isothermal–isobaric (*NpT*) ensemble with Gromacs 4.5.2 package [28,29] and visualizations were made using VMD [30]. All bonds that involve H-atoms were fixed. A time step of 2 fs was used with atom coordinates saved every 1 ps. A temperature of 310 K and a pressure of 101.3 kPa was maintained using Berendsen method [31]. The CHARMM27 all-atoms (AA) force field [32] was used for describing the peptide and the CNT parameters were supplemented [33]. The atoms of the CNT remain fixed. The particle mesh Ewald (PME) summation [34] was used to calculate the full-system periodic electrostatic interactions, with a cutoff of 1.2 nm for the separation of the direct and reciprocal space summation. Carbon atoms of the CNTs are modeled to be uncharged. The cutoff distance for van der Waals interaction was 1.2 nm, and the parameters of the Lennard-Jones potential for the cross interactions between nonbonded atoms were obtained from the venerable Lorentz–Berthelot combination rule [35].

The instantaneous interaction energy between the peptide and the CNT is defined similarly to our previous work [9] as

$$E_{\mathrm{int}}(t) = E_{\mathrm{peptide+CNT}}(t) - E_{\mathrm{peptide}}(t) - E_{\mathrm{CNT}}(t) \quad (1)$$

where $E_{\mathrm{int}}(t)$ stands for the interaction energy between the peptide and the CNT, and $E_{\mathrm{peptide+CNT}}(t)$ refers to the total potential energy of the peptide–CNT complex. $E_{\mathrm{peptide}}(t)$ and $E_{\mathrm{CNT}}(t)$ are the potential energy of the peptide and that of the CNT, respectively. Each term indicates the energy as a function of the simulation time.

The free energy profile (represented by potential of mean force, PMF) was calculated by using the umbrella sampling [36–38]. The PMF was calculated along the reaction coordinate ξ, which was defined as the z-component difference between the center-of-mass (CoM) of the peptide and that of the CNT, describing the entering path of the peptide. The entering path was divided into 1 Å wide equidistant windows perpendicular to the tube axis with the center of each window representing an umbrella center. To enhance sampling, the biased simulations were performed in 41 sampling windows, in which the CoM of the peptide was harmonically restrained in z direction with a harmonic force constant of 400 $\mathrm{kJ\cdot mol^{-1}\cdot nm^{-2}}$. After carefully analysis, the first 6 ns was removed in each umbrella simulation for thermodynamic equilibration, followed by a 14 ns of production run. The PMFs were then unbiased and combined via the weighted histogram analysis method (WHAM) [39].

To clarify the behavior of the water molecules affected by the CNT, the density profiles of water molecules inside the CNTs were calculated based on the simulations of only a CNT (zigzag or amchair) in aqueous solution, regardless of the peptide. The two CNTs mentioned above were immersed respectively in an aqueous solvent box, with the shortest distance from the carbon atoms in the CNT to the box wall of 1.0 nm in radial direction and 3.0 nm in axial direction. Then 30 ns MD simulations were performed for the two CNT-water systems under the same conditions of temperature and pressure used in the peptide confining case, producing trajectories with 25,000 frames. The first 5000 frames (namely 6 ns) were discarded for thermodynamic equilibration, and the following 20,000 frames were used to extract density profiles of water molecules.

3. Results and discussion

3.1. Spontaneous encapsulation of the peptide into CNTs

Fig. 1 shows the normalized CoM distance, d/d_0, between the peptide and the CNTs as a function of the simulation time. First the peptide was placed close to the entrance of each type of the nanotube respectively, and for each complex a 5-ns simulation *in vacuo* was performed. As shown in Fig. 1, the normalized CoM distances decreased dramatically to around 0.0 within 1 ns simulations in both armchair and zigzag systems. It means that *in vacuo* both CNTs can encapsulate the peptide fast when the macromolecule was placed close to the entrance of the tube, and the geometry of the CNT (armchair or zigzag) barely affected the encapsulation for a given tube length and diameter. This is because the main driving force of the encapsulation is the van der Waals interaction between the peptide and the CNT [8], and the carbon atoms in CNTs with diverse geometry hardly affected their van der Waals attraction to a macromolecule, for example, a peptide. However, for small molecules such as water molecules, the effect of geometry of the CNTs on the confined guest molecules could not be negligible. In our previous work [22], the different potential energy surfaces of the water molecules inside the CNTs with different topologies have been observed. The potential energy surfaces reflected by the geometry of the CNT suggest obviously higher energy barrier of water molecules in a zigzag (24, 0) CNT compared to that in an armchair (14, 14) CNT in the axial direction.

Based on these literatures, it is conceivable that the encapsulation of the confined macromolecules would be modulated or controlled through the equilibrium conformation of the solvent molecules inside the CNTs. We subsequently repeated the simulations in aqueous solution by immersing the peptide-CNT complex