ISSN : 0974 - 7524 Volume 9 Issue 7

Physical CHEMISTRY
An Indian Journal

Full Paper

PCAIJ, 9(7), 2014 [220-224]

Steered molecular dynamics investigations of Na^+ transport through cyclic peptide nanotube

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ABSTRACT

In order to explore Na^+ constrained in cyclic octa-peptide nanotube, $\{cyclo[(-D\text{-}Ala\text{-}L\text{-}Ala)_4\text{-}]\}_{10}$ was selected as the model to investigate the mechanisms of cyclic peptide nanotube-mediated transmembrane transport of Na^+ using steered molecular dynamics (SMD). Results show that Na^+ adopt an leaping transport mode, and the leap distance is just the distance between neighboring rings. The transport speed of Na^+ during the entire process is 0.00637 Å /ps. The instantaneous speed is nearly zero at ring plane and it is 3.3-3.5 Å/ps at inter ring. Na^+ tends to stayed at the center axis of nanotube at the ring planes, and approaches to the side of the wall at the ring plane under the electrostatic interactions come from the nanotube.

KEYWORDS

Self-assembled cyclic peptide nanotube;
Steered molecular dynamics (SMD);
Ion transport.

Cyclic peptide nanotubes (SPNs) are composed of cyclic peptides consisting of alternating chirality[1,2]. The cyclic peptide rings adopt a flat-ring shape conformation and the C=O and N-H groups roughly perpendicular to the ring plane, which facilitates the ring stacking by means of inter-ring H-bonds and self-assembling into extended hollow tubular structures[3,4].

The peptide nanotubes have the simple structures and stable properties with the prospect application in materials, biological and chemical fields[5,7]. By controlling the number and types of amino acid of cyclic peptide, we can get the appropriate nanotubes with diameters and wall properties, which can incorporate into the cell membrane to transport mediated ions and small molecules. Owing to the special structure and properties of cyclic peptide nanotubes, they can be used as transmembrane ions channels, the drug molecular design, and biosensors etc[6-8].

The first artificial design of cyclic peptide nanotubes is synthesized by Ghadiri and his group in 1993[9]. Subsequently, a number of investigations on cyclic peptide nanotubes have been reported concerning the syntheses, characterization and specific functional applications of cyclic peptide nanotubes[10-12].

However, because of the cyclic peptide nanotubes are especially prone to congregate, it is difficult to characterize their structures and properties in the experiment instrument, especially, to obtain the ion transtransport information and mechanisms base on current experiments[13].

Therefore, in this study, we investigated transport behavior and mechanism of Na^+ constrained in a single cyclic peptide nanotube at atomic level. We

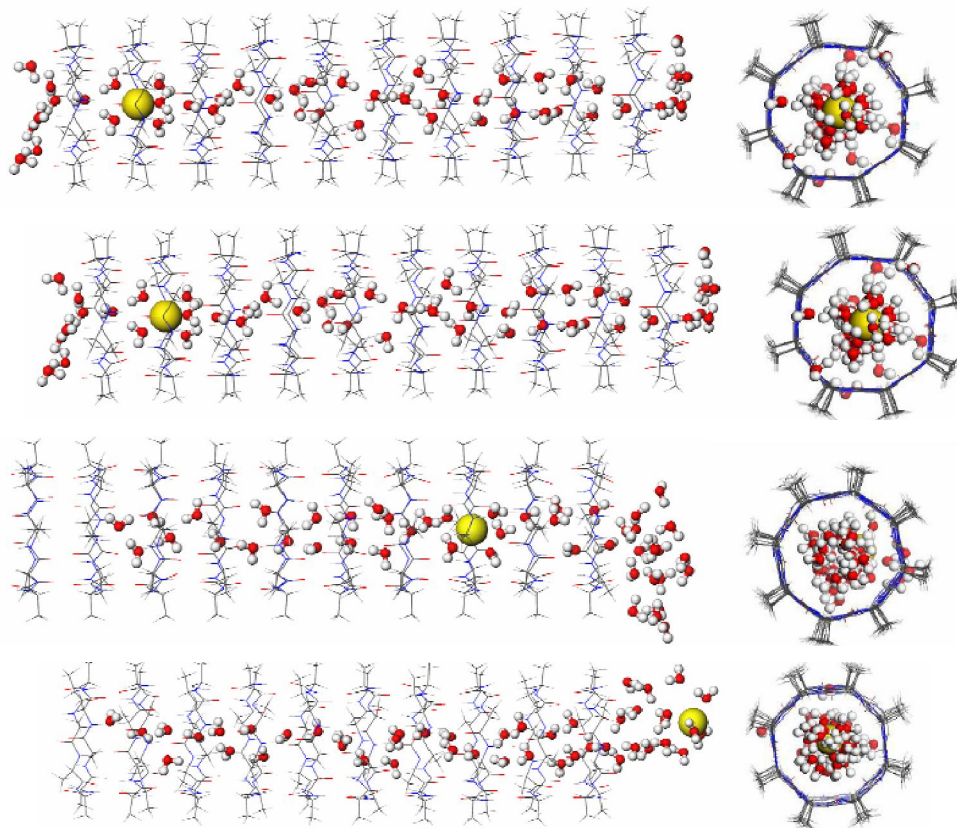

Figure 1 : Snapshot of Na^+ transport through cyclic peptide nanotube, in which the nanotube composed of 10 rings and Na^+ surrounded by 48 water molecules. (a) t=0ps; (b) t=2995ps; (c) t=3800ps; (d) t=4690ps. Na^+ is at ring plane in (a) and (c) and Na^+ is at middle rings in (b). The left pictures are side views and the right pictures are top views

hope this may provide evidences for their applications as sensors or transport channels.

Due to the ion transport is only related to the cyclic peptide nanotube inner-diameter, we selected the simplest cyclo[(D-Ala-L-Ala-)$_4$-] as the studing system. Firstly, we build a nanotube composed of 10 rings of with antiparallel stacking mode under referencing the experimental and calculated data[12,13]. Models were optimized by molecular mechanics. After optimization, diameter and ring spacing of cyclic peptide nanotubes were 4.78 Å and 7.5 Å, which are consistent with the results of experiment and calculation[14-16]. Then, put a Na^+ at the center of second ring plane, 48 water molecules randomly distributed in nanotubes and aroud it's ports, as shown in Figure 1. In order to make a reasonable distribution of water molecules, alternating molecular mechanics and 500 ps molecular dynamics are used to equilibrite the ion transport model. During the optimization process, 2.1 kcal/mol/Å^2 external force is exert on α-C atoms and Na^+ ion to fix their position. Then force of 1 kcal/mol/Å^2 along the nanotube axis exerted on Na^+ to pull it through the nanotube.

All calculations and analysises use the software NAMD 2.8[17] and VMD1.9[18] based on Charmm 27[19,20] force field.

The movement trajectory of Na^+ along *z*-axis, as shown in Figure 2, show that the initial position (0 Å) is the second ring, and the position of Na^+ come out of the nanotube is the tenth ring (38.24 Å). Na^+ passed through the nanotube in 6000 ps and vibrate at 5 Å away from the mouth of the nanotubes. We also calculate the total speed of Na^+ passing through the nanotube, which is 0.00637 Å /ps, corresponding to the experiment results of Ghadiri et al[21] and calculating results of Huang et al[22].

The transportation style of Na^+ is an leaping style. As shown in Figure 2., the Na^+ stay at the ring plane platform for a long time, then leap through the inter rings to another ring plane fast. The leap distance is just the distance between neighboring rings (4.78 Å). Na^+ stay at every inter rings is only about 20 ps; while stay at

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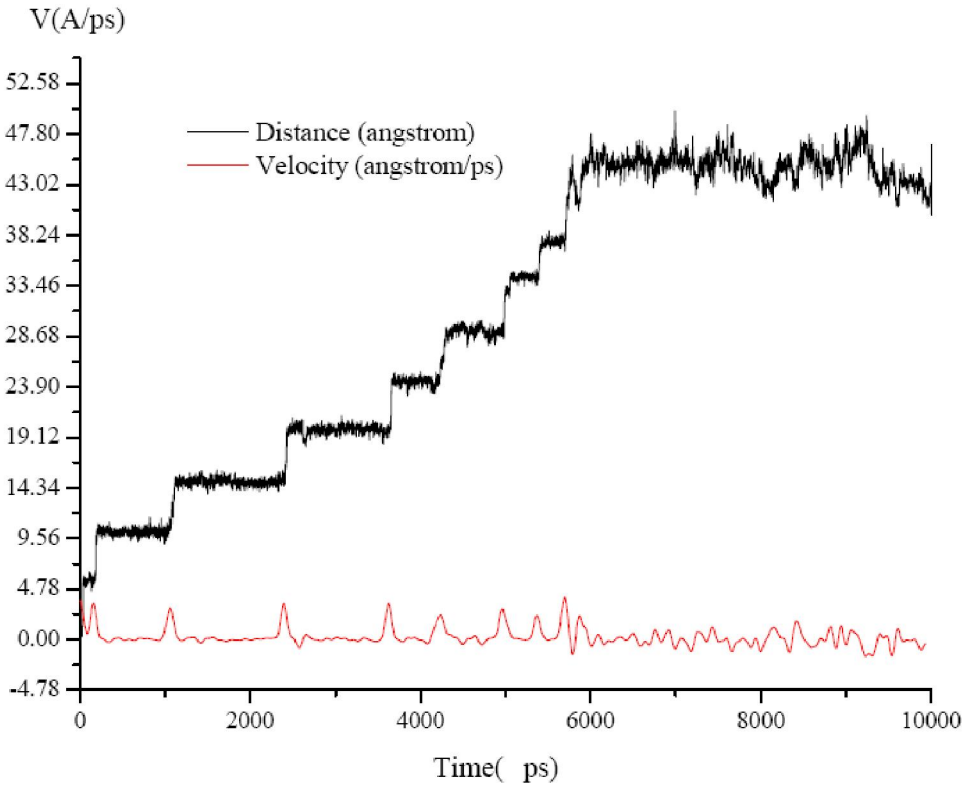

Figure 2 : Trajectory along *z*-axis and instant velocity of Na^+ transport through nanotube. The dark line is trajectory and red line is the instant velocity

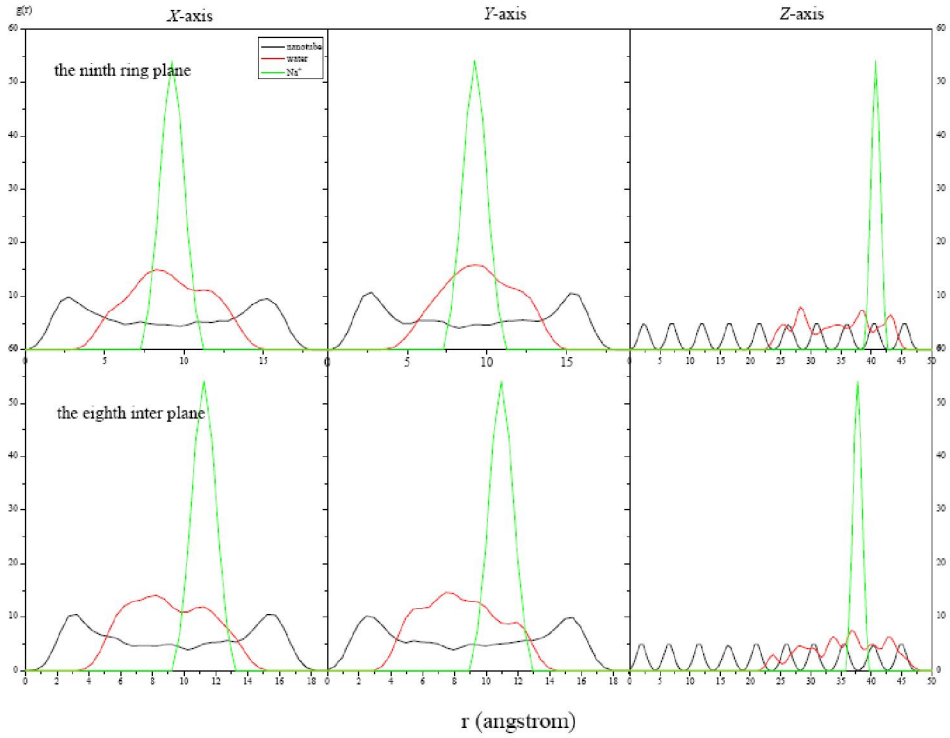

Figure 3 : Relative concentrations of Na^+, H_2O and nanotube at the ninth ring plane and eighth inter ring

every ring plane is about 600-1000 ps. So we analyzed the average speed of Na^+ every 20 ps. As shown Figure 2. the red line is the speed line. The speed of Na^+ at ring plane is nearly zero and at inter ring is about

3.3-3.5 Å/ps, which is further proved the Na^+ leaping transport mode.

Na^+ transport position can be reflected from the relative concentrations of Na^+, H_2O and nanotube at the ninth ring plane and eighth inter ring. From Figure 3., we can see that at the ring planes, Na^+ tends to stayed at the center axis of nanotube, while at the ring plane, Na^+ approaches to the side of the wall (Figure 3). This may attribute to the electrostatic interactions come from the nanotube, which can produced instantaneous dipole and give Na^+ powerful attraction at inter rings. But at the ring planes, the Na^+ subject to balanced electrostatic interactions, so Na^+ is trapped.

In conclusion, by steered molecular dynamics, we study the transportation of Na^+ in the cyclic peptide nanotubes. Results show that the transport speed of Na^+ is 0.00637 Å /ps, corresponding to the experiment and calculating results. Na^+ adopt an leaping transport mode, and the leap distance is just the distance between neighboring rings. At ring plane, the instantaneous speed of Na^+ is nearly zero; while at inter ring, the instantaneous speed can reach to 3.3-3.5 Å/ps. Due to the electrostatic interactions come from the nanotube, Na^+ tends to stayed at the center axis of nanotube at the ring planes, and approaches to the side of the wall at the ring plane. This work is up to now. We hope this work provides evidences for cyclic peptide nanotubes in applications as ion transport membrane channels.

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