Dynamic mechanism for encapsulating two HIV replication inhibitor peptides with carbon nanotubes*

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Encapsulation of biomolecules inside a carbon nanotube (CNT) has attracted great interest because it could enable the delivery of nanoscale pharmaceutical drugs with CNT-based devices. Using a molecular dynamics simulation, we investigate the dynamic process by which human immunodeficiency virus (HIV) replication inhibitor peptides (HRIPs) are encapsulated in a water solution contained inside a CNT. The van der Waals attraction between the HRIPs and the CNT and the root-mean-square deviation are used to analyse the evolution of the encapsulation. It is found that the interaction between the HRIPs and the CNT is the main driving force for the encapsulation process, which does not cause an obvious conformational change to the HRIPs.

Keywords: molecular dynamics simulation, drug delivery, peptide-CNT interaction, spontaneous encapsulation, conformational change

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1. Introduction

In recent years, the applications of carbon nanotubes (CNTs) have attracted the wide attention and great expectation of many researchers in biosensing, drug delivery, biomedical therapies, clinical diagnosis, and nanowires.[1−5] Owing to its intrinsic structure and amazing properties,[6−8] (e.g., hollow cylindrical structure, deep potential well inside the interior, biocompatibility, and low toxicity after functionalization) the CNT has been proved to be an excellent transport candidate for many biomolecules. Based on this background, both the experimental work and the molecular simulations focus on the encapsulation of DNA,[9,10] peptides,[11] proteins,[12,13] amylase,[14] drugs,[15,16] and so on inside single-walled carbon nanotubes (SWCNTs). In spite of these studies greatly extending our understanding of the encapsulation mechanism of biomolecules into SWCNTs, a report on the spontaneous insertion of multi-biomolecules into SWCNTs has not been found. Therefore, we perform a molecular dynamics (MD) simulation on the dynamic mechanisms of two HIV replication inhibitor peptides (HRIPs) encapsulated in a CNT to understand the interactions between HRIPs and a CNT at a molecular level.

2. Model and method

The present HRIPs-CNT system consists of two HRIPs respectively with 21 amino acids known as LGIGSCNDFAGCGYAVVCFW and an uncapped armchair (17,17) SWCNT (3.193 nm long and 2.302 nm in diameter). The stable configuration of P1–(17,17) CNT system, which is obtained by our previous MD simulations,[17] is used as the initial structure to encapsulate HRIP (P2). The P1 is located in the CNT about 6 Å (1 Å=0.1 nm) away from the CNT end near P2. The P2 is set to align along the nanotube axis, about 2 Å away from the end of CNT which is close to P1, as shown in Fig. 1. The CNT axial direction is placed parallel to the z axis, the centre of the CNT is set as the origin of the z-coordinate directing from P2 to P1. The P1–P2–CNT complex is solvated in a rectangular periodic box of TIP3P[18] water molecules in which the shortest distances between the complex surface and the box walls are larger

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than one-half of the cutoff distance. Sodium ions are added to neutralize the system. The total number of atoms of the system is 7383. Although the density functional theory (DFT) method is accurate and has an advantage over the force field in the calculation of interaction energy, the computation cost of the DFT method is too high for a large system.[19,20] QM/MM treatment can obtain some details of several atoms in the system,[21] but the present simulations focus on the whole behaviour of the HRIP. Therefore, we employ the force field to describe the interaction energy among the atoms in the present system. Its dynamics within 15 ns at temperature 310 K and pressure 101.3 kPa is simulated. A time-step of 2 fs is used and the full-precision trajectory is recorded every 1 ps. The CHARMM27 All-Atoms (AA) force field[22] is used with the supplemented CNT parameters[23] for the simulation system. Carbon atoms on CNTs are modeled to be uncharged and fixed in accordance with some previous reports.[10,14,24] In this work, the MD simulation is performed in the isothermal-isobaric (NPT) ensemble with the Nanoscale Molecular Dynamics Package (NAMD),[25] and visualizations and data are post-processed with the Molecular Graphics Viewer (VMD).[26] The van der Waals (vdW) interaction parameters between pairs of non-identical atoms are calculated using the Lorentz–Berthelot combination rule.[27] The cutoff distance for the pairwise Lennard–Jones nonbonded interactions is set at 12 Å with the pair list distance extended to 13.5 Å. The particle-mesh Ewald (PME) summation[28] is used to evaluate the full-system periodic electrostatic interaction, with a cutoff of 12 Å for the separation of the direct and reciprocal space summation.

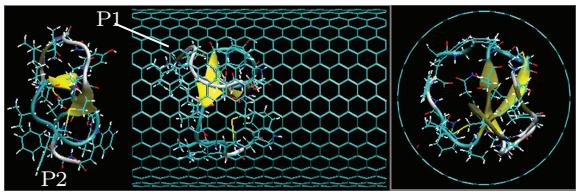


Fig. 1. (colour online) MD simulation snapshots of the initial configuration of the investigated P1–P2–(17, 17) CNT system. The lines model for the peptide shows the details of residues. Water molecules are not displayed for clarity.

3. Results and discussion

The snapshots of the P1–P2–CNT system in Fig. 2 are used to show the insertion process of P2 into a nanotube. The P1 or P2 centre-of-mass (COM) coordinate, the distance between the COM of HRIPs in Fig.3, are used as a reference point for the entering process and the matter movement. It is found from Fig. 3 that there is little change of the P2 COM coordinate in the first 0.6 ns, but some fluctuations of the distance between the COM of HRIPs take place, which indicates the self-adjustment of P2 before it begins to enter into the CNT. The P2 COM coordinate begins to increase at 0.6 ns, and a stagnation appears in the interval of 0.6 ns$< t <$1.6 ns, which indicates that P2 encounters resistance at the mouth of the CNT after it has approached the end of the CNT and undergoes a self-adjustment. Comparing with Fig. 2, we find that one quarter of the HRIP has entered into the CNT at the moment. Then, the coordinate of P2 COM increases more quickly, indicating that the adjusted HRIP smoothly enters the CNT. At 3.3 ns, HRIP has been completely encapsulated into the CNT. A snapshot taken at the moment is presented in Fig. 2. It is noteworthy that the 3.3 ns of P2 insertion time is less than 6.0 ns of P1. The changes of vdW interaction energies between P1 and CNT or P2 and CNT are presented in Fig. 4(a), while those of nobond interaction energies between P1 and P2 are shown in Fig. 4(b). During the insertion, the interaction energy of P2-CNT is reduced by 207.6 kcal·mol^{-1} with the increase of the value of the P2 COM coordinate, and the nobond interaction energy (vdW and electrostatic) of P1–P2 is reduced by 27.5 kcal·mol^{-1}. Those two interactions are both acceleration factors in the encapsulation process of P2. By comparing the changes of those two interaction energies, we find the interaction between P2 and the CNT plays an important role in the encapsulation process, as indicated by some other reports on biomolecule–CNT complexes.[9,10,17] The nobond interaction between P1 and P2 plays an auxiliary attraction role in the axial direction of the CNT for the insertion of P2. As shown in Figs. 3 and 4, the values of COM coordinate and vdW interaction energy oscillate with a small amplitude after 3.3 ns, which indicates that the system has reached an equilibrium state. The figures also show that from that point on, there is neither an obvious difference nor change of vdW interaction energy for the P1–CNT system and the P2–CNT system.

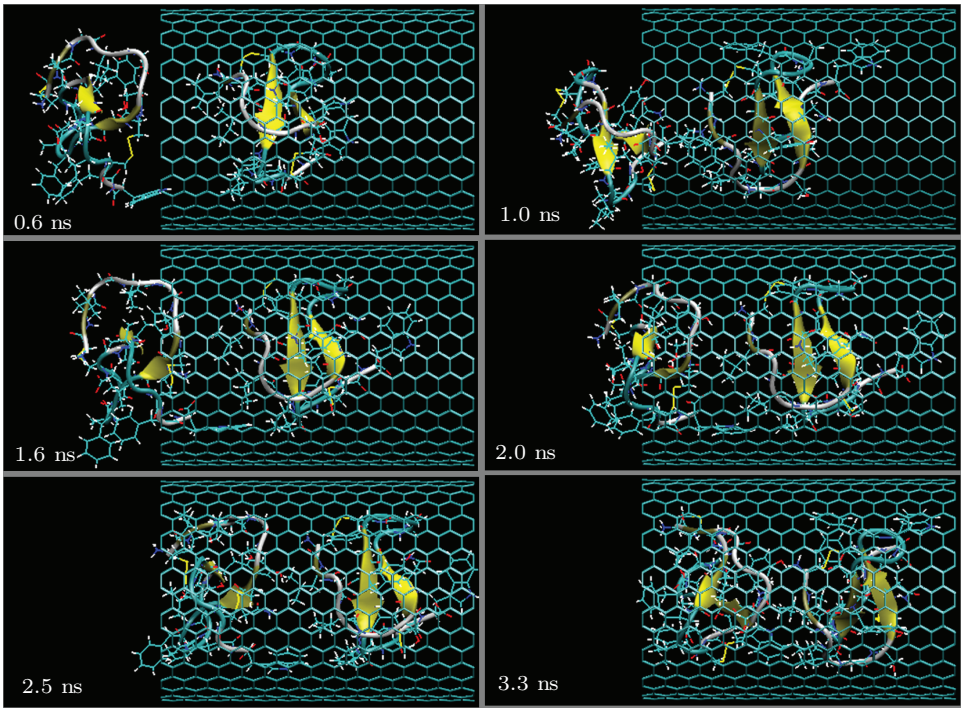


Fig. 2. (colour online) MD simulation snapshots of the spontaneous insertion of HRIP (P2), which is the system corresponding to Fig. 1 at 0.6, 1.0, 1.6, 2.5, and 3.3 ns. Water molecules and ions are not displayed for clarity.

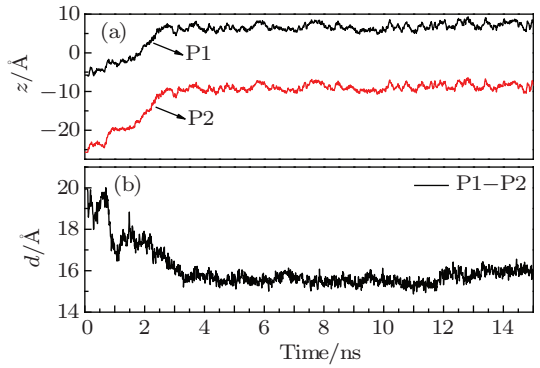


Fig. 3. (colour online) (a) The z coordinates of the COM of P1 and P2 each as a function of simulation time. (b) The COM distance between P1 and P2 as a function of simulation time.

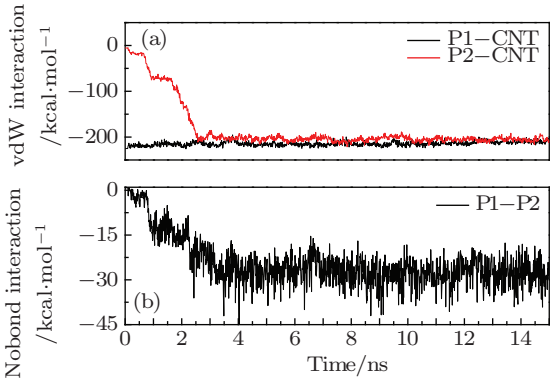


Fig. 4. (colour online) (a) The vdW interaction energies between the HRIP and the (17,17) CNT each as a function of simulation time, (b) vdW interaction energy between P1 and P2 as a function of simulation time.

The root-mean-square deviation (RMSD) of peptide/protein in a dynamics process can be used to measure its conformational change. Figure 5 shows that the RMSDs of P1 and P2 evolve with the time. On the whole, the RMSD of P2 has a similar trend to that of HRIP when it is encapsulated only by CNT.[17] In the first 0.6 ns, P2 undergoes a rapid self-adjusted conformational change mainly because of the attraction from the CNT. In the following period, P2 encounters a dramatically conformational change because the near and far parts of P2 from the end of the CNT are subjected to different interactions from the CNT, which corresponds to the process of P2 inserting into the CNT. Meanwhile, P1 undergoes a conformational change due to the mutual attraction with P2 with the distance becoming close along the axial direction of CNT. After P2 is entirely encapsulated, the area of water molecules between P1 and P2 in CNT is compacted, which provides a force to reduce the attraction effects between P2 and P1 as well as the CNT and make P1 and P2 almost stop in the axial direction. Finally, the RMSDs of P1 and P2 last around 1.7 Å and show a little oscillation, which implies that the conformation of P1 approaches its normal form in the CNT and the interaction between molecules and the CNT also reaches an equilibrium state.

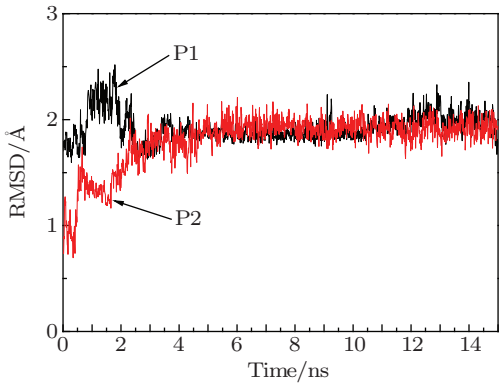


Fig. 5. (colour online) Root-mean-square deviations (RMSDs) of P1 and P2 each as a function of simulation time.

4. Conclusion

In this paper, the dynamic process of two HRIPs encapsulated into a CNT are demonstrated via molecular dynamics simulation. The results show that an HRIP molecule can spontaneously enter into the CNT including one encapsulated HRIP. It is found that the vdW attractive force between P2 and CNT is the main driving force in the encapsulation process. However, the nobond attractive force between P1 and P2 also accelerates the encapsulation process. The continuous encapsulation has not obviously affected the conformations of HRIPs. It is expected that a more helpful insight will be provided for manufacturing practical CNT-based devices for the delivery of inhibitors, genes, and drugs in the future.

References

[1] Veetil J V and Ye K 2007 *Biotechnol. Prog.* **23** 517
[2] Dhar S, Liu Z, Thomale J, Dai H J and Lippard S J 2008 *J. Am. Chem. Soc.* **130** 11467
[3] Bao W X and Zhu C C 2006 *Acta Phys. Sin.* **55** 3552 (in Chinese)
[4] Meng L J, Xiao H P, Tang C, Zhang K W and Zhong J X 2009 *Acta Phys. Sin.* **58** 7781 (in Chinese)
[5] Wang Y, Wang X X, Ni X G and Wu H A 2003 *Acta Phys. Sin.* **52** 3120 (in Chinese)
[6] Iijima S 1991 *Nature* **56** 354
[7] Lin Y, Taylor S, Li H, Fernando K A S, Qu L, Wang W, Gu L, Zhou B and Sun Y P 2004 *J. Mater. Chem.* **14** 527
[8] Lacerda L, Bianco A, Prato M and Kostarelos K 2006 *Adv. Drug. Deliv. Rev.* **58** 1460
[9] Gao H, Kong Y, Cui D and Ozakan C S 2003 *Nano Lett.* **3** 471
[10] Pei Q X, Lim C G, Cheng Y and Gao H 2008 *J. Chem. Phys.* **129** 125101
[11] Kang Y, Wang Q, Liu Y C, Wu T, Chen Q and Guan W J 2008 *J. Phys. Chem.* B **112** 4801
[12] Tsang S C, Davis J J, Green M L H, Hill H A O, Leung Y C and Sadler P J 1995 *Chem. Commun.* **17** 1803
[13] Kang Y, Liu Y C, Wang Q, Wu T and Guan W J 2009 *Biomaterials* **30** 2807
[14] Xie Y H and Soh A K 2005 *Mater. Lett.* **59** 971
[15] Hilder T A and Hill J M 2008 *Micro & Nano Lett.* **3** 41
[16] Chen Q, Wang Q, Liu Y C, Wu T, Kang Y, Moore J D and Gubbins K G 2009 *J. Chem. Phys.* **131** 015101
[17] Chen B D, Yang C L, Yang J S, Wang M S and Ma X G *Mol. Phys.* (in revision)
[18] Jorgensen W L, Chandrasekhar J, Madura J D, Impey R W and Klein M L 1983 *J. Chem. Phys.* **79** 926
[19] Yang Z Y and Zhao Y P 2007 *Engineering Analysis with Boundary Elements* **31** 402
[20] Li R, Hu Y Z and Wang H 2011 *Acta Phys. Sin.* **60** 016106 (in Chinese)
[21] Yang Z Y and Zhao Y P 2006 *Materials Science and Engineering* A **423** 84
[22] MacKerell A D, Bashford D, Bellott M, Dunbrack R L, Evanseck J D, Field M J, Fischer S, Gao J, Guo H, Ha S, Joseph-McCarthy D, Kuchnir L, Kuczera K, Lau F T K, Mattos C, Michnick S, Ngo T, Nguyen D T, Prodhom B, Reiher W E, Roux B, Schlenkrich M, Smith J C, Stote R, Straub J, Watanabe M, Wiorkiewicz-Kuczera J, Yin D and Karplus M 1998 *J. Phys. Chem.* B **102** 3586
[23] Walther J H, Jaffe R, Halicioglu T and Koumoutsakos P 2001 *J. Phys. Chem.* B **105** 9980
[24] Kang Y, Wang Q, Liu Y C, Shen J W and Wu T 2010 *J. Phys. Chem.* B **114** 2869
[25] Phillips J C, Braun R, Wang W, Gumbart J, Tajkhorshid E, Villa E, Chipot C, Skeel R D, Kalé L and Schulten K 2005 *Comput. Chem.* **26** 1781
[26] Humphrey W, Dalke A and Schulten K 1996 *J. Mol. Graphics* **14** 33
[27] Hirschfelder J O, Curtiss C F and Brid R B 1964 *Molecular Theory of Gases and Liquids* 2nd edn. (New York: John Wiley)
[28] Darden T, York D and Pedersen L 1993 *J. Chem. Phys.* **98** 10089