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Published on Web 02/10/2009

Manipulating Biomolecules with Aqueous Liquids Confined within Single-Walled Nanotubes

Peng Xiu,[†,‡] Bo Zhou,[‡,§] Wenpeng Qi,[†,‡] Hangjun Lu,[‡,⊥] Yusong Tu,[‡,§] and Haiping Fang*[,‡,¶]

School of Physics, Shandong University, Jinan, 250100, China, Shanghai Institute of Applied Physics, Chinese Academy of Sciences, P.O. Box 800-204, Shanghai 201800, China, Graduate School of the Chinese Academy of Sciences, Beijing 100080, China, Department of Physics, Zhejiang Normal University, 321004, Jinhua, China, and Theoretical Physics Center for Science Facilities (TPCSF), CAS, 19(B) Yuquan Road, Beijing 100049, China

Received June 16, 2008; E-mail: fanghaiping@sinap.ac.cn

Abstract: Confinement of molecules inside nanoscale pores has become an important method for exploiting new dynamics not happening in bulk systems and for fabricating novel structures. Molecules that are encapsulated in nanopores are difficult to control with respect to their position and activity. On the basis of molecular dynamics simulations, we have achieved controllable manipulation, both in space and time, of biomolecules with aqueous liquids inside a single-walled nanotube by using an external charge or a group of external charges. The remarkable manipulation abilities are attributed to the single-walled structure of the nanotube that the electrostatic interactions of charges inside and outside the single-walled nanotube are strong enough, and the charge-induced dipole-orientation ordering of water confined in the nanochannel so that water has a strong interaction with the external charge. These designs are expected to serve as lab-in-nanotube for the interactions and chemical reactions of molecules especially biomolecules, and have wide applications in nanotechnology and biotechnology.

1. Introduction

Confinement of molecules inside nanoscale pores can lead to interesting properties and behaviors that differ from those of bulk systems.[1−18] Some examples are enhanced catalysis[3,4] and enhanced stability of the native structure of proteins,[6] new folding mechanisms of proteins,[8,9] the ordered water structure,[10−12] non-Fickian-type diffusion,[13] extrafast motion of water molecules,[1,2,14] and excellent on−off gating behavior.[16,17] Furthermore, when the molecules are confined in nanosized water droplets,[19,20] their structures and hydrophobic and ionic interactions differ from those in bulk water.[21−24]

The determination of the positions of the molecules encapsulated in the nanopores with respect to time is important for controlling the interactions and chemical reactions of the molecules. Numerous studies have examined the translocation of charged and uncharged molecules along nanochannels.[25−34] Yeh and Hummer used an electric field to drive the charged

[†] School of Physics, Shandong University.
[‡] Shanghai Institute of Applied Physics, Chinese Academy of Sciences.
[§] Graduate School of the Chinese Academy of Sciences.
[⊥] Department of Physics, Zhejiang Normal University.
[¶] Theoretical Physics Center for Science Facilities (TPCSF).

(1) Hummer, G.; Rasaiah, J. C.; Noworyta, J. P. *Nature* **2001**, *414*, 188–190.
(2) Won, C. Y.; Aluru, N. R. *J. Am. Chem. Soc.* **2007**, *129*, 2748–2749.
(3) Pan, X. L.; Fan, Z. L.; Chen, W.; Ding, Y. J.; Luo, H. Y.; Bao, X. H. *Nat. Mater.* **2007**, *6*, 507–511.
(4) Yang, H. Q.; Zhang, L.; Zhong, L.; Yang, Q. H.; Li, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6861–6865.
(5) Shin, K.; Obukhov, S.; Chen, J. T.; Huh, J.; Hwang, Y.; Mok, S.; Dobriyal, P.; Thiyagarajan, P.; Russell, T. P. *Nat. Mater.* **2007**, *6*, 961–965.
(6) Eggers, D. K.; Valentine, J. S. *Protein Sci.* **2001**, *10*, 250–261.
(7) Sorin, E. J.; Pande, V. S. *J. Am. Chem. Soc.* **2006**, *128*, 6316–6317.
(8) Lucent, D.; Vishal, V.; Pande, V. S. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 10430–10434.
(9) Zhang, S. Q.; Cheung, M. S. *Nano Lett.* **2007**, *7*, 3438–3442.
(10) Koga, K.; Gao, G. T.; Tanaka, H.; Zeng, X. C. *Nature* **2001**, *412*, 802–805.
(11) Noon, W. H.; Ausman, K. D.; Smalley, R. E.; Ma, J. P. *Chem. Phys. Lett.* **2002**, *355*, 445–448.
(12) Mashl, R. J.; Joseph, S.; Aluru, N. R.; Jakobsson, E. *Nano Lett.* **2003**, *3*, 589–592.
(13) Striolo, A. *Nano Lett.* **2006**, *6*, 633–639.
(14) Holt, J. K.; Park, H. G.; Wang, Y. M.; Stadermann, M.; Artyukhin, A. B.; Grigoropoulos, C. P.; Noy, A.; Bakajin, O. *Science* **2006**, *312*, 1034–1037.
(15) Gong, X. J.; Li, J. Y.; Lu, H. J.; Wan, R. Z.; Li, J. C.; Hu, J.; Fang, H. P. *Nat. Nanotechnol.* **2007**, *2*, 709–712.
(16) Wan, R. Z.; Li, J. Y.; Lu, H. J.; Fang, H. P. *J. Am. Chem. Soc.* **2005**, *127*, 7166–7170.
(17) Li, J. Y.; Gong, X. J.; Lu, H. J; Li, D.; Fang, H. P.; Zhou, R. H. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 3687–3692.
(18) Loong, C. K.; Thiyagarajan, P.; Kolesnikov, A. I. *Nanotechnology* **2004**, *15*, S664−S671.
(19) Dokter, A. M.; Woutersen, S.; Bakker, H. J. *Phys. Rev. Lett.* **2005**, *94*, 178301.
(20) Ju, S. P.; Yang, S. H.; Liao, M. L. *J. Phys. Chem. B* **2006**, *110*, 9286–9290.
(21) Vaitheeswaran, S.; Thirumalai, D. *J. Am. Chem. Soc.* **2006**, *128*, 13490–13496.
(22) Rao, P. V. G.; Gandhi, K. S.; Ayappa, K. G. *Langmuir* **2007**, *23*, 12795–12798.
(23) Sykes, M. T.; Levitt, M. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 12336–12340.
(24) Tang, J.; Jofre, A. M.; Lowman, G. M.; Kishore, R. B.; Reiner, J. E.; Helmerson, K.; Goldner, L. S.; Greene, M. E. *Langmuir* **2008**, *24*, 4975–4978.
(25) Okada, T.; Kaneko, T.; Hatakeyama, R.; Tohji, K. *Chem. Phys. Lett.* **2006**, *417*, 288–292.

 10.1021/ja804586w CCC: $40.75

macromolecules through nanopores.[26] Král used laser to excitate an electric current in the carbon nanotube, resulting in a net force on ions absorbed in the nanotube.[28] Longhurst and Quirke made use of capillary force to draw decane molecules into a single-walled carbon nanotube (SWNT) and temperature differences to drive their transport through the SWNT.[30] Very recently, Zhao et al. demonstrated experimentally that a water flow can be driven by the applied current of the SWNT.[32] However, to our knowledge, there is no report on the controllable manipulation of the biomolecules in a nanopore both in space and time.

In this paper, we propose an approach toward this direction by using the charge(s) outside single-walled nanopores to manipulate the biomolecules with aqueous liquids on the basis of molecular dynamics (MD) simulations, benefiting from the single-walled structure of the nanotube and the unique properties of water.[15,17,35−42] We used the SWNT as an example for the demonstration, because carbon nanotubes have outstanding potentials for applications in nanoscale sensors/devices/machines.[43−49] Explicitly, a drop of water−peptide mixture is controllably moved by manipulating a charged atom/molecule/cluster outside the nanotube, no matter if the peptide has any charged residue or not; if the peptide has charged residue(s), it can also be controllably moved by manipulating a group of charges outside the nanotube even if the nanotube is fully filled with water. These remarkable manipulation abilities are attributed to the single-walled structure of the nanotube that the electrostatic interactions of charges inside and outside the SWNT are strong enough, and the preferential dipole orientation distribution of the water molecules under confinement so that the water inside the nanochannel has a strong interaction with the external charge. Considering that the external charges required for these manipulations are quite small, which are still available after taking into account the screening effect of many nanotubes, these designs are expected to serve as laboratory-in-nanotube for the interactions and chemical reactions of molecules especially biomolecules, and have wide applications in nanotechnology and biotechnology.

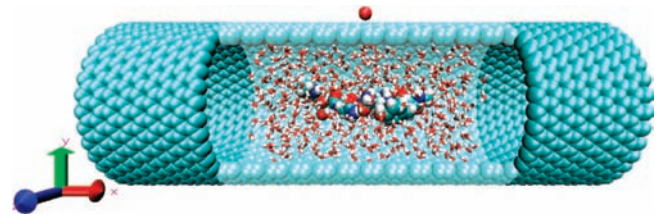

Figure 1. Initial framework of the system I, side-view. The peptide (GNNQQNY) is solvated with a small quantity of water molecules. The other space of the single-walled carbon nanotube (SWNT) is in vacuum. The large red sphere is the external charge, and the red−white pillars are the water molecules. The light-blue spheres represent the SWNT. Some carbon atoms of SWNT are not shown or drawn as transparent for ease of demonstration. The other colored spheres in the middle of SWNT are the atoms of the peptide.

2. Computational Methods

We have prepared two systems. The first one, namely, the system I, contains a peptide solvated in 463 TIP3P[50] water molecules inside a (35,0) zigzag SWNT with dimensions of 15.05 nm in length and 2.7 nm in diameter. This is shown in Figure 1. The peptide used here is a seven-residue capped peptide (Ace-GNNQQNY-NMe, GNNQQNY's Protein Data Bank code 1YJP) whose residues have no net charge and whose aggregation is associated with fatal diseases such as Alzheimer's.[51] We note that water usually spontaneously accumulates close to a peptide in an environment with moderate humidity. This SWNT was aligned along the *x*-axis in a periodic box of 15.12 nm × 8 nm × 8 nm. The peptide−water mixture was ∼4 nm in length. A single charge was allocated above the peptide−water mixture at 3.5 Å from the SWNT wall. The other space of the system I was in vacuum. Considering the screening effect of many single-walled nanotubes, as discussed by Wang and Kral,[35] the quantity of the external charge q, which we have used here, can be regarded as the effective charge after taking into account the screening effect. The counterion was constrained at the right edge of the box far from the SWNT in order to neutralize the net charge of the system and so as not to affect the dynamical properties of the peptide−water mixture.

The second one, namely, the system II, contains a peptide called Aβ_{16-22}[52] (Ace-KLVFFAE-NMe) inside a (29,0) zigzag SWNT with dimensions of 8.33 nm in length and 2.24 nm in diameter (see also Figure S2 in Supporting Information). This peptide is an Alzheimer's-disease-related peptide, having a lysine (K) residue with one positive charge ($+1e$) at one end and a glutamic acid (E) residue with one negative charge ($-1e$) at the other end. The other space in SWNT was fully filled with

(26) Yeh, I. C.; Hummer, G. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12177–12182.
(27) Zimmerli, U.; Koumoutsakos, P. *Biophys. J.* **2008**, *94*, 2546–2557.
(28) Kral, P.; Tomanek, D. *Phys. Rev. Lett.* **1999**, *82*, 5373–5376.
(29) Insepov, Z.; Wolf, D.; Hassanein, A. *Nano Lett.* **2006**, *6*, 1893–1895.
(30) Longhurst, M. J.; Quirke, N. *Nano Lett.* **2007**, *7*, 3324–3328.
(31) Savariar, E. N.; Krishnamoorthy, K.; Thayumanavan, S. *Nature Nanotechnol.* **2008**, *3*, 112–117.
(32) Zhao, Y. C.; Song, L.; Deng, K.; Liu, Z.; Zhang, Z. X.; Yang, Y. L.; Wang, C.; Yang, H. F.; Jin, A. Z.; Luo, Q.; Gu, C. Z.; Xie, S. S.; Sun, L. F. *Adv. Mater.* **2008**, *20*, 1772–1776.
(33) Wang, Z. K.; Ci, L. J.; Chen, L.; Nayak, S.; Ajayan, P. M.; Koratkar, N. *Nano Lett.* **2007**, *7*, 697–702.
(34) Ho, C. M, *Tech. Digest 14th IEEE Intl. MEMS Conf.* 14th IEEE International Micro-Electro-Mechanical-Systems (MEMS) Conference, Interlaken, Switzerland, 2001; pp 375−384.
(35) Wang, B.; Kral, P. *J. Am. Chem. Soc.* **2006**, *128*, 15984–15985.
(36) Tajkhorshid, E.; Nollert, P.; Jensen, M. O.; Miercke, L. J. W.; O'Connell, J.; Stroud, R. M.; Schulten, K. *Science* **2002**, *296*, 525–530.
(37) Zhou, R. H.; Huang, X. H.; Margulis, C. J.; Berne, B. J. *Science* **2004**, *305*, 1605–1609.
(38) Horinek, D.; Serr, A.; Geisler, M.; Pirzer, T.; Slotta, U.; Lud, S. Q.; Garrido, J. A.; Scheibel, T.; Hugel, T.; Netz, R. R. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 2842–2847.
(39) Li, J. C.; Ross, D. R. *Nature* **1993**, *365*, 327.
(40) de Groot, B. L.; Frigato, T.; Helms, V.; Grubmuller, H. *J. Mol. Biol.* **2003**, *333*, 279–293.
(41) Verdaguer, A.; Sacha, G. M.; Bluhm, H.; Salmeron, M. *Chem. Rev.* **2006**, *106*, 1478–1510.
(42) Ball, P. *Chem. Rev* **2008**, *108*, 74–108.
(43) Sun, L.; Crooks, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 12340–12345.
(44) Regan, B. C.; Aloni, S.; Ritchie, R. O.; Dahmen, U.; Zettl, A. *Nature* **2004**, *428*, 924–927.
(45) Bourlon, B.; Wong, J.; Miko, C.; Forro, L.; Bockrath, M. *Nature Nanotechnol.* **2007**, *2*, 104–107.
(46) Besteman, K.; Lee, J. O.; Wiertz, F. G. M.; Heering, H. A.; Dekker, C. *Nano Lett.* **2003**, *3*, 727–730.
(47) Ghosh, S.; Sood, A. K.; Kumar, N. *Science* **2003**, *299*, 1042–1044.
(48) Siwy, Z.; Fulinski, A. *Phys. Rev. Lett.* **2002**, *89*, 198103.
(49) Fan, R.; Yue, M.; Karnik, R.; Majumdar, A.; Yang, P. D. *Phys. Rev. Lett.* **2005**, *95*, 086607.
(50) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926–935.
(51) Nelson, R.; Sawaya, M. R.; Balbirnie, M.; Madsen, A. O.; Riekel, C.; Grothe, R.; Eisenberg, D. *Nature* **2005**, *435*, 773–778.
(52) Balbach, J. J.; Ishii, Y.; Antzutkin, O. N.; Leapman, R. D.; Rizzo, N. W.; Dyda, F.; Reed, J.; Tycko, R. *Biochemistry* **2000**, *39*, 13748–13759.

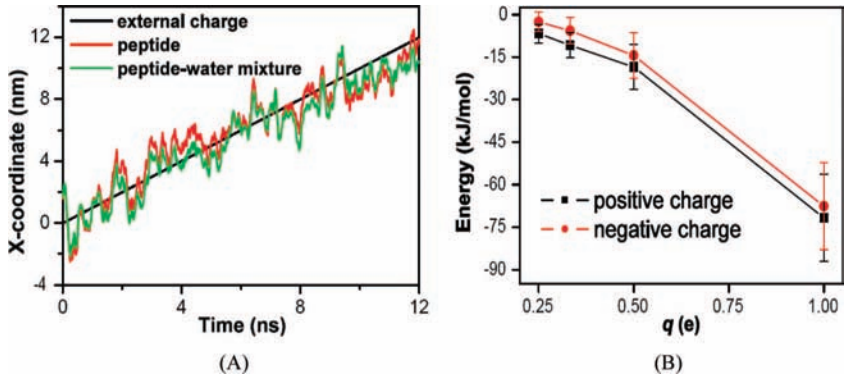

Figure 2. Manipulating the peptide−water mixture. (A) *x*-Coordinate of the center of mass of the peptide (GNNQQNY) and the peptide−water mixture as a function of time, together with the *x*-coordinate of the external charge for the effective charge $q = 0.5e$. (B) Electrostatic interaction energies between the external charge and the water molecules with respect to q. The error bars show the fluctuations due to thermal noise.

water. The SWNT was aligned along the *x*-axis in a periodic box of 8.4 nm × 12 nm × 12 nm. A group of external charges that contained 12 charges forming a 3 × 4 array was allocated at 3.5 Å from the SWNT wall and initially above the glutamic acid residue of the peptide. The distance between the nearest adjacent charges was 2.88 Å. This charge pattern is very similar to that of the Au(100) crystal face. We note that other patterns of the external charge group do not change the conclusion we obtained here, provided that the external charges are densely packed in two dimensions. The quantity of each charge is also denoted by q. The corresponding counterions were constrained at the right edge of the box to make the system neutral.

The SWNT was left free to vibrate so that the peptide and water molecules could relax by collisions with the tube, except for a few constrained atoms that hold the SWNT in space and separate it from exquisite oscillation (some carbon atoms were constrained by using the position restraints with a length interval of 2.5 nm along the axial direction of SWNT. Totally, about 5% carbon atoms were constrained). The carbon atoms were modeled as uncharged Lennard-Jones particles with a cross section of $\sigma_{cc} = 3.400$ Å and a depth of the potential well of $\varepsilon_{cc} = 0.3598$ kJ mol^{-1}.[1] Carbon−carbon bond lengths of 1.4 Å and bond angles of 120° were maintained by harmonic potentials with spring constants of 392460 kJ mol^{-1} nm^{-2} and 527 kJ mol^{-1} rad^{-2}. In addition, a weak dihedral angle potential was applied to bonded carbon atoms.[1]

The energy of the system was minimized with a steepest descent algorithm, followed by 1 ns relaxation with the peptide atoms constrained. Then a 0.5 ns simulation was carried out for equilibrium, with the peptide atoms left free. In all these steps, the external charge(s) was constrained at its original site. After the equilibrium, the external charge(s) moved along the *x*-axis for 12 ns with the velocity of 1 m/s by using AFM pulling with the spring constant 10000 kJ mol^{-1} nm^{-2}.

All MD simulations were performed using Gromacs 3.3.1[53] in an NVT ensemble at a temperature of 300 K. The OPLSAA force field was used.[54] We applied stochastic dynamics which was based on the Langevin equation. The damping coefficient, ξ, was 0.01 ps^{-1}. This was a compromise between the 0.001 ps^{-1} rate, valid for intertube coupling, which could apply also to the neutral part of the molecule, and the 0.1 ps^{-1} damping, which might be correct for polar groups and water.[35] Moreover, this small damping coefficient could minimize the unphysical loss of momenta to the reservoirs.[55] Some modifications of the value of ξ did not change the results much in this paper (see more in the Supporting Information). The particle-mesh Ewald method[56] with a real space cutoff of 1 nm was used to treat long-range electrostatic interactions. Lincs was applied to constrain all bonds connecting the hydrogen atoms of the peptide, and a time step of 2.0 fs was used. The data were collected every 0.5 ps. The technique of center of mass motion removal was not used.

3. Results and Discussion

3.1. Manipulating the Peptide−Water Mixture. For the system I, Figure 2A shows a typical example for the *x*-coordinate of the center of mass (COM) of the peptide and the peptide−water mixture as a function of time, together with the *x*-coordinate of the external charge. Herein, we mainly present the simulation results for the case of positive charge $q = 0.5e$. The other choices of the values of q will be discussed later. The peptide−water mixture follows well the external charge. The fluctuations on the *x*-coordinate of the COM result from the thermal noise of the environment. It is clear that the peptide−water mixture can be controlled well both in space and time through the manipulation of external charge.

To understand the mechanism of this remarkable manipulating phenomenon, we calculated the electrostatic interaction energy of the external charge with the peptide and water. The average value of the electrostatic interaction energy between the external charge and the peptide was much smaller than the electrostatic interaction energy between the external charge and the water molecules in the peptide−water mixture. For example, when $q = 0.5e$, the former was only about −0.5 kJ/mol, while the latter is -18.5 ± 7.9 kJ/mol ($\sim 7.4\ k_BT$). The electrostatic interaction energies between the external charges and the water molecules for different values of q are shown in Figure 2B. We also found that the positively external charges interacted with the water molecules more effectively than the negatively external charges, probably because the charge on oxygen is larger than that of hydrogen.[35] In the calculation, for values of $q = \pm 1e$ and $\pm 0.5e$, the results were obtained by averaging over three successful

(53) Lindahl, E.; Hess, B.; van der Spoel, D. *J. Mol. Model.* **2001**, *7*, 306–317.
(54) Jorgensen, W. L.; Maxwell, D. S.; TiradoRives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225–11236.
(55) Wang, B. Y.; Kral, P. *Phys. Rev. Lett.* **2007**, *98*, 266102.
(56) Darden, T.; York, D.; Pedersen, L. *J. Chem. Phys.* **1993**, *98*, 10089–10092.

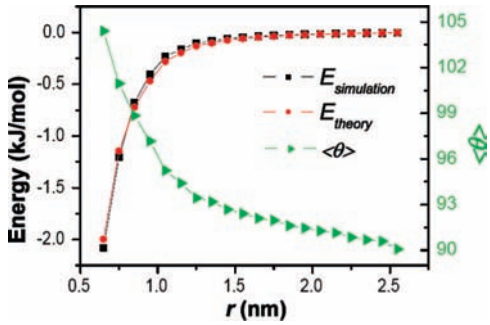

Figure 3. Manipulating the peptide−water mixture. The water-charge electrostatic interaction energy and the averaged dipole orientation of water molecules with respect to the distance between a water molecule and the external charge for $q = 0.5e$. Green triangles: the averaged dipole orientation $\langle\theta\rangle$ of water molecules (right y-axis). Red circles: the average electrostatic interaction energy (E_{theory}) between the external charge and the dipole moment of one water molecule at r, computed from the $\langle\theta\rangle$ distribution. Black squares: the average electrostatic interaction energy ($E_{simulation}$) between the external charge and one water molecule, determined directly from numerical simulations.

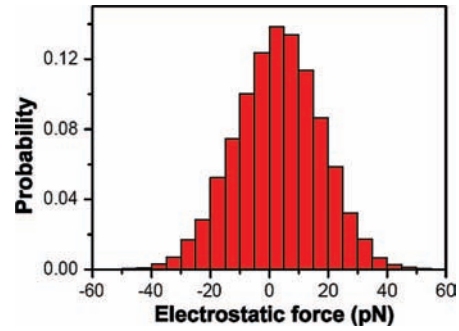

Figure 4. Manipulating the peptide−water mixture. The electrostatic forces by the external charge for $q = 0.5e$ exerting on the peptide−water mixture along the x-axis. The positive direction of the force is the positive direction of the x-axis, and a 5 pN force interval is used.

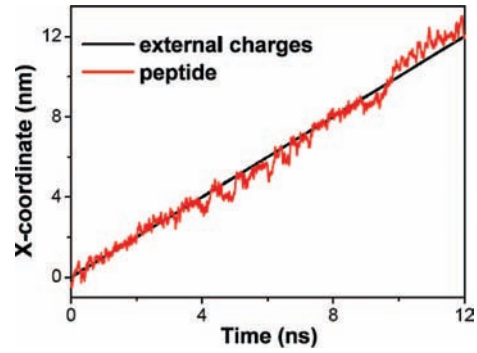

Figure 5. Manipulating the peptide with charged residues inside a water-filled nanotube. The x-coordinate of the center of mass of the Aβ_{16-22} peptide (red line) as a function of time, together with the x-coordinate of the geometrical center of the external charges (black line).

manipulation cases of 12 ns simulations. In cases where $q = \pm$ 0.33e and $\pm$ 0.25e, since the probabilities for successful manipulations were low, the electrostatic interaction energies were computed from a 12 ns simulation with the external charge and the atoms of peptide constrained.

The key point of this strong water-charge electrostatic interaction is the charge-induced dipole-orientation ordering of the water molecules confined in the nanochannel. In Figure 3, we show the averaged dipole orientation of water molecules, denoted by $\langle\theta\rangle$, as a function of the distance between a water molecule and the external charge, defined by the term r. θ is defined as the angle between the dipole orientation of the water molecule and the line connecting the oxygen of the water molecule and the external charge, and the average runs over all the water molecules at r. It is clear that $\langle\theta\rangle$ departs from 90°, and the closer the water molecules are located to the external charge, the larger the departure from the perpendicular orientation. From this $\langle\theta\rangle$ distribution, we can predict the electrostatic interaction energy of the external charge with a water molecule at r, denoted by E_{theory}, where the dipole moment for each water molecule in the calculation is assumed as 0.489 e Å from the TIP3P water model. As shown in Figure 3 (red circles), E_{theory} agrees well with the numerical result $E_{simulation}$ (black squares). The electrostatic interaction energies between the external charge and the water molecules shown in Figure 2B can be obtained by integrating $E_{simulation}$ for all water molecules in the mixture.

We have also calculated the electrostatic force that the external charge exerted on the peptide−water mixture along the x-axis. The electrostatic forces dominatively range from −40 pN to +40 pN (see Figure 4), which fall within the working ranges of many existing techniques such as STM and AFM. This result suggests that the AFM/STM tip carrying charge(s) may be able to manipulate the peptide with aqueous liquids according to the method described here.

Thermal fluctuation will sometimes make the manipulation unsuccessful, but for $q = \pm 1.0e$, this is a rare event. When $q = \pm 0.5e$, we observed that the peptide−water mixture followed the external charge in 8 of the 11 simulations for the same systems with different initial conditions. In cases where $q = \pm 0.33e$ and $\pm 0.25e$, the peptide−water mixture had low probabilities to follow the external charge. Moreover, we found that the speed of the external charge had a remarkable influence on the manipulation. When the speed of the external charge increased from 1 to 10 m/s, only one successful manipulation was observed in 10 simulations with different initial conditions. We expect that, as the speed of the external charge decreases, the probabilities for these unsuccessful cases decrease. Usually, the speed of the AFM/STM tip is within the magnitudes from 1 nm/s to 1 μm/s. Considering that the speed of the external charge in our simulation is up to 1 m/s, the efficiency for successful manipulation may even be higher for a much lower speed under experimental conditions. When the peptide is substituted by a larger molecule such as a protein, the effective value of the external charge required for successful manipulation should be larger. We note that in the case where the probability of the successful manipulations by a single charge is low, we can use a series of charges, which can greatly enhance the probabilities.

3.2. Manipulating the Peptide with Charged Residues Inside a Water-Filled Nanotube. For the system II, Figure 5 shows a typical example for the x-coordinate of the center of mass (COM) of the peptide as a function of time, together with the x-coordinate of the geometrical center of the external charges for $q = 0.5e$ per atom. The peptide follows the external charges very well. In the six simulations we performed with different initial conditions, only in one simulation, the peptide did not follow the external charges. We have computed the electrostatic interaction energy of the external charges with the peptide, averaged over five successful manipulation cases, which is −704 $\pm$ 142 kJ/mol. In all simulations, the distances between the COM of the peptide and the geometrical center of the external

charges ranged from 1.2 to 2.6 nm with an average value of 1.6 nm. We note that the deprotonated carboxyl group (COO) on the glutamic acid residue of the peptide carries most ($-0.9e$) of the negative charge of the whole residue ($-1e$). Since the external charges are positive, the interaction between the peptide and the external charges is dominated by the interaction between the COO group and the external charges. Numerically, we found that the electrostatic interaction energy of the external charges with the COO group was -973 ± 143 kJ/mol, quite close to the electrostatic interaction energy of the external charges with the peptide. Likewise, the distances between the COM of the COO group and the geometrical center of the external charge ranged from 0.6 to 2.2 nm with an average value of 0.8 nm. These distances were smaller than the distances between the COM of the peptide and the geometrical center of the external charges. Consequently, the manipulation of the peptide mainly resulted from the tight trapping of the COO group by the external charges. We have also calculated the electrostatic forces that the peptide and water inside the nanochannel exerted on the external charges along the x-axis. The forces ranged from -600 pN to $+600$ pN, which also fall within the working ranges of many existing techniques such as STM and AFM.

The number of charges in the externally charged group is important for the manipulation. We found only one successful case in five simulations with different initial conditions when there were only 9 charges in a 3×3 array for $q = 0.5e$ per atom. When the group of external charges was substituted by one externally charged atom, the minimal value of the external charge required for manipulation was around $+3e$. It seems that the manipulation of the peptide inside a water-filled SWNT is much difficult than the manipulation of the peptide in a drop of peptide−water mixture inside an empty SWNT.

The peptide used here only has one negatively and one positively charged residue, and is neutral as a whole. We note that, many biomolecules have highly charged fragments may not be neutral. For example, the peptide LDTGADDTVLE,[57] which is the fragment 24−34 of the protease of the human immunodeficiency virus type 1, has a total of $-4e$ charges because of the presence of three aspartic acid (D) residues and one glutamic acid (E) residue, all of which are negatively charged, and the absence of positively charged residue. One could expect that, for this kind of biomolecule, the manipulation becomes more effective.

3.3. Screening Effect and Practical Feasibility of the Design. In practical applications, the screening effect on the electric field must be considered. The screening factor depends on the particular nanochannels used. Considering that the screening factor for the zigzag SWNT is only about 2−4,[35] the effective charge $q = 0.5e$ can easily be achieved. It is clear that as q increases, the interactions between the external charge(s) and the water molecules or the charged residue(s) of the peptide inside the channel increase. Consequently, the manipulation becomes more effective for a smaller screening factor. This is particularly true when using insulator nanochannels, which may be fabricated in the near future.[15]

Experimentally, when there is no water or other liquid outside the SWNT, there are at least two ways to realize the external charge(s) on the facilities: a bias voltage applied on an AFM/STM tip and the AFM/STM tip modified with the compounds carrying charge(s). The method to apply a bias voltage on the AFM tip has already been used to manipulate the nanometer-size liquid droplets on the surface of graphite.[58] Usually, it is difficult to modify the AFM/STM tip with the compounds carrying charge(s) in air. Recently, the modification/coating of the AFM tip with metal ions, biomolecules or compounds carrying charge(s) has been realized[59,60] by using the dip pen nanolithography technique.[61] In this case, as the tip works in vacuum or in air under low humidity conditions, the electrostatic screening effect is not significant, and the tip can be brought close enough to the nanochannel. When the space outside the SWNT is filled by the solution, the method to apply a bias voltage on an AFM/STM tip is still available,[62] and the modifications of the AFM/STM tip with the compounds carrying charge(s) become relatively easier. However, the interactions of the external charge(s) with the peptide and water inside the nanochannel will decrease remarkably due to the screening effect of the solution on the external charge(s). Furthermore, the externally charged atom(s) may not be brought close enough to the nanochannel. In this case, larger quantities of charges are required, and sometimes, the manipulation may not be available.

4. Conclusions

We have shown that the positions of the peptides with aqueous liquids inside a single-walled nanotube can be controllably manipulated by a charge or a group of charges outside the nanotube. If the peptide has charged residue(s), it can follow the external charges moving along the nanochannel even when the nanochannel is fully filled with water. When most of the space inside the nanochannel is empty, a drop of the water−peptide mixture will follow the external charges moving along the nanochannel regardless if there is any charged residue on the peptide. The remarkable manipulation abilities are attributed to the single-walled structure of the nanotube that the electrostatic interactions of charges inside and outside the single-walled nanotube are strong enough, and the charge-induced dipole-orientation ordering of water confined in the nanochannel so that water has a strong electrostatic interaction with the external charge. Experimentally, the drop of peptide−water mixture used in this paper can be realized through spontaneous accumulation of the water molecules surrounding the biomolecules in an environment with moderate humidity.

The electrostatic forces which the peptide and the water inside the nanochannel exert on the external charge(s) along the x-axis fall within the working range of many existing techniques such as STM and AFM. One could expect that when an AFM/STM tip modified with charged molecules or applied with a bias voltage moves on the outside wall of a SWNT, the peptide−water mixture or the peptide with charged residues inside the nanotube can move in response.

Our designs are expected to serve as laboratory-in-nanotube for interactions or chemical reactions of molecules especially biomolecules (see, i.e., the controllable moving of two biomol-

(57) Bonomi, M.; Gervasio, F. L.; Tiana, G.; Provasi, D.; Broglia, R. A.; Parrinello, M. *Biophys. J.* **2007**, *93*, 2813–2821.
(58) Hu, J.; Carpick, R. W.; Salmeron, M.; Xiao, X. D. *J. Vac. Sci. Technol., B* **1996**, *14*, 1341–1343.
(59) Ginger, D. S.; Zhang, H.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 30.
(60) Sistiabudi, R.; Ivanisevic, A. *J. Phys. Chem. C* **2007**, *111*, 11676–11681.
(61) Piner, R. D.; Zhu, J.; Xu, F.; Hong, S.; Mirkin, C. A. *Science* **1999**, *283*, 661.
(62) Wierzbinski, E.; Arndt, J.; Hammond, W.; Slowinski, K. *Langmuir* **2006**, *22*, 2426–2429.

ecule-water mixtures together convenient for the interaction of the two biomolecules as the movie in the Supporting Information), and have wide applications in nanotechnology and biotechnology.

Acknowledgment. We thank Profs. Jun Hu and Chunhai Fan, Drs. Bo Song, Jingyuan Li, Rongzheng Wan, Hai Li, and Xiaojing Gong, and Ms. Lihua Wang, Mr. Peng Wang, Zaixing Yang, and Liumin Yu for helpful discussions and comments. This work is supported by grants from Chinese Academy of Sciences, the National Science Foundation of China under Grants 10674146 and 10825520, the National Basic Research Program of China under Grants 2007CB936000 and 2006CB933000, and Shanghai Supercomputer Center of China.

Supporting Information Available: Some related discussions and a movie to show the controllable moving of two biomolecule−water mixtures together. This material is available free of charge via the Internet at http://pubs.acs.org.

JA804586W