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Enhancement of water permeation across nanochannels by partial charges mimicked from biological channels*

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In biological water channel aquaporins (AQPs), it is believed that the bipolar orientation of the single-file water molecules inside the channel blocks proton permeation but not water transport. In this paper, the water permeation and particularly the water-selective behaviour across a single-walled carbon nanotube (SWNT) with two partial charges adjacent to the wall of the SWNT are studied by molecular dynamics simulations, in which the distance between the two partial charges is varied from 0.14 nm to 0.5 nm and the charges each have a quantity of 0.5 e. The two partial charges are used to mimic the charge distribution of the conserved non-pseudoautosomal (NPA) (asparagine/proline/alanine) regions in AQPs. Compared with across the nanochannel in a system with one +1 e charge, the water permeation across the nanochannel is greatly enhanced in a system with two +0.5 e charges when charges are close to the nanotube, i.e. the two partial charges permit more rapid water diffusion and maintain better bipolar order along the water file when the distance between the two charges and the wall of SWNT is smaller than about 0.05 nm. The bipolar orientation of the single-file water molecules is crucial for the exclusion of proton transfer. These findings may serve as guidelines for the future nanodevices by using charges to transport water and have biological implications because membrane water channels share a similar single-file water chain and positive charged region at centre and provide an insight into why two residues are necessitated in the central region of water channel protein.

Keywords: aquaporins, water-selectivity, carbon nanotube, molecular dynamics simulation
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Water channels of nanometre dimensions are central to biological membrane transport.[1−10] Recently, it has been recognized that the existence of the charged residues in these water channels greatly reduces the permeation of protons across the channel but maintains quite stable water flows.[4,5,11,12] How the behaviour of water molecules depends on the charged residues of biological pores is currently a subject of interest. By using molecular dynamics simulations, it has been found that in channel proteins, such as AQP1 and GlpF (a kind of aquaporin), the charged groups of the conserved NPA and ar/R regions that dominate energetics of water permeation in these regions can interrupt the hydrogen bond along the water chain and generate the electrostatic field to exclude proton transfer.[11−15] Unfortunately, the complicated structure of biological water channels and the protein–water interactions often make their direct investigations highly complicated. On the other hand, primary characteristics can usually be explored by studying a similar but structurally less complicated problem. Carbon nanotubes are molecular-scale tubes of graphitic carbon with outstanding properties.[16−20] In 2001, Hummer *et al*[21] showed that single-walled carbon nanotubes (SWNT) could be designed as molecular channels for water. The single-file arrangement and the concerted movement of water molecules through the channel, together with the liquid–vapour transition in the channel due to the modification of the water–channel interaction, were thought to be the major characters shared by the biological channels.[21−24] Zimmerli *et al*[25] studied the effect of the curvature-induced static dipole moment on water conduction in short carbon nanotubes (CNTs). They found the axial electric field to have a significant influence on both the filling behaviour and the orientation of water molecule chains inside the CNT. The results of Beckstein and Sansom indicated that pores with a polar surface were created by placing partial charges of ±0.38 e on atomic sites 0.2 nm apart that is comparable with the dipole moment of the peptide bond.[26] Zhu and Schulten[27] also

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assigned charges to the atoms of SWNTs to mimic the biological channel and found that similar dipole orientation of water molecules to that in AQPs could be generated, along with a greatly reduced mobility for the water chain inside the SWNT. Li *et al*[28] explored the water permeation across an SWNT under the influence of a mobile external charge. This designed nanopore shows an excellent on–off gating behaviour by a single external charge with a value of $1.0\,e$. Very recently, Gong *et al*[29] have shown how a precise arrangement of charges on the surface of a nanotube can push water molecules into a single file from one end to another.

Despite these great efforts, the dependence of the dynamics of water molecules inside a channel on charges is still far from being understood. In this study, an SWNT with two external positive charges is used as a prototype to study the water-selective capability. Molecular dynamics, which has been widely used for the study of water dynamics in SWNT, is adopted here for this work. Hydrostatic pressure is used in this study between two ends of the SWNT to investigate the change of the net flux and bipolar conformation due to the imposed charges. We find that, compared with one $+1\,e$ charge adjacent to the nanochannel, two $+0.5\,e$ charges can permit more rapid water transport and meanwhile maintains better bipolar orientation of water molecules inside the channel when the distance between the charges and the wall of SWNT is less than 0.05 nm. It may implicate that two partial charges are better for nanopores to control the proton inhibition and water-selective capability. We believe that this excellent property has biological implications and provides an insight into why two residues are necessitated in the central region of water channel protein, because membrane water channels share a similar single-file water chain and partial charges in the central region.

The simulation framework is shown in Fig.1. To mimic the biological channels in a membrane, an uncapped, single-walled carbon nanotube[30] with 1.34 nm in length and 0.81 nm in diameter was embedded along the z direction in a graphite sheet that subdivides the SWNT and space into two equal parts. To study the behaviour of the water permeation and bipolar orientation across the channel due to external charges on or outside the channel, two positive charges with a quantity of $0.5\,e$ were set to move on at a constant high speed, we refer to this system as two-charge system. The radial distance of the imposed charge from the carbon atoms of the nanotube is denoted by δ. The system composed of SWNT and $+1\,e$ charge in our previous paper,[28] namely one-charge system, is used for comparison.

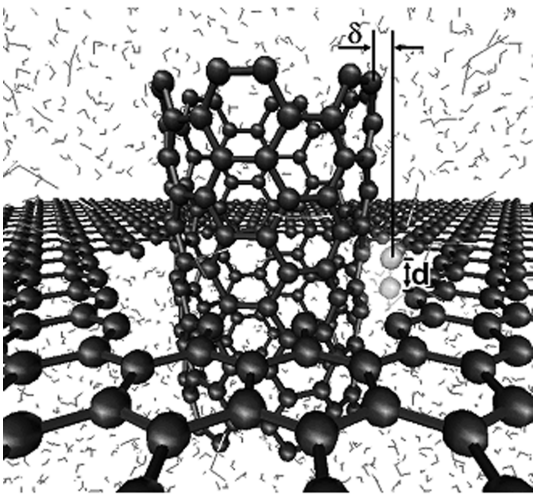


Fig.1. The simulation system (side view). The dark grey cycles are the carbon atoms of the nanotube and the graphite. The light grey points are the imposed charges, and the water molecules are represented by grey lines. Note that the figure is not drawn to scale. There is no physical hole between the SWNT and the graphite plate. The gap between the graphite plane and the SWNT is too small for a water molecule to penetrate.

When two sides of a membrane have the same hydrostatic pressures but different concentrations of impermeable solute, an osmotic pressure difference is established, and water flows from the side with lower solute concentration to another side. Following the method proposed by Zhu *et al*[31] and our previous paper,[28,32] an external force is applied to each water molecule along the z direction (The z axis is defined to be along the axis of the SWNT with the origin in the graphite plane) to obtain a pressure difference between two ends of the SWNT. This pressure difference is something like the osmotic pressure difference[31] and is 181 MPa between two ends of the SWNT or an additional acceleration of $0.1\,\mathrm{nm^{-1}\cdot ps^{-2}}$ at each atom.[32]

All simulations were carried out at a constant pressure of 1×10^5 Pa with an initial box size $L_x = 5.0$ nm, $L_y = 5.0$ nm and $L_z = 5.0$ nm, and a temperature of 300 K with Gromacs 3.2.1 (www.gromacs.org) and by using the particle mesh Ewald (PME) method[33] for full electrostatics. The carbon–carbon interaction parameters were adopted from the previous work by Brenner[34] using the

Tersoff formulism.[35] Periodic boundary conditions were applied to all directions. Here the TIP3P water model[36] was applied. A time step of 2 fs was used, and data were collected every 1 ps. In the simulations, the carbon atoms were modelled as uncharged Lennard–Jones particles with a cross-section of $\sigma_{CC} = 0.34\,\text{nm}$, $\sigma_{CO} = 0.3275\,\text{nm}$, and a depth of the potential well of $\varepsilon_{CC} = 0.3612\,\text{kJ}\cdot\text{mol}^{-1}$, $\varepsilon_{CO} = 0.4802\,\text{kJ}\cdot\text{mol}^{-1}$.[21] The positions of the carbon atoms at inlet and outlet, and the charges are constrained and carbon sheet is frozen.

To our surprise, the average water flow and flux in the two-charge system are enhanced in a range of $0\,\text{nm} \leq \delta \leq 0.05\,\text{nm}$ compared with that in the one-charge system. In an interval of $0.05\,\text{nm} < \delta < 0.15\,\text{nm}$, the flow and the flux are less than those in the one-charge system. The flow and the flux are approximately equal to those in the one-charge system when the distance δ is $\geq 0.15\,\text{nm}$, as shown in Fig.1. Here, The flow is defined as the total number of water molecules leaving from the SWNT (entering from the opposite side) per nanosecond, while the net flux is the difference in number of water molecules between leaving from one end and entering from the opposite end per nanosecond. It is noted that the average flow and net flux are $0.7\,\text{ns}^{-1}$ and $0.6\,\text{ns}^{-1}$, respectively, at $\delta = 0$ in the one-charge system, while in the present study, there are a flow of $2.8\,\text{ns}^{-1}$ and a flux of $2.4\,\text{ns}^{-1}$ at $\delta = 0$, the values are four times larger than those in the one-charge system and the flux is comparable with the measured rate of $3.0 \times 10^{-9}\,\text{s}^{-1}$ per channel for aquaporin-1 at a low osmotic pressure.[3] Thus two partial charges allow more rapid water transportation with a small δ. The on-off gating effect is still obvious in the two-charge system with two $+0.5\,e$ charges. It is both sensitive to the available charge signal when it is close and effectively resistant to the charge noise, i.e. the effect on the flow and the net flux across the channel is found to be sharply decreased when the charge is more than 0.1 nm away from the wall of the nanopore.

To further characterize the dipole orientation of the water chain, the average value of φ along the SWNT channel is shown in Fig.2(c), where φ is the angle between a water dipole and the nanotube axis (z axis), and the average is taken over all of the data from simulations. When $\delta = 0\,\text{nm}$, $<\varphi>$ varies around 90° in the region facing charges and has values $\approx 30°$ and 150° in the other regions, showing the bipolar orientation. To obtain a quantitative description of the transition from a concerted orientation to a bipolar orientation as δ decreases from 0.15 nm to 0 nm, we have computed the probability of bipolar orientation. Here we assume that the system shows a bipolar orientation when all of the water dipoles in the outer-region are pointed away from the centre of the SWNT. The probability is calculated based on the data from all simulations.

A comparison of probability of bipolar orientation between the two-charge system and the one-charge system is shown in Fig.2(d). It is interesting to find that the probability increases linearly from 1% to 99% when δ decreases from 0.15 nm to 0 nm. In an interval of $0\,\text{nm} \leq \delta \leq 0.5\,\text{nm}$ for the two-charge system, the possibility of the two-charge system is similar to that of the one-charge system, and when δ increases from 0.05 nm to 0.15 nm, the probability of the two-charge system is 45% higher than that of the one-charge system. It is noted that the average water flow and flux are enhanced while the bipolar orientation of the water single file is maintained at a small value of δ ($\leq$0.05 nm), i.e. the two partial charges permit more rapid water diffusion and maintain better bipolar order along the water file when δ is small. With δ increasing in an interval of $0.05\,\text{nm} < \delta < 0.15\,\text{nm}$, the bipolar orientation of the water single file is better remained while the flow and the flux are smaller than those in the one-charge system. The flow/flux and probability of bipolar orientation are approximately equal to those in the one-charge system when δ is larger than 0.15 nm.

To understand the mechanism behind this phenomenon, we calculate the interaction energies of the water molecule at position z inside the SWNT (about five such water molecules in total) with its neighbouring water molecules, denoted by P_{WW}, and the electrostatic potential with the imposed charge, P_{WC} (data are not shown in paper). According to our previous paper,[28] competition between P^{C}_{WC} and P^{C}_{WW}, the values of P_{WC} and $P_{WW}/2$, respectively, as a function of δ at $z = 0$, is the reason to induce the excellent on-off effect. So, we compare the P^{C}_{WC} and P^{C}_{WW} with those in the one-charge system. As shown in Fig.3(a), P^{C}_{WW} is similar to that of the one-charge system, while P^{C}_{WC} is less than that of the one-charge system in the interval of $0\,\text{nm} \leq \delta \leq 0.05\,\text{nm}$, which is a key factor leading to higher water flow and flux in the two-charge system. It is clear that when δ increases from 0.05 nm to 0.15 nm, P^{C}_{WC} is larger than that of the one-charge system, which induces the lower water transportation

and the better bipolar configuration in the two-charge system. At $\delta = 0.15\,\mathrm{nm}$, $P^{\mathrm{C}}_{\mathrm{WC}}$ of the two-charge system is approximately equal to that of the one-charge system.

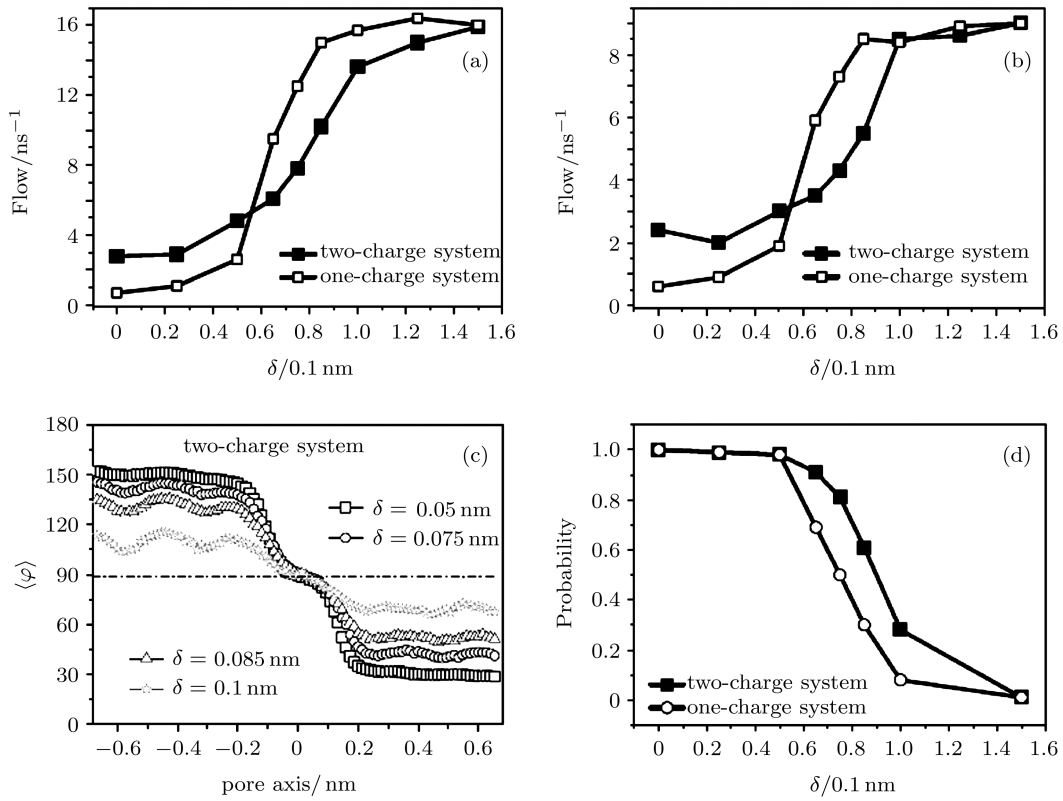


Fig.2. Comparison of flow (a) and flux (b) between the two-charge system and the one-charge system. (c) Profile of $<\varphi>$ along the SWNT channel in the two-charge system. (d) Comparison of probability of bipolar orientation between the two systems.

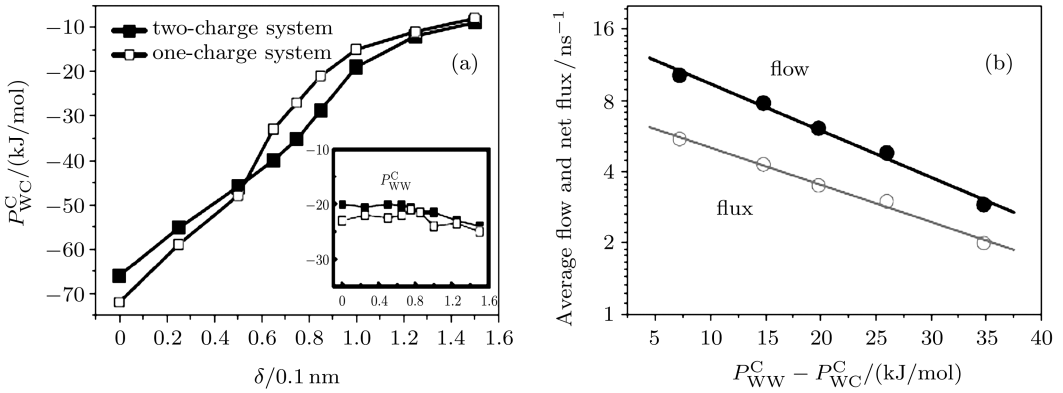


Fig.3. (a) Comparison of $P^{\mathrm{C}}_{\mathrm{WC}}$ and $P^{\mathrm{C}}_{\mathrm{WW}}$ (insert) between the two-charge and one-charge systems. (b) The average value of flow and the net flux versus $P^{\mathrm{C}}_{\mathrm{WW}} - P^{\mathrm{C}}_{\mathrm{WC}}$. Exponential laws can fit the data very well in an interval of $0.025\,\mathrm{nm} \le \delta \le 0.085\,\mathrm{nm}$.

In an interval of $0.025\,\mathrm{nm} \le \delta \le 0.085\,\mathrm{nm}$, both the average flow and the net flux can be respectively fit to the following exponential functions of $(P^{\mathrm{C}}_{\mathrm{WW}} - P^{C}_{WC})$ very well as shown in Fig.3(b):

$$\text{Flow} = \text{flow}_0 \times \exp\left(-(P^{\mathrm{C}}_{\mathrm{WW}} - P^{\mathrm{C}}_{\mathrm{WC}})/\varepsilon_{\mathrm{flow}}\right),$$

and

$$\text{Net flux} = \text{flux}_0 \times \exp\left(-(P^{\mathrm{C}}_{\mathrm{WW}} - P^{\mathrm{C}}_{\mathrm{WC}})/\varepsilon_{\mathrm{flux}}\right),$$

where $\text{flow}_0 = 14.9\,\mathrm{ns}^{-1}$ and $\text{flux}_0 = 7.2\,\mathrm{ns}^{-1}$, slightly smaller than the values of $16.2\,\mathrm{ns}^{-1}$ and $9.2\,\mathrm{ns}^{-1}$ for the system without extra charge respectively. $\varepsilon_{\mathrm{flow}} \approx \varepsilon_{\mathrm{flux}} = 25\,\mathrm{kJ/mol}$, implying a similar rule governing the behaviours of the flow and the net flux. While

in the one-charge system, the flow and the flux are fit to their corresponding exponential functions of $(P^{C}_{WW} - P^{C}_{WC})$, however the parameters are different in two cases and the reason for that is still not clear. The further study is underway.

We also change the distance between the two $+0.5\,e$ charges, denoted as d. Figure 4 plots the flow, the flux and the possibility of bipolar orientation versus d. It is clear that the larger d is corresponding to larger flux and smaller probability of bipolar orientation. When d is larger than the width of a water molecule, the bipolar orientation is not maintained well. In AQPs, the rapid water transport but proton exclusion (water-selective effect) are crucial to biological activities, so the charged residues need to be in appropriate sites to obtain the important functions. In the SWNT model, the optimum combination of flow/flux and bipolar order is at $d = 0.14\,\mathrm{nm}$, which is similar to the distance between the two Asn residues in AQP1.

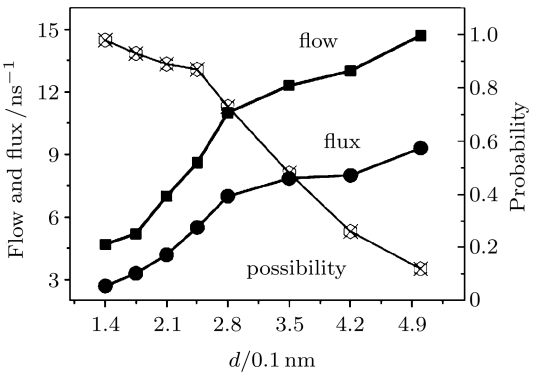


Fig.4. The flow, flux and probability versus the distance d. The left axis is for flow and flux. The right axis is for probability.

In AQPs, the bipolar water order stops proton permeation but not water transport. The current results show that it is possible to have both the bipolar water order and obvious water transport at the same time. Compared with that for the one-charge system, the flux for the two-charge system can be increased by one order meanwhile the bipolar configuration is maintained very well when δ is $\leq 0.05\,\mathrm{nm}$. This discrepancy may help us to understand the functional importance of two Asn residues in the centre of AQP1. The Asn residues with partial charges are conserved in AQPs, so it is crucial to the water permeation and the proton exclusion. But no mutation experiment can be done to test their functions if the two Asn residues are replaced by one residue with a double charge. A comparison between the simplified SWNT system with one $+1\,e$ charge and the system with two $+0.5\,e$ charges provides an insight into the functional importance of two partial charged residues in AQPs.

In summary, we use the SWNT as the prototype of the complex biological channels and explore the primary characteristics. Two external $+0.5\,e$ charges adjacent to the SWNT allow more rapid water molecule transport and maintain better bipolar water molecule orientation, which are correlated with the water-selective property. When the radial distance of the imposed charges to the carbon atom of the SWNT is somewhere in an interval of $0\,\mathrm{nm} \leq \delta \leq 0.05\,\mathrm{nm}$, the average flow and the net flux of water across the channel are greatly enhanced in comparison with those of a system having only one $+1\,e$ charge and meanwhile the probability of bipolar orientation is kept about 98%. This shows that although the total quantity of charge is the same, the distribution of charges can induce different permeabilities and water molecule orientations. The results may have the biological significance because there are two Asn residues in the central region of water channel (AQPs). These two residues have partial charges and play an important role in maintaining the structure and the water-selective function. We are reasonably confident that biological water channels share the properties of this simple nanochannel due to similar single-file water molecule chain and bipolar orientation to those of charges on the proteins. Our findings may help us to have a further understanding of the importance of two partial charges and serve as guidelines for the future nanodevices by using charges to transport water effectively.

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