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MODELLING ION, WATER AND ION–WATER CLUSTER ENTERING PEPTIDE NANOTUBES

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Abstract

Recently, organic nanostructures have attracted much attention, and amongst them peptide nanotubes are of interest in many fields of application including medicine and nanobiotechnology. Peptide nanotubes are formed by self-assembly of cyclic peptides with alternating L- and D-amino acids. Due to their biodegradability, flexible design and easy synthesis, many applications have been proposed such as artificial transmembrane ion channels, templates for nanoparticles, mimicking pore structures, nanoscale testing tubes, biosensors and carriers for targeted drug delivery. The mechanisms of an ion, a water molecule and an ion–water cluster entering into a peptide nanotube of structure cyclo[(-D-Ala-L-Ala-)$_4$] are explored here. In particular, the Lennard-Jones potential and a continuum approach are employed to determine three entering mechanisms: (i) through the tube open end, (ii) through a region between each cyclic peptide ring and (iii) around the edge of the tube open end. The results show that while entering the nanotube by method (i) is possible, an ion or a molecule requires initial energy to overcome an energetic barrier to be able to enter the nanotube through positions (ii) and (iii). Due to its simple structure, the D-, L-Ala cyclopeptide nanotube is chosen in this model; however, it can be easily extended to include more complicated nanotubes.

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1. Introduction

Cyclic peptide nanotubes are prepared from cyclic peptide rings with an even number of alternating L- and D-amino acids. These rings then self-assemble into hollow, tubular structures through a network of hydrogen bonding that connects the adjacent rings [7, 11, 18, 21]. The self-assembly process is also due to other molecular interactions, such as van der Waals, electrostatic and aromatic stacking. The combination of these interactions results in the formation of a stable peptide nanotube

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[8, 18, 20]. Peptide nanotubes possess many useful properties including the ease of their synthesis and their modifiable outer surface properties, based on the selected amino acid side chains. Furthermore, the internal diameter of a peptide nanotube can be controlled by adjusting the number of amino acids forming the cyclic rings [4, 11, 13]. For example, nanotubes formed by eight, 10 and 12 cyclic peptide rings have the internal diameters of approximately 7, 10 and 13 Å, respectively. Due to the pore dimensions of the nanotubes and the sequence of the cyclic peptide rings, peptide nanotubes can be used as highly selective and efficient transmembrane channels for ions and small molecules, such as water [9, 14]. Also, peptide nanotubes can be used to mimic naturally occurring ion channels, which are found in cell membranes. This paper aims to provide a detailed understanding of the interaction between ions and peptide nanotubes, which is vital for the development of artificial transmembrane ion channels.

This paper proposes the study of an ion, a water molecule and an ion–water cluster entering a peptide nanotube of structure cyclo[(-D-Ala-L-Ala-)$_4$], which is comprised entirely of alanine amino acids. Note that this model is applicable for any ion. However, as an example, a lithium ion is employed in this study. Following [2], three possible scenarios are considered for a nanostructure to enter into a peptide nanotube. The first scenario is referred to as a head-on configuration, where a molecule is located on the tube axis outside the tube and then accepted through the tube open end. The second scenario is the suction of a molecule through a region between each cyclic peptide ring. The entering of a nanostructure around the edge of the tube is the final possible scenario discussed in this paper.

To study the interaction between a molecule and a peptide nanotube, a continuum approach together with the Coulomb and the Lennard-Jones potentials has been adopted. The Lennard-Jones potential for two atoms at a distance ρ apart is given by

$$\Phi(\rho) = -\frac{A}{\rho^6} + \frac{B}{\rho^{12}},$$

where A and B are the attractive and repulsive constants, respectively. Note that $A = 4\epsilon\sigma^6$ and $B = 4\epsilon\sigma^{12}$, where ϵ and σ are the well depth and the van der Waals diameter, respectively. For the interaction between different kinds of atoms i and j, A and B can be calculated from $A = 4\epsilon_{ij}\sigma_{ij}^6$ and $B = 4\epsilon_{ij}\sigma_{ij}^{12}$, where $\epsilon_{ij} = (\epsilon_i\epsilon_j)^{1/2}$ and $\sigma_{ij} = (\sigma_i + \sigma_j)/2$. The values of A and B used in this paper are given in Table 1 [17].

The Coulomb potential is given by

$$U(\rho) = \frac{1}{4\pi\varepsilon_0}\frac{q_1 q_2}{\rho},$$

where q_1 and q_2 are the electrostatic charges, and ε_0 denotes the electrical permittivity of space.

In general, for an ion or a water molecule interacting with a peptide nanotube, one needs to consider energy contributions from both the van der Waals force (through the Lennard-Jones potential) and the electrostatic force (through the Coulomb

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Table 1. Numerical values of constants used in this paper.

Interaction	A (kcal mol^{-1} Å^{-6})	B (kcal mol^{-1} Å^{-12})
C–Li	100.30	4.91×10^4
H–Li	23.95	4.32×10^3
N–Li	67.60	2.75×10^4
O–Li	53.76	1.87×10^4
C–H	198.60	1.45×10^5
C–O	391.38	4.82×10^5
H–H	50.85	1.47×10^4
H–O	108.90	5.77×10^4
N–H	135.47	8.32×10^4
N–O	270.91	2.85×10^5
O–O	220.59	2.03×10^5

potential [15]). However, in this paper, the isoelectric point (pH associated with zero net charge) for the amino acid alanine (pH 7.4) [12, 16] is assumed, so that the peptide nanotube is neutral and the electrostatic energy in the model is neglected. Therefore, the interaction energy is calculated based only on the Lennard-Jones potential. Note that the results obtained from considering only the van der Waals interaction are consistent with molecular dynamics studies and experiments, as shown by Rahmat et al. [17].

For the continuum approach, assume that the atoms of each molecule are uniformly distributed over its surface and, together with the Lennard-Jones potential, the total interaction energy can be expressed as

$$E = \eta_1 \eta_2 \int_{S_1} \int_{S_2} \left\{ -\frac{A}{\rho^6} + \frac{B}{\rho^{12}} \right\} dS_1 \, dS_2, \tag{1.1}$$

where η_1 and η_2 denote the mean surface densities of atoms on the interacted nanostructures, and ρ is the distance between typical elements dS_1 and dS_2 on two different molecules. Note that for the interaction between an ion and a peptide nanotube, equation (1.1) can be reduced to

$$E = \eta \int_S \left\{ -\frac{A}{\rho^6} + \frac{B}{\rho^{12}} \right\} dS,$$

where η denotes the mean surface density of atoms on the nanotube, and ρ is the distance between an ion and a typical surface element dS on the nanotube.

Following Rahmat et al. [17], let us assume an equilibrium structure of a peptide nanotube made up of n cyclic peptide rings, where each ring comprises an inner tube and an outer tube. Let a_1 and a_2 be the radii of the inner and outer tubes, respectively, L the length of each ring and d the distance between the centres of the neighbouring rings (see Figure 1). Further, the length of the region between two cyclic peptide rings is denoted by δ. Here, we study the cyclo[(-D-Ala-L-Ala)$_4$-] peptide nanotube because

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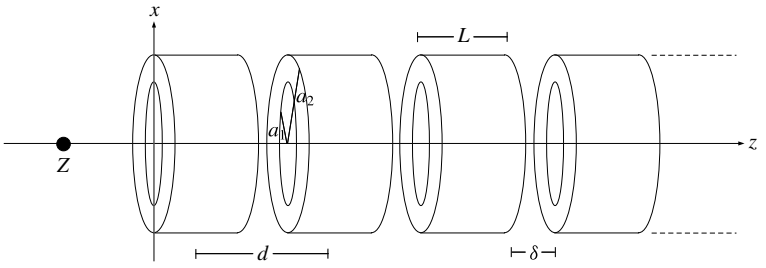

FIGURE 1. Geometry of an ion entering a peptide nanotube from the open end.

TABLE 2. Structure of a cyclo[(-D-Ala-L-Ala)$_4$-] peptide nanotube.

Inner tube radius	$a_1 = 4.25$ Å
Outer tube radius	$a_2 = 7.95$ Å
Average length of each peptide ring	$L = 1.7$ Å
Average length of the region between two peptide rings	$\delta = 3.15$ Å
Average distance between centroids of neighbouring rings	$d = 4.85$ Å

of its simple form. Each cyclo[(-D-Ala-L-Ala)$_4$-] peptide ring has eight amino acid residues. The 48 backbone atoms are located on the inner tube and consist of 16 carbon, 16 hydrogen, eight nitrogen and eight oxygen atoms. The outer tube has 32 side chain atoms comprising eight carbon and 24 hydrogen atoms. For the cyclo[(-D-Ala-L-Ala)$_4$-] peptide nanotube, the radii for the inner and outer tubes are $a_1 = 4.25$ Å and $a_2 = 7.95$ Å, respectively, and the distance between centroids of neighbouring rings is in the range $d = 4.5$–5.2 Å [3]. According to the structure of the cyclo[(-D-Ala-L-Ala)$_4$-] peptide nanotube shown by Cheng et al. [3], the length of the region between neighbouring peptide rings is $\delta \approx 3.15$ Å. Thus, the length of each peptide ring is $L \approx 1.7$ Å. Note that the atomic density η for each inner and outer tube can be obtained from $\eta = \text{number of atoms}/(2\pi a L)$, where $a \in \{a_1, a_2\}$. The values of the parameters used in this paper are summarized in Table 2.

Further, observe that the attractive and repulsive constants, A and B, can be averaged based on the pair of interacting molecular structures. For example, one can calculate A and B for the Li ion interacting with the the inner and outer nanotubes as

$$A_{\text{Li-inner}} = \frac{16A_{\text{Li–C}} + 16A_{\text{Li–H}} + 8A_{\text{Li–N}} + 8A_{\text{Li–O}}}{48},$$
$$B_{\text{Li-inner}} = \frac{16B_{\text{Li–C}} + 16B_{\text{Li–H}} + 8B_{\text{Li–N}} + 8B_{\text{Li–O}}}{48},$$
$$A_{\text{Li-outer}} = \frac{8A_{\text{Li–C}} + 24A_{\text{Li–H}}}{32}, \quad B_{\text{Li-outer}} = \frac{8B_{\text{Li–C}} + 24B_{\text{Li–H}}}{32}, \tag{1.2}$$

where A_{i-j} and B_{i-j} are given in Table 1.

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The following three sections analyse the possibilities for an ion, a water molecule and an ion–water cluster to enter a peptide nanotube based on three scenarios. Finally, some concluding remarks are given in Section 5.

2. Entering head-on at an open end

In this section, let us first consider the head-on encapsulation of an ion into a peptide nanotube at the tube open end, as shown in Figure 1. In this scenario, it is assumed that the ion is originally located at a distance Z along the central axis of the peptide nanotube. This scenario is equivalent to the work by Rahmat et al. [17]. Therefore, only the results are stated here.

The total interaction energy between the ion and a peptide ring comprising the inner and the outer tubes is given by

$$E_H = E_1(a_1) + E_1(a_2),$$

where $E_1(a_1)$ and $E_1(a_2)$ are the energies from the interaction of the ion with the inner and outer tubes, respectively, and a_1 and a_2 are the radii of the inner and the outer tubes, respectively. For $E_1(a_1)$ one may use $A = A_{\text{Li-inner}}$ and $B = B_{\text{Li-inner}}$ and for $E_1(a_2)$ $A = A_{\text{Li-outer}}$ and $B = B_{\text{Li-outer}}$. Following Rahmat et al. [17],

$$E_1(a) = -2\pi a\eta \int_{\psi_1}^{\psi_2} \left\{ -\frac{A}{a^5}\cos^4\psi + \frac{B}{a^{11}}\cos^{10}\psi \right\} d\psi,$$

where $\psi_1 = \arctan(Z/a)$ and $\psi_2 = \arctan([Z - L]/a)$. For the derivation of the analytical expression of $E_1(a)$, the reader is referred to the work of Rahmat et al. [17].

Throughout this paper, MAPLE is used to illustrate graphically the interaction energy of the systems. For all results presented, the unit of energy is kcal mol^{-1} and the unit of length and distance is Å. In Figure 2, the potential energy is plotted for a lithium ion entering head-on at the open end of a peptide nanotube. Various graphs in the figure correspond to different numbers of cyclic peptide rings making up the peptide nanotube. Note that $Z = 0$ is the location of the ion at the first open end of the peptide nanotube. An ion will enter into the interior of a peptide nanotube if the potential energy is lower inside the tube compared to that outside. Thus, one can see from Figure 2 that the lithium ion is accepted into all peptide nanotubes of various lengths. Also, note that for more than one peptide ring, as the ion passes through the nanotube it experiences an undulating effect. This behaviour is consistent with the results of Dehez et al. [6], and is due to the structure of the nanotube which comprises cyclic peptide rings and regions in between. Observe that each peak in Figure 2 corresponds to the ion situated inside the cyclic peptide rings [17].

The effect of an ion in water can be incorporated as shown by Rahmat et al. [17], where the interaction energy between a lithium ion with water molecules and a peptide nanotube is investigated by introducing a spherical structure of an ion–water cluster, where the ion is modelled as a point, and water molecules are assumed to be located on the surface of the sphere. From [17], the lithium–water cluster is also accepted

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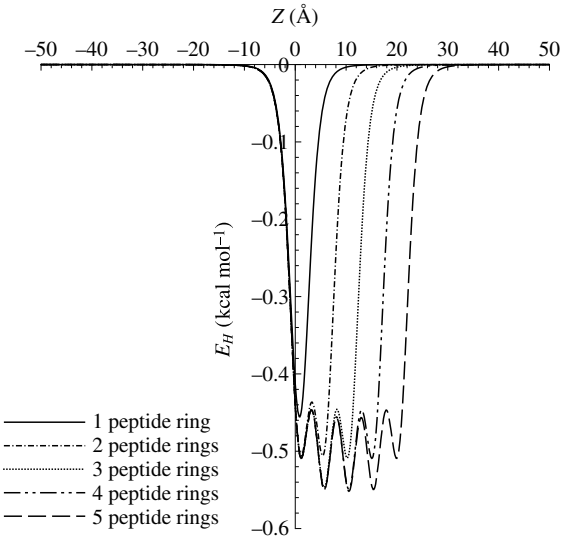

FIGURE 2. Potential energy for a lithium ion entering various sizes of peptide nanotubes for head-on configuration.

into the cyclo[(-D-Ala-L-Ala-)$_4$] peptide nanotube with the interaction energy much lower compared to that of the Li ion alone. This is mainly due to the larger mass of water molecules. Furthermore, it has been shown by Tiangtrong et al. [19] that a water molecule is accepted inside the cyclo[(-D-Ala-L-Ala-)$_4$] in the head-on configuration.

3. Entering a region between each cyclic peptide ring

In this section, first the possibility of an ion entering a peptide nanotube through a region between peptide rings is considered. It is assumed that an ion is located directly above the region of the two peptide rings, as shown in Figure 3. Because of the symmetry of the problem considered, the total potential energy of the system is twice the energy of the ion interacting with one peptide unit, namely,

$$E_2 = 2a\eta \int_{-\pi}^{\pi} \int_{\delta/2}^{L+\delta/2} \left(-\frac{A}{\rho^6} + \frac{B}{\rho^{12}} \right) dz\, d\theta, \tag{3.1}$$

where ρ is the distance between the atom located at $(X, 0, 0)$ and a surface element of the entire nanotube, which is given by

$$\begin{aligned} \rho^2 &= (a\cos\theta - X)^2 + a^2 \sin^2\theta + z^2 \\ &= (a^2 + X^2) - 2aX\cos\theta + z^2. \end{aligned} \tag{3.2}$$

Thus, the total interaction energy for an ion entering a peptide nanotube through the region between cyclic peptide rings is given by

$$E_R = E_2(a_1) + E_2(a_2),$$

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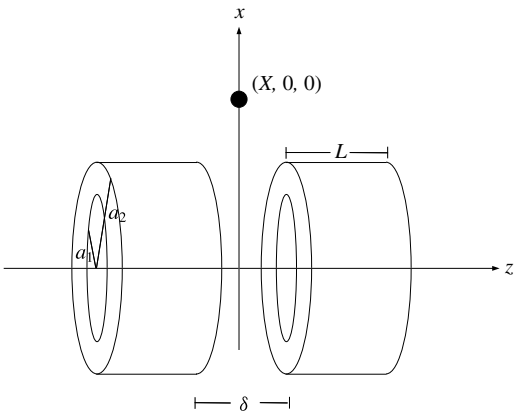

FIGURE 3. Geometry of an ion entering a peptide nanotube from the region between cyclic peptide rings.

where a_1 and a_2 are the radii of the inner and the outer tubes of the peptide rings, respectively. For $E_2(a_1)$, let us use $A = A_{\text{Li-inner}}$ and $B = B_{\text{Li-inner}}$ and, for $E_2(a_2)$, $A = A_{\text{Li-outer}}$ and $B = B_{\text{Li-outer}}$.

To evaluate (3.1) analytically, E_2 can be written as

$$E_2 = 8a\eta \int_0^{\pi/2} \int_{\delta/2}^{L+\delta/2} \left(-\frac{A}{(\alpha^2 + z^2)^3} + \frac{B}{(\alpha^2 + z^2)^6} \right) dz\, d\theta, \tag{3.3}$$

where $\alpha^2 = (a^2 + X^2) - 2aX\cos\theta$. Substituting $z = \alpha\tan\psi$ into (3.3) yields

$$E_2 = 8a\eta \int_0^{\pi/2} \int_{\psi_1}^{\psi_2} \left\{ -\frac{A}{\alpha^5}\cos^4\psi + \frac{B}{\alpha^{11}}\cos^{10}\psi \right\} d\psi\, d\theta, \tag{3.4}$$

where $\psi_1 = \arctan[\delta/(2\alpha)]$ and $\psi_2 = \arctan[(L + \delta/2)/\alpha]$. Since

$$\int \cos^{2p}\psi\, d\psi = \frac{1}{2^{2p}} \left[\binom{2p}{p}\psi + \sum_{l=0}^{p-1} \binom{2p}{l} \frac{\sin(2(p-l)\psi)}{p-l} \right],$$

one can evaluate the integral with respect to ψ and subsequently integrate with respect to θ. There are three forms for the integral for $\theta \in [0, \pi/2]$ which need to be determined, namely,

$$I_s = \int_0^{\pi/2} \frac{d\theta}{\alpha^s}, \quad J_{s,t} = \int_0^{\pi/2} \frac{d\theta}{\alpha^t(\alpha^2 + Z^2)^s}, \quad K_s = \int_0^{\pi/2} \frac{\arctan(Z/\alpha)}{\alpha^s}\, d\theta. \tag{3.5}$$

The analytical solutions and the detailed evaluation of these integrals can be found in the literature [1, 2].

The potential energies for an ion inside and outside the region are plotted in Figures 4 and 5, respectively. If the ion is originally inside the region between the peptide rings, then Figure 4 shows that there is a strong repulsion near the boundary of

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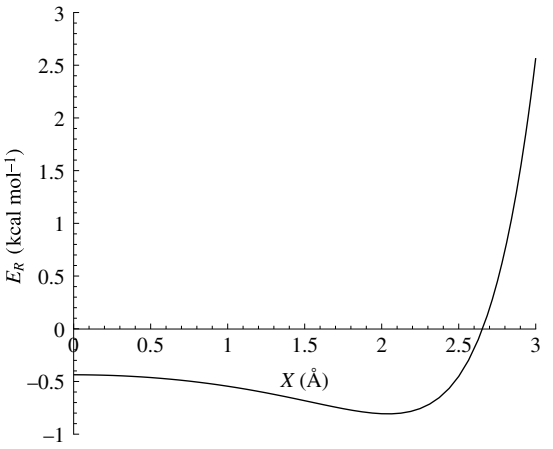

FIGURE 4. Potential energy for a lithium ion inside the region between two peptide rings with strong repulsion close to the boundary of the region and the equilibrium location inside the tube.

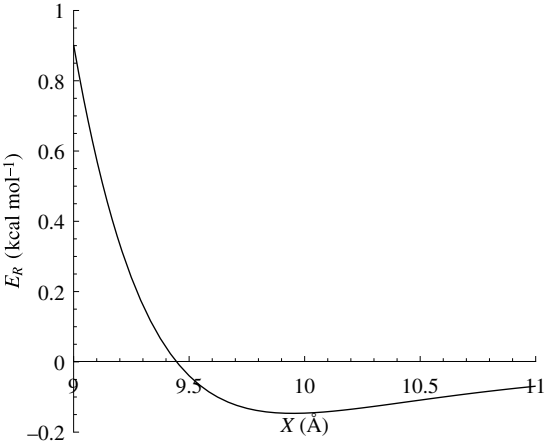

FIGURE 5. Potential energy for a lithium ion outside the region between two peptide rings with strong repulsion close to the boundary of the region and the equilibrium location outside the tube.

the region preventing the ion from escaping from the nanotube through this region. Figure 4 also indicates that the equilibrium location of the ion inside the tube is at an offset distance of 2.06 Å away from the tube axis. The ion needs an initial energy of at least 0.807 kcal mol^{-1} to escape from the nanotube through this region. For an ion outside a peptide nanotube, Figure 5 shows that the ion cannot enter the nanotube through the region between two peptide rings. This is because there is a strong repulsion near the boundary of this region, which prevents the ion from being accepted inside the peptide nanotube. This is not surprising as, in fact, this region is

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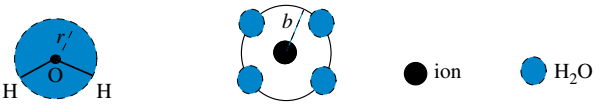

FIGURE 6. Structures of a water molecule (left) and a Li–water cluster (right).

dominated by six pairs of hydrogen bonding between two peptide rings. Further, from Figure 5, the minimum energy occurs at $X = 9.96$ Å, implying that the ion prefers to be at 9.96 Å away from the external surface of the peptide nanotube. Also note that the ion cannot enter at the area between the inner and outer tubes, where there are covalent bonds between backbone atoms and amino acids side chains. In order to penetrate to the nanotube through this region, the ion requires an initial energy of at least 0.147 kcal mol^{-1}. Note that this value is less than the escaping energy for an ion inside the nanotube. This is due to the fact that the internal ion is within close proximity of atoms making up both inner and outer tubes.

Next, let us explore whether it is possible for a water molecule and a Li^+–water cluster to enter the peptide nanotube from the region between cyclic peptide rings. As seen in Figure 6, the water molecule is modelled as comprising an oxygen atom at the centre of the sphere and two hydrogen atoms on the spherical surface. The radius of the sphere is $r = 0.958$ Å, which is based on the H–O bond length. For the Li–water cluster, it is assumed that the ion is surrounded by four water molecules, which is the preferred coordination number of water molecules, resulting in the global minima for a lithium ion [10, 17].

First, the case of a single water molecule is considered. It is similar to the configuration shown in Figure 3, but here the ion is replaced with the water molecule as shown in Figure 6. The centre of the water molecule is assumed to be located at $(X, 0, 0)$. For this case, the total energy can be obtained based on the four interactions, namely an oxygen atom–inner tube, an oxygen atom–outer tube, a sphere of hydrogen atom–inner tube and a sphere of hydrogen atom–outer tube. This is given by

$$E_R = E_2(a_1) + E_2(a_2) + W_1(a_1) + W_1(a_2), \tag{3.6}$$

where E_2 is defined by (3.4) and $W_1(a)$ is the energy between a peptide nanotube interacting with a spherical shell, namely,

$$W_1(a) = 2a\eta \int_{-\pi}^{\pi} \int_{\delta/2}^{L+\delta/2} P \, dz \, d\theta. \tag{3.7}$$

Following Cox et al. [5], P is the potential energy between a spherical shell of radius r and a typical point on a nanotube of radius a, given by

$$P = 4\pi r^2 \eta_w \left[\frac{B}{5} \left\{ \frac{5}{(\rho^2 - r^2)^6} + \frac{80r^2}{(\rho^2 - r^2)^7} + \frac{336r^4}{(\rho^2 - r^2)^8} + \frac{512r^6}{(\rho^2 - r^2)^9} + \frac{256r^8}{(\rho^2 - r^2)^{10}} \right\} - A \left\{ \frac{1}{(\rho^2 - r^2)^3} + \frac{2r^2}{(\rho^2 - r^2)^4} \right\} \right], \tag{3.8}$$

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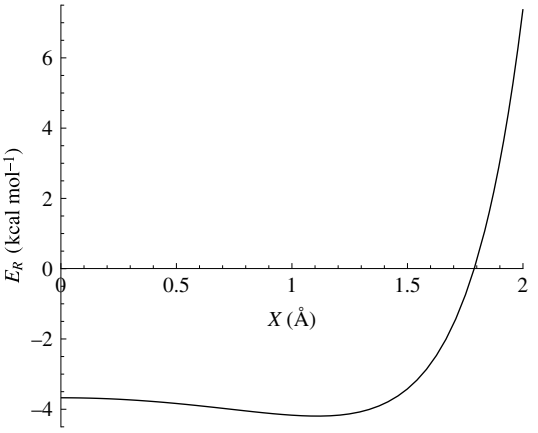

FIGURE 7. Potential energy for a water molecule inside the region between two peptide rings with strong repulsion close to the boundary of the region and the equilibrium location inside the tube.

where ρ is the distance between the centre of the sphere at $(X, 0, 0)$ and a surface element of the nanotube given by (3.2), and η_w is the average surface atomic density of the sphere. In the case of a water molecule with two hydrogen atoms on the sphere of radius $r = 0.958$ Å, $\eta_w = 2/(4\pi r^2) = 0.1734$ Å^{-2}. From (3.2) and the expression of P, evaluating (3.7) involves the integral

$$I_n = \int_{-\pi}^{\pi} \int_{\delta/2}^{L+\delta/2} \frac{1}{(\rho^2 - r^2)^n}\, dz\, d\theta.$$

For an analytical solution for I_n, we refer the reader to the work of Baowan et al. [2]. Note that for this case, one can use $A = A_{\text{O-inner}}$ and $B = B_{\text{O-inner}}$ in $E_2(a_1)$ and, for $E_2(a_2)$, we adopt $A = A_{\text{O-outer}}$ and $B = B_{\text{O-outer}}$. Further, for $W_1(a_1)$ we use $A = A_{\text{H-inner}}$ and $B = B_{\text{H-inner}}$ and for $W_1(a_2)$ we use $A = A_{\text{H-outer}}$ and $B = B_{\text{H-outer}}$. For any atoms i, the constants $A_{i\text{-inner}}$, $B_{i\text{-inner}}$, $A_{i\text{-outer}}$ and $B_{i\text{-outer}}$ can be found similarly to those shown in (1.2).

The energy for a water molecule inside and outside the region between two peptide rings is plotted in Figures 7 and 8, respectively. Similar to the case of a single atom, the water molecule can be accommodated within the region between the peptide rings, but cannot escape from the nanotube through this region. Inside this region, the centre of the water molecule tends to be offset at a distance of 1.12 Å from the central axis of the nanotube, and this result agrees with the findings of Tiangtrong et al. [19]. The water molecule needs an initial energy of at least 4.195 kcal mol^{-1} to escape from this region. Also, Figure 8 indicates that the external water molecule cannot be accepted through this region, but prefers to be 10.78 Å away from the boundary of the nanotube. To penetrate into this region, the water molecule requires an initial energy of at least 0.552 kcal mol^{-1}. Again, escaping from the nanotube requires higher energy than penetrating the nanotube from outside.

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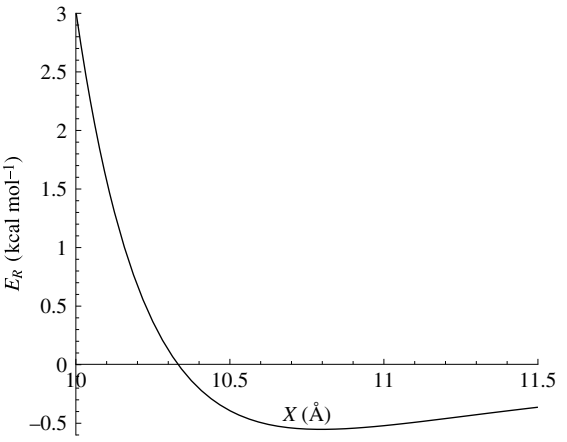

FIGURE 8. Potential energy for a water molecule outside the region between two peptide rings with strong repulsion close to the boundary of the region and the equilibrium location outside the tube.

Next, consider the possibility of the Li–water cluster entering a peptide nanotube between two cyclic peptide units. Again, it is assumed that the configuration is similar to that shown in Figure 3, but the ion is replaced with a Li–water cluster as shown in Figure 6. The lithium ion, which is at the centre of the cluster, is assumed to be located at $(X, 0, 0)$, and the radius of the cluster is $b = 1.5$ Å. For this case, the total energy can be obtained based on the four interactions, namely, the ion–inner or –outer nanotubes and a sphere of four water molecules–inner or –outer nanotubes. We can use the expression in (3.6) to represent the total energy, but here we replace r by b in (3.8) and we use $A = A_{\text{Li-inner}}$ and $B = B_{\text{Li-inner}}$ in $E_2(a_1)$ and for $E_2(a_2)$ we have $A = A_{\text{Li-outer}}$ and $B = B_{\text{Li-outer}}$. Further, for $W_1(a_1)$ we use $A = A_{\text{water-inner}}$ and $B = B_{\text{water-inner}}$ and for $W_1(a_2)$ we use $A = A_{\text{water-outer}}$ and $B = B_{\text{water-outer}}$. Note that $A = A_{\text{water-inner}}$ and $B = B_{\text{water-inner}}$ can be found from

$$A_{\text{water-inner}} = \frac{16A_{\text{water-C}} + 16A_{\text{water-H}} + 8A_{\text{water-N}} + 8A_{\text{water-O}}}{48},$$
$$B_{\text{water-inner}} = \frac{16B_{\text{water-C}} + 16B_{\text{water-H}} + 8B_{\text{water-N}} + 8B_{\text{water-O}}}{48},$$
$$A_{\text{water-outer}} = \frac{8A_{\text{water-C}} + 24A_{\text{water-H}}}{32},$$
$$B_{\text{water-outer}} = \frac{8B_{\text{water-C}} + 24B_{\text{water-H}}}{32},$$

where the attractive and repulsive constants for four water molecules interacting with an atom of type i are given by

$$A_{\text{water}-i} = \frac{8A_{H-i} + 4A_{O-i}}{12}, \quad B_{\text{water}-i} = \frac{8B_{H-i} + 4B_{O-i}}{12}.$$

In Figures 9 and 10, the energy is plotted as a function of X for the Li–water cluster inside and outside the region between two peptide rings, respectively. From

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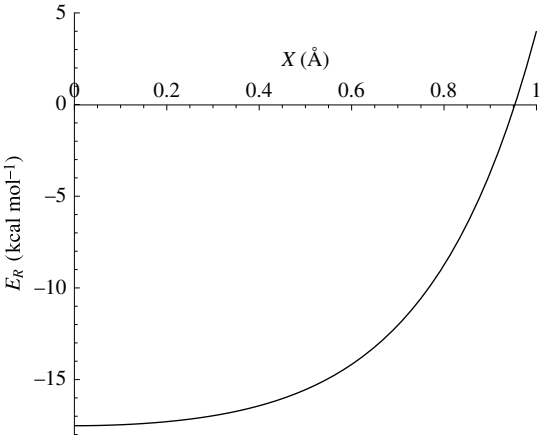

FIGURE 9. Potential energy for a Li–water cluster inside the region between two peptide rings with strong repulsion close to the boundary of the region and the equilibrium location inside the tube.

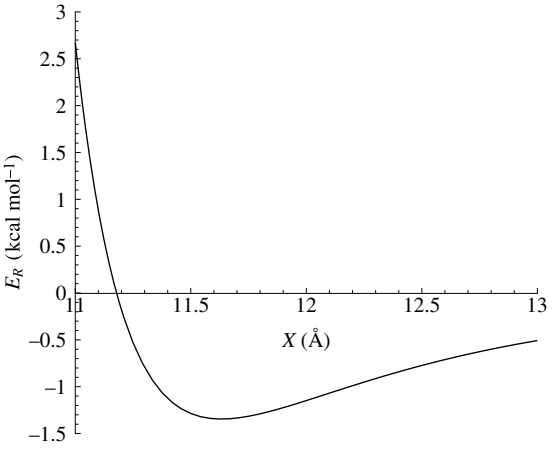

FIGURE 10. Potential energy for a Li–water cluster outside the region between two peptide rings with strong repulsion close to the boundary of the region and the equilibrium location outside the tube.

Figure 9, the cluster inside the region prefers to be at the centre of the nanotube where the energy is minimum. Approaching the boundary, the energy becomes repulsive implying that the cluster is not able to escape through this region, unless an initial energy is given to the cluster. In this case, the cluster requires an initial energy as high as 17.517 kcal mol^{-1}. Similarly, the external cluster is not able to penetrate the nanotube through this region due to the high energy barrier. In fact, the cluster prefers to be at a distance of 11.62 Å away from this region. However, the initial energy of at least 1.345 kcal mol^{-1} can be given to the cluster to facilitate the penetration.

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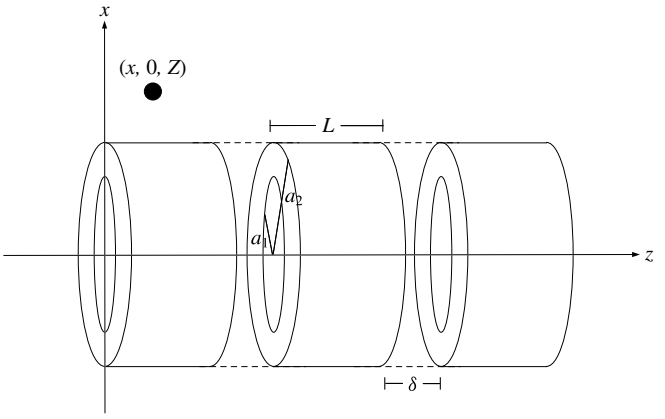

FIGURE 11. Geometry of an ion entering a peptide nanotube from the edge of the nanotube's open end.

4. Entering around the edge at an open end

This section first considers whether an ion located along the nanotube can move across the edge and enter the tube through its open end. Here, the energy is determined for an ion entering a peptide nanotube around its edge at the open end as shown in Figure 11. Note that a nanotube with only three peptide units is considered, due to the short-range interaction of the van der Waals force. Since the ion or a molecule cannot enter the tube from the region between two neighbouring rings, it is assumed in this case that the peptide nanotube is a continuous cylinder. Based on this assumption, one needs to adjust the surface atomic densities for the inner and outer nanotubes to be $\eta_1 = 144/(2\pi a_1[3L + 2\delta])$ and $\eta_2 = 96/(2\pi a_2[3L + 2\delta])$, respectively.

With reference to the rectangular Cartesian coordinate system (x, y, z), a typical point on the surface of the tube has the coordinate $(a\cos\theta, a\sin\theta, z)$, where $\theta \in [-\pi, \pi]$, $z \in [0, \infty)$ and a is the radius of the tube. Here, $a = a_1$ and a_2 correspond to the inner and the outer tubes, respectively. The Cartesian coordinate of an ion is given by $(x, 0, Z)$, where Z is the distance in the z-direction, which can be either positive or negative. Thus, the distance ρ between the atom and a typical point on the tube is given by

$$\rho^2 = (a\cos\theta - x)^2 + a^2\sin^2\theta + (z - Z)^2, \tag{4.1}$$

and the total potential energy for an ion entering around the edge at an open end of a peptide nanotube is given by

$$E_E = E_3(a_1) + E_3(a_2),$$

where

$$E_3 = a\eta \int_{-\pi}^{\pi}\int_{0}^{3L+2\delta}\left[-\frac{A}{\rho^6} + \frac{B}{\rho^{12}}\right] dz\, d\theta.$$

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Substituting $\lambda^2 = (a\cos\theta - x)^2 + a^2\sin^2\theta$ yields

$$E_3 = a\eta \int_{-\pi}^{\pi}\int_{0}^{3L+2\delta}\left[-\frac{A}{\{\lambda^2+(z-Z)^2\}^3} + \frac{B}{\{\lambda^2+(z-Z)^2\}^6}\right] dz\, d\theta. \tag{4.2}$$

Further, by letting $w = z - Z$ and substituting $w = \lambda\tan\psi$, equation (4.2) reduces to

$$E_3 = a\eta \int_{-\pi}^{\pi}\int_{\psi_1}^{\psi_2}\left\{-\frac{A}{\lambda^5}\cos^4\psi + \frac{B}{\lambda^{11}}\cos^{10}\psi\right\} d\psi\, d\theta, \tag{4.3}$$

where $\psi_1 = -\arctan(Z/\lambda)$ and $\psi_2 = \arctan[(3L + 2\delta - Z)/\lambda]$. Similar to equation (3.4), to evaluate equation (4.3) it is required to evaluate the three integrals as shown in equation (3.5), where in this case α is replaced by λ.

Now, the potential energy for an ion at the edge of a peptide nanotube is plotted, as shown in Figure 12. The energy well is located where x is approximately 10.6 Å from the nanotube outer surface in the positive z-direction. This implies that the ion prefers to be outside at a certain distance along the side of the nanotube. As the energy is higher in the negative z-direction, the ion is not able to move across the edge of the nanotube to be accepted inside the tube by a head-on configuration. However, if an initial energy is applied to the ion, then it is likely that the ion will move to the negative z-direction and enter the nanotube head-on.

Note that one can extend this scenario for a water molecule and a Li–water cluster with structures shown in Figure 6. However, a similar behaviour to that of a single lithium atom is expected; therefore, only the analytical expressions for the interaction energies are stated here. For a water molecule, the interaction energy is given by

$$E_E = E_3(a_1) + E_3(a_2) + W_2(a_1) + W_2(a_2), \tag{4.4}$$

where E_3 is defined by (4.3) and $W_2(a)$ is the energy between a peptide nanotube interacting with a sphere centred at $(x, 0, Z)$, namely,

$$W_2(a) = 2a\eta \int_{-\pi}^{\pi}\int_{0}^{3L+2\delta} P\, dz\, d\theta, \tag{4.5}$$

where P is given by (3.8), and ρ is the distance between the centre of the sphere at $(x, 0, Z)$ and a surface element of the nanotube given by (4.1). From (3.8) and (4.1), evaluating (4.5) involves performing the integral of the form

$$J_n = \int_{-\pi}^{\pi}\int_{0}^{3L+2\delta} \frac{1}{(\rho^2 - b^2)^n}\, dz\, d\theta.$$

For an analytical solution of J_n, the reader is referred to the work of Baowan et al. [2]. For this case, one needs to use $A = A_{\text{O-inner}}$ and $B = B_{\text{O-inner}}$ in $E_3(a_1)$ and, for $E_3(a_2)$, $A = A_{\text{O-outer}}$ and $B = B_{\text{O-outer}}$. Further, for $W_2(a_1)$, we use $A = A_{\text{H-inner}}$ and $B = B_{\text{H-inner}}$ and for $W_2(a_2)$ we use $A = A_{\text{H-outer}}$ and $B = B_{\text{H-outer}}$.

Similarly, one can consider the possibility of the Li–water cluster entering a peptide nanotube around the edge at an open end. It is assumed that the configuration is similar

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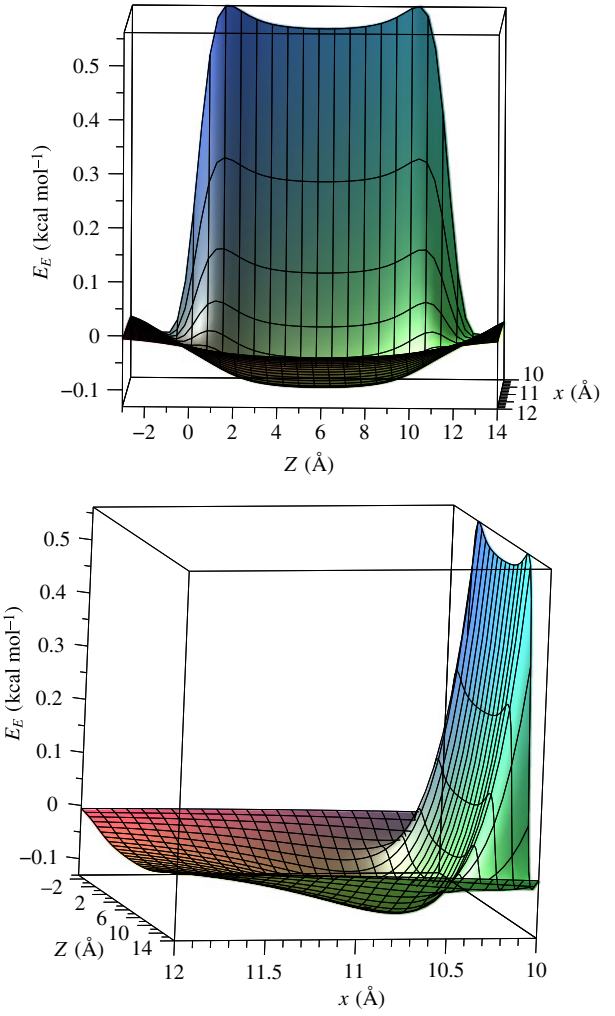

FIGURE 12. Potential energy E_E for a lithium ion near the edge of a nanotube's open end (two different views). (Colour available online.)

to that shown in Figure 11, but the ion is replaced with a Li–water cluster as shown in Figure 6. The lithium ion, which is at the centre of the cluster, is assumed to be located at $(x, 0, Z)$, and the radius of the cluster is $b = 1.5$ Å. For this case, the total energy can be obtained based on the four interactions, namely, the lithium ion–inner or –outer nanotubes and a sphere of four water molecules–inner or –outer nanotubes. One can use the expression in (4.4) to represent the total energy, but here r needs to be replaced by b in (3.8) and, for $E_3(a_1)$, $A = A_{\text{Li-inner}}$ and $B = B_{\text{Li-inner}}$ should be used, while, for $E_3(a_2)$, $A = A_{\text{Li-outer}}$ and $B = B_{\text{Li-outer}}$. Further, for $W_2(a_1)$ use $A = A_{\text{water-inner}}$ and $B = B_{\text{water-inner}}$ and for $W_2(a_2)$ use $A = A_{\text{water-outer}}$ and $B = B_{\text{water-outer}}$.

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5. Conclusions

Using a continuum approach together with the Lennard-Jones potential, this paper has investigated the possibility of an ion entering the cyclo[(-D-Ala-L-Ala-)$_4$] peptide nanotube from various configurations. The approach presented in this paper can be easily extended to model the interaction of any ion and other types of peptide nanotubes. For charged nanotubes, incorporating the electrostatic effect based on the Coulomb potential is relatively straightforward, since it only involves the integration of $1/\rho$.

For the cyclo[(-D-Ala-L-Ala-)$_4$] peptide nanotube, these results indicate that an ion or a molecule located near an open end enters the nanotube. It is also shown that an ion or a molecule cannot enter the nanotube from the region between two neighbouring peptide rings and from around the edge of the nanotube. However, an initial energy may be applied to overcome the energetic barrier enabling the entrance of an ion or a molecule from these positions. The findings in this paper may contribute to the development of a peptide nanotube as an artificial transmembrane ion channel.

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