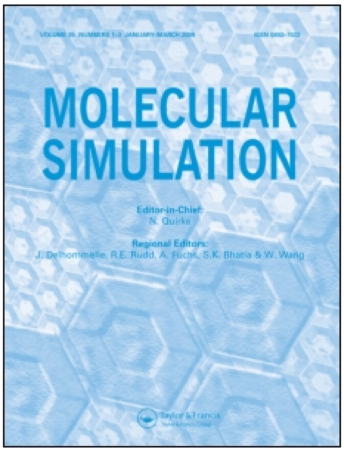

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Molecular dynamics simulation of ion selectivity process in nanopores

Hongmei Liu[a]; Cynthia J. Jameson[a]; Sohail Murad[a]
[a] Department of Chemical Engineering, University of Illinois at Chicago, Chicago, USA

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Molecular dynamics simulation of ion selectivity process in nanopores

Hongmei Liu, Cynthia J. Jameson and Sohail Murad*

Department of Chemical Engineering, University of Illinois at Chicago, Chicago, USA

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The behaviour of cations in nanopores plays an important role in transport processes in the biological and industrial membranes, porous electrodes, ion channels, and nanomaterials in general. Molecular dynamics simulations have been carried out to study the selectivity mechanism of nanopores by studying the ion permeation events through non-charged carbon nanotubes (10,0) which have an effective diameter of 0.4374 nm. We have investigated pure NaCl, pure KCl and equimolar mixture of NaCl and KCl (50/50) aqueous solutions. Our results show that a membrane of uncharged nanotubes of the appropriate diameter can select K^+ against Na^+ without the presence of external electric field or surface charges. The key to the ion selectivity is that Na^+-H_2O clusters are more stable than K^+-H_2O clusters, and Na^+ ions have higher desolvation energy than K^+ ions. When both Na^+ and K^+ are present in the same solution, there is a competition between the two types of cations and the nanotubes select K^+ over Na^+.We also studied the effects of temperature and pressure to find the conditions, which permit Na^+ to permeate through the nanotubes.

Keywords: ion selectivity; potassium; sodium; channel

1. Introduction

The selective transport of ions through nanopores is of significant fundamental interest in a range of physical, chemical and biological (especially ion channels) processes. Ion channels are found in organisms ranging from viruses and bacteria to mammals, and play a key role in the electrical properties of neurons and muscle. Ion channels are a special class of proteins that conduct small ions such as Na^+, K^+, Ca^{2+} or Cl^-. They represent the basic electrically conductive component of the nervous system and are the target of roughly a third of all drugs [1]. Gating and selectivity are the two most important characteristics of biological ion channels. The opening and closing of ion channels may depend on membrane voltage or the binding of molecules. The property of ion selectivity of nanochannels is also of great interest for a number of applications in separations, sensors etc.

Potassium ions control many cell processes in the human body. These include for example nerve functions and osmotic balance between cells and interstitial fluids. The balance of sodium and potassium ions in muscle cells leads to either the resting or action potential [2–4]. Many characteristics of biological ion channels responsible for the observed selectivity of K^+ are known, but the selectivity is not yet completely understood and has been the subject of many investigations as described below. It has been speculated that Coulombic interactions between the charges on the ion channels and K^+ must be responsible for the selectivity, since it cannot be explained by steric effects only (K^+ are larger than Na^+ ions). Another possibility is that the details of the solvation shell of the ion are primarily responsible for the observed selectivity [5–7].

Potassium ion channels are membrane-spanning proteins that provide an energetically favourable pathway for the selective conduction of K^+ ions across the membrane. One of the most striking properties of potassium ion channels is their remarkable ability to conduct K^+ ions near the diffusion limit while simultaneously maintaining a selectivity of K^+ over Na^+ of over ~ 1000 to 1. The precise mechanism that allows such high level of discrimination between K^+ and Na^+ is therefore rather fascinating since these two monovalent cations superficially are very similar, differing only slightly in their atomic radius (by ~ 0.038 nm) [8].

Since the publication of the 2.0 Å resolution crystal structure of KcsA, the gating mechanism and cation selectivity of ion channels have been extensively studied and reported in the literature [9–17]. To discriminate between different ion types, ion channels must find a physical property such as the size, charge, or charge density that is different between the desired ion type and the rest. It has been suggested that the diameter of the potassium channel's selectivity filter should be about the same as the size of a Cs^+ ion (diameter $= 0.33$ nm) because Cs^+ is the largest ion, which can barely pass through the potassium ion channel [18]. While a narrow pore will block the passage of large organic ions

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*Corresponding author. Email: murad@uic.edu

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or proteins and allow small ions to pass, to be able to differentiate between small ions with similar sizes such as K^+ and Na^+, more detailed interactions between the ions and the protein are required. The recent availability of structures at 2.0 Å resolution has meant that the group of atoms responsible for this interaction, the so-called selectivity filters, can be pinpointed [19]. For K ion channels the selectivity filter involves coordination with eight carbonyl oxygens. Despite the increasing number of research articles and reviews on these topics, many questions about the molecular mechanism for ion selectivity and dynamic details of the transport process remain.

Brownian dynamics and molecular dynamics (MD) simulation methods are the two most commonly used and the most appropriate tools for the purpose of computer simulation of selectivity of ion channels. Brownian dynamics simulations have been employed to investigate the physical mechanisms involved in the transport of ions across the potassium ion channel. They suggest that ion selectivity arises from the ability of the channel protein to completely solvate potassium ions but not the smaller sodium ions [20–22]. The MD simulation technique can directly investigate the microscopic details of permeation through ion channels of known structure. As a result, numerous MD simulations have been performed since the X-ray structure of KcsA was reported [23–26], and valuable insights have been gained into the molecular details of ion permeation in this system. Previous MD studies have been used to study the effective short-time local diffusion coefficients of K^+ and Cl^- in a series of ion channel models (idealised β barrel and α helix bundle proteins) [27,28]. The differences in ion mobilities were studied for solutions with varying ratios of Na^+ and K^+ concentrations in aqueous solutions These MD results showed that the diffusion coefficients of both ions are appreciably reduced in the narrower channels, the extent of the reduction being similar for both the anionic and cationic species. It was therefore suggested that differences in the mobilities couldn't be the primary cause of the ion selectivity exhibited by biological channels.

The goal of the present work is to investigate relative selectivities of uniform atomistic cylindrical nanochannels to Na^+ and K^+ ions, in order to discover a general molecular mechanism for ion selectivity by nanochannels, a mechanism which does not require the presence of dynamic coordinating chemical groups at particular sites, the so-called biological selectivity filters.

2. Method

Our simulation method is adapted from the model first introduced by one of us in 1993 [29]. The simulation box consists of two compartments separated by two symmetric carbon nanotube membranes. Periodic boundary conditions then lead to a system infinite in the y and z directions (parallel to the membranes). A schematic diagram is shown in Figure 1. Four carbon nanotubes (CNT) of the zigzag type in a cubic arrangement constitute each membrane. In our simulations the membranes are formed by tethering the carbon sites by a simple harmonic potential ($\Phi_{T=}(1/2) k\delta^2$). Here δ corresponds to the distance between the centre of mass of the tethered carbon and the tethering site, and k, the tethering force constant, is set equal to 900 reduced units or 277 N m^{-1} for most of the simulations, leading to a fairly rigid membrane. Dummy atoms (with parameters identical to those of carbon atoms) were placed strategically at the entrances to inter-tube regions of the membrane to prevent water molecules and ions from entering these regions, since we are not interested in the behaviour of water and ions on the outside surface of the nanotubes. The compartment in the middle of the simulation box is initially under vacuum.

Two types of membranes were used in the studies reported here. The first consisted of four CNT of the zigzag (11,0) type, which have a diameter of 0.8551 nm. The effective internal diameter of these tubes is 0.5151 nm, using 0.34 nm as the diameter of the carbon sites. The second membrane consisted of tubes of the (10,0) type with a diameter of 0.7774 nm and corresponding effective internal diameter of 0.4374 nm. We chose a suitably long tube (2.36 nm) to be able to effectively study the behaviour of the ions under minimal influence of end effects on the permeation of ions in these tubes. Both these systems were studied at two temperatures (298 and 325 K), and pressures between 5 and 3500 MPa and two concentrations (1.85 and 4.98 mole percentages) of NaCl/KCl. The density and temperature of the liquid water or salt solution can be fixed to correspond to the state condition of interest. Once the density is fixed and the number of molecules in the solution is known, this establishes the volume of the compartments. At the beginning of each simulation, the contents of the compartments are electrically neutral, and the membrane is likewise electrically neutral.

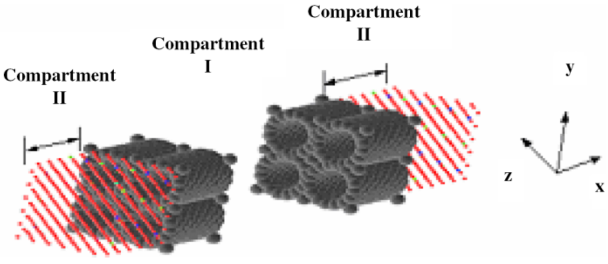

Figure 1. The basic simulation system used in this investigation, with the electrolyte solutions only in Compartment II at the beginning of the simulations.

Furthermore, the only partial charges assigned are those to the water molecules, and the ions carry their usual charges of + e and − e. The carbon sites only interact with water and the ions *via* van der Waals forces, since there are no charges on these membrane atoms. Surface charges have an important role in governing ionic conductance; in a subsequent paper we carry out separate studies using partially charged tube atoms, with net overall neutral nanotubes, or with net overall charged nanotubes balanced by excess ions in the solution compartments, to study the combined effect of hydration and Coulombic effects on selectivity. In the present work, the solution compartment consisted of typically 1664 water molecules and 32 Na^+ and 32 Cl^- ions.

The simple point charge (SPC) model was used for liquid water in pure water and also in the salt solutions. The SPC potential had been shown to give reasonable agreement with a range of experimental observations in liquid water [30]. For ions we used the primitive model. The parameters for Na^+ and Cl^- were obtained from Chandrasehkar et al. [31]. Finally to ensure compatibility of the K^+ and Na^+ potential models used we followed the usual convention of making their energy parameters (ϵ) equivalent [32–35] and fixed the ratio of the size parameter (σ) to conform to those used in several recent studies [32–36]. The mobility of ions in aqueous solutions is primarily determined by their surface charge density. The behaviour of ions is therefore strongly influenced by the Lennard-Jones (LJ) σ parameter while it is not sensitive to the LJ ϵ parameter. It is therefore standard practice to assume ϵ as a constant parameter for a diverse range of ions (Li^+, Na^+, K^+, Rb^+, CS^+, etc) [35] The parameters for the CNT were obtained from Turner et al. [37] The potential was used with a spherical cut-off of 0.7887 nm and the reaction field method was used to account for long range interactions. The site-site interaction potential used is of the form,

$$U\text{ij} = \sum 4\varepsilon_{\text{ij}}[(r_{\text{ij}}/\sigma_{\text{ij}})^{-12} - (r_{\text{ij}}/\sigma_{\text{ij}})^{-6}] + q_{\text{i}}q_{\text{j}}/r_{\text{ij}} \quad (1)$$

where ϵ and σ are LJ parameters and r is the distance between the sites. The Coulombic interaction terms were included in the potential for charged sites only. Table 1 lists the model parameters for ions and water molecules. The LJ energy (ϵ) and diameter (σ) parameters of the cross-interactions are calculated on the basis of the Lorentz-Berthelot combining rules.

The molecules were given a Gaussian distribution corresponding to the desired temperature of 298 K. The temperature was subsequently held constant at 298 K using a Gaussian thermostat. The time evolution of this initial system set up was then followed using a fifth order predictor-corrector scheme for the translational motion, a fourth order scheme [38] using the quaternion formulation of the equations of rotational motion about the centre of mass of the water molecules [39]. The simulation system was allowed to equilibrate for 10,000 time steps (each of length 0.35181 10^{-15} s), followed by production runs for 1,000,000 time steps. In our initial studies at room temperature and normal pressures, using tubes of the (11,0) type, our results from the simulation showed that both Na^+ ions from a NaCl solution and K^+ ions from the KCl solution could readily permeate the uncharged nanotubes. Results obtained are shown in Table 2, which shows that the permeation rate of both ions in comparable solutions was very similar and such a membrane does not behave as an effective ion filter. Since the goal of this work was to investigate the relative selectivity of pores to Na^+ and K^+ ions, we did not study this membrane further extensively. The discussion in the following section is therefore limited to the CNT (10,0) membranes.

Table 1. Parameters[a] (in Equation (1)) of the potential models used in this investigation.

Interacting sites		σ (10^{-10} m)	ϵ (kJ/mol)	q (e)
Water	O	3.17	0.65	− 0.82
	H	0	0	0.41
Membrane	C	3.40	0.23	0
Ions	Cl	4.42	0.49	− 1.00
	K	2.52	6.69	1.00
	Na	1.90	6.69	1.00

[a] From [29–33], see text.

3. Results

Our preliminary studies with CNT (10,0) membranes did show that such a membrane could effectively discriminate between Na^+ and K^+ ions from NaCl and KCl solutions. Therefore, we carried out an extensive study of this system, by varying the temperature, pressure and concentration. The results obtained are shown in Figure 2(a–c) and are summarised in Table 2. The results show conclusively that membranes with the smaller diameter (10,0) CNTs can be effective selectivity filters.

Our results at 298 K and an initial pressure of 5 MPa with a concentration of 1.85 mole percentage (either pure NaCl, or pure KCl) show that one K^+ ion entered the membrane and was able to travel the entire length of the membrane and exit it. In contrast, none of the Na^+ ions were able to even enter the membrane. When the solution contained equal amounts of NaCl and KCl (total concentration unchanged), once again one K^+ ion entered and exited the membrane, and once again none of the Na^+ ions were able to permeate or exit the membrane at all. After 0.35 ns, additional K^+ ions (between 1–8) were also present inside the CNTs (but had not yet exited the system).

Table 2. The summary of statistics for separate simulations using membranes of (10,0) CNTs and membranes of (11,0) CNTs.

(10,0) CNTs	Observed ion permeation events		
	NaCl solution	KCl solution	NaCl/KCl solution
Compartment II	32 Na^+,32 Cl^-	32 K^+,32 Cl^-	16 Na^+,16 K^+,32Cl^-
298 K, $P = 5*$ Mpa	No Na^+	1 K^+	No Na^+, 1 K^+
298 K, $P = 3000$ Mpa	No Na^+		
325 K, $P = 55$ Mpa	No Na^+	2 K^+	No Na^+, 2 K^+
325 K, $P = 3500$ Mpa	2 Na^+	4 K^+	No Na^+, 3 K^+
(10,0) CNTs		**Observed ion permeation events**	
		KCl solution	
Compartment II		86 K^+, 86Cl^-	
298 K, $P = 5$ Mpa		1 K^+	
325 K, $P = 3500$ Mpa		4 K^+	
(11,0) CNTs		**Observed ion permeation events**	
	NaCl solution		NaCl/KCl solution
Compartment II	48 Na^+, 48Cl^-	KCl solution 48 K^+, 48Cl^-	24 Na^+, 24 K^+, 48Cl^-
298 K,$P = 5$ Mpa	2 Na^+	2 K^+	1 Na^+, 2 K^+
325 K, $P = 55$ Mpa	3 Na^+	2 K^+	

Note: A permeation event is counted when an ion passes through the virtual surface at the entrance to the CNT and does not return through it during the simulation.

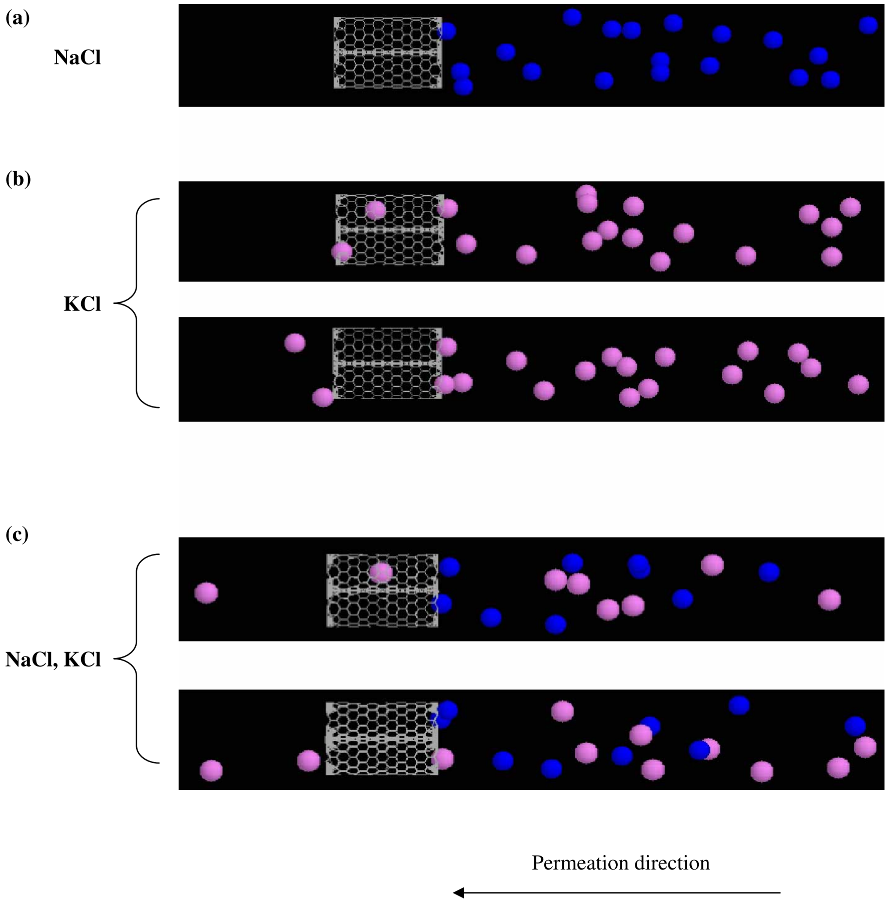

Figure 2. Snapshots of simulations in a membrane system of (10,0) nanotubes showing permeation of K^+ ions (pink) and Na^+ ions (blue), into CNT (10,0) (a) from NaCl solution, at 0.35 ns, (b) from KCl solution at 0.069 ns upper picture, and 0.35 ns lower picture (c) from an equilmolar NaCl-KCl solution, at 0.069 ns upper picture and 0.35 ns lower picture. For clarity, only one membrane is illustrated in each picture and the water and Cl^- ions are not shown.

In contrast, Na^+ ions never succeeded in entering the CNTs. We believe this conclusively shows that this membrane behaved as an effective selectivity filter.

Our findings can be explained by the differences in the energy of solvation of Na^+ and K^+ ions in the solution [40]. The average value from reported experimental studies for Na^+ is 92.4 kcal/mol, while for K^+ it is 75.0 kcal/mol. The effect of this difference is evident in Figure 3 where only the water molecules in the first hydration shell of the potassium ion and the carbon atoms are displayed. In bulk solution, both K^+ and Na^+ ions have approximately four water molecules in the first hydration shell, and inside nanotubes of larger diameter than this one, our earlier investigations have shown that Na^+ ions have an average 3.5 water molecules in the first hydration shell.

Figure 3 shows a mechanism by which the K^+ can effectively enter the uncharged CNT membrane. Snapshots were taken every 0.00176 ns (5000 time steps). Potassium ions are shown in violet, carbon atoms in white, water molecules in red. For clarity only one K^+ ion is shown and only the waters in its first hydration shell are depicted with red spheres; all other waters and ions are omitted. Figure 3(b) shows clearly how the hydration shell of K^+ can be partially stripped off to make the solvated ion effectively linear, so that the K^+ ion can not only enter the membrane, but can also be readily transported across the entire length of the membrane (which in our case is about 10 molecular diameters of K^+). Our results show that only two are stripped off but these can be relegated to the position water molecules normally occupy in the second hydration shell. We expect that the energetic cost of partially desolvating the K^+ ion is probably significantly lower than the cost of completely stripping all water molecules from it. Since the Na^+ ion is much smaller than the K^+ ion (in our model about a third smaller), clearly the higher solvation energy, and the corresponding higher energetic barrier to distorting the solvation shell, of Na^+ ion in comparison with K^+ ions is primarily responsible for the observed difference. We also carried out the same simulation at a higher temperature of 325 K, and still found no evidence of Na^+ permeation, while the number of permeating K^+ ions approximately doubled. Only when both the pressure and temperature are increased in pure NaCl solutions (325 K, $P = 3500$ MPa), did we observe some permeation of Na^+ ions. These results are not surprising. At increased temperature and pressure, the energetic cost of desolvating a Na^+ is available. Under the same conditions for a comparable KCl solution, the number of permeating K^+ ions effectively doubled. In a mixed solution of NaCl and KCl, only K^+ ions were able to permeate the nanotube, while none of Na^+ succeeded. When both ions are competing to enter the CNT, then K^+ would win, because of the lower energetic cost of partial desolvation. The smaller Na^+ ion requires greater dehydration energy than the K^+ ion because of its higher surface charge density (in our model about 75% higher, and in experimental and theoretical studies with similar models, it leads to a difference of about 17.5 kcal/mol in dehydration energy).

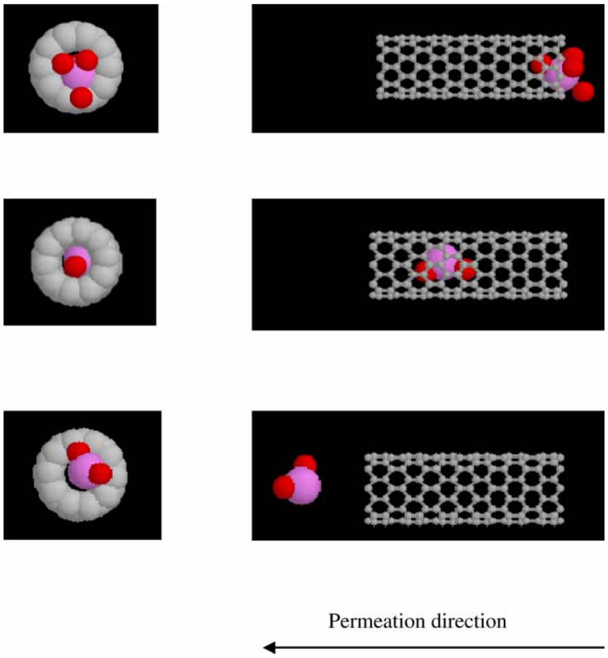

Figure 3. End view and side view in three snapshots of a K^+ ion permeating through a CNT (10,0) during a simulation. For clarity only one K^+ ion is shown and only the waters in its first hydration shell are depicted with red spheres; all other waters and ions are omitted.

Recent Monte Carlo simulations of a single hydrated ion with up to 70 water molecules constrained inside a cylinder with hard walls were carried out at fixed density and variable cylinder radius [41]. The authors determined the energetic cost of constraining the ion (K^+, Na^+, or Li^+) to a cylinder of particular radius (defined as the difference between the total energy of the system at a radius of 0.675 nm and at this radius). They found that K^+ could be constrained into pores 0.10 nm to 0.25 nm (in the range of biological channels) at a smaller energy cost than Na^+, whereas Na^+ is favoured over K^+ for pore radii 0.275–0.40 nm. In a cylinder of 0.15 nm radius all ions have two neighbouring waters and the free energy clearly favours K^+ whereas the potential energy favours Na^+ and Li^+. The authors suggested that this is relevant to the molecular basis of ion selective channels. These results from a minimalist model of a single ion in a hard-wall cylindrical pore are consistent with our findings that the flexibility of the hydration shell of K^+ ion permits it to maintain a better coordination inside nanochannels of dimensions similar to biological channels. Our work has the advantage that we actually followed at an atomistic level the permeation and transport of K$^+$ vs. Na$^+$ ions and thus has described the molecular mechanism of ion selectivity of nanochannels of diameter 0.437 nm. This mechanism does not depend on having dynamic, flexible coordinating groups acting as selectivity filters, and is therefore expected to operate in general in nanochannels of this approximate size.

4. Conclusions

Our results in membranes consisting of uncharged CNT have shown that an ion filter can be effective even in the absence of Coulombic exclusion, based exclusively on the characteristics of the hydrated ion, and the corresponding energy of partial desolvation. Therefore, we believe that the desolvation energy plays an important role in the permeation process in small diameter nanopores, and may be an important factor even for nanotubes with surface charges.

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