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Molecular control of ionic conduction in polymer nanopores

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Abstract

Polymeric nanopores show unique transport properties and have attracted a great deal of scientific interest as a test system to study ionic and molecular transport at the nanoscale. By means of all-atom molecular dynamics, we simulated the ion dynamics inside polymeric polyethylene terephthalate nanopores. For this purpose, we established a protocol to assemble atomic models of polymeric material into which we sculpted a nanopore model with the key features of experimental devices, namely a conical geometry and a negative surface charge density. Molecular dynamics simulations of ion currents through the pore show that the protonation state of the carboxyl group of exposed polyethylene terephthalate residues have a considerable effect on ion selectivity, by affecting ionic densities and electrostatic potentials inside the nanopores. The role of high concentrations of Ca^{2+} ions on charge inversion effects, earlier reported in experiments, were investigated in detail.

Keywords

polymer nanopores; polyethylene terephthalate; ion current; charge inversion

1 Introduction

Solid-state nanopores are small pores with radii of a few nanometers that are built in synthetic materials, such as silicon nitride^{1,2}, silicon oxide³, silicon⁴, and polymer films^{5–8}. An atomic model of a polymer nanopore immersed in electrolyte solution is shown in Fig. 1. Due to their tunable geometry, resistance to harsh solvent conditions, and selectivity for surface modifications, solid-state nanopores have become promising tools in nanotechnology. To date, they have been used to unravel the finely-tuned interactions between DNA and proteins^{9,10}, to build proteinaceous channels that mimic trafficking in cells¹¹ and to evaluate the feasibility of a fast-sequencing DNA technique^{12–14}. Besides this wide range of applications, solid-state nanopores have also been used as models to test fundamental theories about ion dynamics in nanoscale confinements^{15,16}. Studying ionic transport on the nanoscale is crucial not only for controlling the flow of ions across the nanopore^{15–20}, but also for understanding how biological channels function. In this regard, theoretical and computational modeling have been of critical importance, since experimental techniques are not yet able to resolve the dynamics of the few ions contained in the nanopore volume.

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Modeling based on the Poisson-Nernst-Planck (PNP) equations, Monte Carlo (MC) as well as molecular dynamics (MD) simulations have accompanied experimental efforts. The continuum approach of PNP successfully described the effect of ion current rectification observed in asymmetric pores^{21–23} as well as ionic selectivity, *i.e.*, a pore preference for transporting one type of ion, cations or anions^{24,25}. However, continuum modeling cannot provide a molecular understanding of how ions compete for space and surface charges in the restricted volume of a nanopore. Monte Carlo simulations, which take into account the finite size of ions, offer more detail on the behavior of ions in nanopores. Applied to calcium-selective channels these simulations successfully described channel selectivity properties²⁶. MD approaches reveal most details about ionic trajectories and their interactions with other ions, water and nanopore surface in equilibrium as well as non-equilibrium conditions. Increases in computational power have extended the duration of MD simulations, approaching today a time scale that is accessible in ion current measurements. Indeed, MD simulations successfully described transport properties of proteinaceous nanopores such as α -hemolysin^{27–29} and solid-state silicon-based nanopores^{30–33}. The MD methodology had not been extended initially to polymer nanopores due to the lack of an accurate model for the chemical features of the pore surface, a key factor that determines the transport properties.

Here, we report all-atom simulations of ion transport through a polyethylene terephthalate (PET) nanopore. PET nanopores have emerged as a nano-scale model system of interest, because of the experimental observation of multiple effects allowing for the control of ion transport properties, *i.e.*, ion current rectification^{8,34}, selectivity^{22,24,25,35}, as well as the realization of ionic diodes^{19,20} and ionic transistors³⁶.

Recently, it has been shown that local charge inversion can be a powerful tool to control ionic transport properties in PET nanopores³⁷. Charge inversion means that the total positive charge brought by the cations close to the surface becomes larger than the total negative surface charge on the walls^{38–41}. Charge inversion can be observed through reversal of the sign of the electrophoretic mobility of charged colloids^{42,43}. In a nanopore with negative walls, charge inversion results in switching the selectivity properties of the nanopore. While a negatively charged nanopore in contact with *e.g.*, KCl, would be cation selective, the same nanopore in contact with multivalent cations, such as Ca^{2+} , will become selective for anions. Such a selectivity switch induced through charge inversion has also been observed in protein pore OmpF⁴⁴ as well as in PET nanopores³⁷. Therefore, studying the interactions of multivalent and monovalent ions with the pore structure is crucial for gaining a better understanding of induced charge inversion.

In this article, we present a procedure to build all-atom models of PET nanopores and use it to accurately replicate experimental devices. After validation of the model, we study the dynamics of K^+ , Cl^- and Ca^{2+} ions inside the nanopore using the MD approach. The following questions are discussed: How does the PET nanopore surface affect the ratio of the current carried by K^+ , Cl^- and Ca^{2+} ions? How does Ca^{2+} interact with the charged groups of the pore walls?

2 Computational methods

In this section, the protocol to build PET nanopores is presented, along with the needed procedures for solvation/ionization, and setup of ionic conduction simulations.

The MD simulations were performed using the program NAMD⁴⁵, the post-processing analysis of the MD trajectories was performed with custom VMD⁴⁶ and MatLab⁴⁷ scripts. The protocols for the MD simulations have been described in detail before^{33,45} and are

briefly stated here. For all simulations, an integration time step of 1 fs was used. For periodic boundary conditions, full electrostatic forces were computed using the particle-mesh-Ewald method with a grid density of $1/\text{\AA}^3$ or finer. For van der Waals and electrostatic interactions in non-periodic boundary conditions, a cut-off of 12 $\text{\AA}$ with a switching function starting at 10 $\text{\AA}$ was assumed. Langevin dynamics was utilized to control system temperature. For MD simulations in the NpT ensemble, the pressure (p) was kept at 1 atm using a hybrid Nosé-Hoover Langevin piston. Force field parameters for K^+ , Cl^- , and Ca^{+2} ions were taken from the CHARMM force field⁴⁸; the TIP3P⁴⁹ model was used for water.

2.1 PET model

A PET monomer can exist as a *trans* or a *cis* isomer, depicted in Fig. 2a and 2b, respectively. Monomers connect to form polymers and terminate in carboxyl groups that are protonated at pH 4 and deprotonated at pH 7 (*cf.* Fig. 2c and 2d). Several MD models of PET polymers had already been developed^{50–52} and successfully used to study the atomic origin of PET mechanical properties^{53–55}. However, these models had been designed to describe properties of the bulk material and used force fields incompatible with explicit water models. To develop a PET model suitable for simulation of ion currents in a nanopore system, we built the PET moiety with the widely used CHARMM force field⁴⁸. This force field was employed extensively to study a variety of biomolecular channels^{29,56–58}, the limitations of the model in representing interactions with water and ions being well-known. The force field parameters for PET were obtained in analogy to previously parameterized model compounds. Topology and parameter files as well as atomic models of the *cis* and *trans* isomers are provided in Supplementary material.

In previous studies^{55,59}, PET bulk models were built using a stepwise procedure⁶⁰, where monomers are added to a growing chain confined within a periodic cell. A disadvantage of such a method is that the accessible space is reduced as the polymer grows, which can lead to residues crossing through the center of aromatic rings. To avoid this problem, we built a periodic PET bulk using a collapsing/annealing MD procedure, presented schematically in Fig. 3.

First, ten PET polymers were generated. The number of subunits for each polymer was set to 9, corresponding to the most abundant polymer length observed in amorphous PET materials⁵⁵. The initial conformation for each 9-mer was linear, the isomeric form (*cis* or *trans*) for each residue was assigned randomly, and carboxyl groups at both ends were protonated. To randomize the structure, each 9-mer was minimized for 200 steps and equilibrated for 1 ns at 1000 K. A single PET 9-mer obtained by this method is shown in Fig. 3a. Subsequently, one of the ten PET 9-mers was randomly selected, reoriented in space, and assigned to a point on a $7 \times 7 \times 5$ grid with 75 $\text{\AA}$ spacing between grid points. After that, the grid was collapsed into a $90 \text{\AA} \times 90 \text{\AA} \times 60 \text{\AA}$ rectangular box by applying forces of 5 pN towards the center of the box to each aromatic carbon atom located outside of the box. This simulation was performed at 1000 K to avoid folding of the 9-mers when they were moving toward the rectangular region. The collapsing grid at 0, 0.4, 0.7 and 2 ns is shown in Fig. 3b, 3c, 3d and 3e, respectively. The collapsed structure was placed within a periodic cell of dimension $120 \text{\AA} \times 120 \text{\AA} \times 90 \text{\AA}$, *i.e.*, sufficiently large to avoid contacts among periodic images, as shown in Fig. 3g. To obtain homogeneous density, the PET structure was annealed in the NpT ensemble. First, the PET cell was simulated for 5 ns at 1000 K. At this temperature, the PET structure is a fluid and fills the entire cell volume. Snapshots of that simulation after 1 and 5 ns are shown in Fig. 3h and 3i, respectively. After that, the temperature was gradually reduced to 400 K, with a cooling step of 0.2 ns per -100 K. The annealing cycle finished with 5 ns of equilibration at 300 K. The resulting amorphous PET is shown in Fig. 3j, the periodic cell having a dimension of $107 \text{\AA} \times 84 \text{\AA} \times 64 \text{\AA}$.

A nanopore was molded into the PET material by defining a conical pore geometry⁸, according to

$$x^2 + y^2 = \left[\left(z + \frac{h}{2} \right) \tan \theta + R_{\min} \right]^2, \quad -\frac{h}{2} \leq z \leq \frac{h}{2} \quad (1)$$

Here, θ is the angle between nanopore wall and pore axis, h is the height of the pore and $R_{\min}$ is the minimum radius of the cone. Through deletion of residues, a pore was created with $R_{\min}=16 \text{ \AA}$, $h=105 \text{ \AA}$, $\theta=3^\circ$. The height of the pore was achieved through replication of the bulk structure unit cell, followed by deletion of residues above $z = h/2$ and below $z = -h/2$. Protonated carboxyl groups were added to all polymer terminals.

Deletion of residues cut some of the 9-mers into smaller segments. To prevent that small segments would be released from the nanopore surface, polymers with a length of three subunits or less were removed. To relax the surface while preserving the optimal geometry, a force of 1 pN guided non-terminal residues entering the pore volume back into the PET bulk during 2000 steps of minimization and 1 ns of simulation. After that, the system was equilibrated in a constant volume simulation without guiding forces for 4 ns. Figure 4b shows the radius of the pore along the Z-axis after the initial cut (circles) and after surface rearrangement (squares). As it can be observed, the conical geometry is preserved during the entire procedure. The narrowest pore region has a radius of 1 nm, resembling the smallest nanopores that can be manufactured by track-etching⁶².

2.2 Ionic current simulations

Simulations of ionic currents closely follow protocols used in earlier MD studies^{29,33,45,56–58}. The PET nanopore was solvated in a rectangular water box using the *Solvate* plugin of VMD⁴⁶. To allow the solvent molecules fill all small voids at the PET surface, the system was simulated for 5 ns at 300 K in the *NpT* ensemble, with the PET structure restrained using harmonic forces with a spring constant of $5 \text{ kcal/mol/\AA}^2$. Subsequently, the restraints were removed, and the system simulated further for 7 ns at 300 K in the *NpT* ensemble. The radius of the pore along the Z-axis after solvation is shown in Fig. 4b (solid line).

The solvated nanopore was used to study ionic conduction at pH 4 and pH 7. To mimic pH 7 conditions, terminal PET residues in contact with water were deprotonated, resulting in a surface charge of $-1.03 e \text{ nm}^{-2}$, which agrees well with experimental values⁶³. The system was neutralized by adding counter ions, either K^+ or Ca^{2+} , using the program *cionize*⁶⁴ that located the ions according to the electrostatic potential of the PET structure. To mimic pH 4 conditions, all carboxyl groups remained protonated. Subsequently, K^+ and Cl^- ions were randomly placed in solvent compartments, corresponding to 1 M KCl concentration. After adding ions, the systems were equilibrated at 300 K for 1 ns in the *NpT* ensemble, followed by 1 ns equilibration in the *NVT* ensemble. The final systems have periodic lattice vectors of $107 \text{ \AA} \times 84 \text{ \AA} \times 265 \text{ \AA}$.

To simulate ionic currents, a uniform electrostatic field E_Z was applied to all atoms of the system along the Z-axis. The voltage difference φ across the simulated cell is

$$\varphi = -L_z \cdot E_Z, \quad (2)$$

where L_z is the dimension of the system in the Z-direction. Table 1 presents a summary of the ion conduction simulations performed. The voltage signs are defined relative to the

lower solvent compartment which is in contact with the narrowest pore opening. A +1 V bias induces cations to move from the lower to the upper solvent compartment. To prevent the PET membranes from drifting, the benzene carbons located in a belt region of 40 Å height and 30 Å away from the pore axis were restrained by harmonic forces with a spring constant value of 1 kcal/mol/Å².

3 Results and Discussion

In this section we present and discuss the results of our simulations. First, we compare our PET bulk model with previously reported PET simulations and the expected values from experimental PET materials. Then, we report the ionic current for different pH conditions and electrolyte solution and relate the observed ionic currents to the individual ionic behavior and surface properties of the pore.

3.1 PET structure

Experimentally, single nanopores in PET are prepared by the track-etching technique described previously⁷. Briefly, PET films are irradiated with single swift heavy ions, which were accelerated to a total kinetic energy of 2.2 GeV (UNILAC, GSI Darmstadt, Germany). This irradiation process causes the formation of a single damage track through the films. It is expected that the impact of the heavy ion modifies the biaxially-oriented PET into an isotropic amorphous structure⁶⁵. Conically shaped nanopores are obtained by asymmetric etching of the irradiated foils in 9 M NaOH while the other side of the membrane is in contact with an acidic stopping medium⁶. The heavy ion irradiation and chemical etching cause formation of 1 carboxyl group per nm²⁶³.

An atomic-model of a PET nanopore should be built from amorphous bulk material, rather than from crystalline material. The procedure for building an amorphous bulk cube has been described in Computational Methods (see Fig. 3). The final step of this procedure involves an annealing cycle, shown in Fig. 5a, with 5 ns equilibration at 1000 K, cooling in 100 K steps with 0.2 ns equilibration per step, and 5 ns equilibration at room temperature (300 K).

To compare our bulk material with other PET models and experimental PET material, we analyzed three measures commonly used to characterize PET bulk properties, namely, volume density, the so-called characteristic ratio for a 9-mer, C_9 , and the glycol dihedral angle between two joint PET residues.

The density of our PET bulk model during the annealing cycle is shown in Fig. 5b. At the initiation of the annealing cycle, densities in the center (x marks) and periphery (solid line) of the bulk cube differed significantly, but both converged to a constant value, demonstrating homogeneity of the bulk material. The equilibrium density of 1.20 g cm⁻³ is in good agreement with previously reported PET models^{51,52,55} with densities of 1.28 g cm⁻³ and 1.13 g cm⁻³, but still slightly lower than the experimental value⁵³ of 1.34 g cm⁻³.

The characteristic ratio is defined as the ratio between the mean-square end-to-end length R of a polymer and the length l_i of each rigid bond within the polymer⁵¹. We calculate the characteristic ratio C_9 according to

$$C_9 = \frac{\langle R^2 \rangle}{\sum_i l_i^2}. \quad (3)$$

At 1000 K, the PET bulk behaves as a fluid and C_9 fluctuates, reaching values up to 5. As the system becomes more dense, C_9 decreases, obtaining a final value of 3.96, which is close to the experimental value of 4 and in good agreement with previously reported simulations⁵¹.

Panel 5d shows the percentage of glycol dihedral in the *trans* conformation, the *trans* angle being defined as $180^\circ \pm 20^\circ$. At the end of the annealing cycle, we obtained 39.4% of *trans* content. Here we found our largest discrepancy with previous atomistic models and experimental values that report 25% *trans*⁵⁵. The percentage of *trans* content is strongly influenced by the values of the O-C-C-O dihedral parameters. Cail *et al.*⁵⁴ have reported that for dihedrals with barrier heights of 1.40, 1.00 and 0.24 kcal mol⁻¹, the *trans* content at 541 K is 19%, 24% and 39%, respectively. The value we used was taken from the propane-1,2-diyl diacetate compound model present in CHARMM, which has a barrier height of 0.2 kcal mol⁻¹ (dihedral parameters available in Supplementary material). In order to obtain 25% *trans* content, a further refinement of this dihedral parameter would be needed.

Finally, the accuracy of the bulk model was evaluated using the pair distribution function $g(r)$. Figure 6 shows $g(r)$ for all carbon-carbon pairs. The overall shape of the curve compares well with previous studies⁵¹. The peaks observed between 1 and 4 Å describe the carbon-carbon distances defined by the connectivity within each polymer⁶⁰. The inset in Fig. 6 shows the $g(r)$ computed for carbon-carbon pairs, where each carbon belongs to a different polymer chain. The shoulder around 5 Å is related to the van der Waals contact between two carbons that are not covalently bonded.

From the PET bulk structure we built a conical PET nanopore with a minimum radius of 10 Å and 100 Å height and with a surface charge density as observed in experiments⁶³. The detailed procedure is described in Computational Methods.

3.2 Ionic currents

Previous sections presented the results from building an amorphous form of the PET polymer material and from modeling a nanopore with conical shape and surface charge density closely matching the experimentally studied systems. Following the validation of material characteristics, we used the nanopore system to study its transport properties. Table 1 lists the ionic conduction simulations that were performed under various electrolyte conditions.

As mentioned in the introduction, we employed MD simulations to obtain information about how the surface charge of the pore walls affects the ion current passing through the pore, and about how the presence of divalent cations such as Ca²⁺ changes the ionic selectivity of the pore.

We performed ten simulations, varying pH values between pH 4, where the carboxyl groups are protonated, and pH 7, where the carboxyl groups are deprotonated, also varying voltage biases between +1 V and -1 V, and choosing different Ca²⁺ concentrations. For each simulation, the instantaneous ionic currents were computed using

$$I(t) = \frac{1}{\Delta t L_z} \sum_{i=1}^N q_i [z_i(t + \Delta t) - z_i(t)], \quad (4)$$

where q_i is the charge of ion i , z_i its Z-coordinate as a function of time t , L_z is the length of the system along the Z-axis, and Δt is 1 ps. The averaged ionic currents over the last 5 ns of

each MD simulation are presented in Table 1. Individual ionic currents for each MD simulation are presented in Fig. 7.

Our simulations suggest a strong dependence of ion selectivity properties of PET nanopores on the nanopore surface charge. At pH 4, when the nanopore surface is not charged, the anionic and cationic currents are of about the same magnitude (simulations 1 and 2), as shown in Fig. 7a and Table 1. As expected, there is no ion current selectivity in a neutral nanopore. At pH 7 however, where the carboxyl groups are negatively charged, the ion current carried by K^+ is about three times larger than the current carried by Cl^- (simulations 3 and 4), as shown in Fig. 7b and Table 1. Ion selectivity is typically expressed as the ratio of the current carried by cations and the total current carried by cations and anions. The ion selectivity value of 0.79, as predicted by our simulations, agrees well with the values measured experimentally at elevated KCl concentrations^{37,66}. Due to the comparatively small volume accessible in all atom simulations, the ion concentration of 1 M KCl is chosen larger than the concentrations typically used in experimental measurements. However, experimental values of ion currents and ion selectivity have been determined at a very wide range of KCl concentrations including 1 M KCl^{37,66}. One should note that due to the required electroneutrality of the system, the number of Cl^- ions changes from 995 in simulations 1 and 2 (pH 4) to 703 in simulations 3 and 4 (pH 7). This change can account for some of the reduction in anionic current. However, the reduction in anionic current by a factor of two is larger than would be expected solely due to the changed concentration.

The pH dependence of the ion selectivity properties of the PET pore can also be seen by analyzing the concentration profiles of different ion species as a function of distance from the center of the nanopore (Fig. 8a and 8b). At pH 4, the concentrations of K^+ and Cl^- ions are practically identical, while at pH 7 there is a huge increase of the K^+ concentration, which agrees well with the observed increase of the cationic current (Table 1).

We also examined ion currents in the presence of both KCl and $CaCl_2$. In a control condition at pH 4 (simulation 5 and 6), with an uncharged surface, addition of $CaCl_2$ had little effect on the total current and the ion selectivity when compared with a pure KCl solution (simulation 1 and 2). The cationic current was simply split between K^+ and Ca^{2+} ions with a ratio roughly corresponding to their relative concentrations. The increase of the anionic current compared to the results of simulations 1 and 2 is due to the increase of the Cl^- concentration (Fig. 8c).

At pH 7, with negatively charged surfaces due to the deprotonated carboxyl groups in the system, the addition of $CaCl_2$ resulted in a more complex and interesting behavior. In simulations 7 and 8, 145 Ca^{2+} ions were added to neutralize the surface charge. In simulations 9 and 10, 291 Ca^{2+} were added, which could, in principle, saturate every carboxyl group, thereby possibly resulting in overcharging of the system walls. In all of the simulations 7–10, Ca^{2+} competed with K^+ ions for locations close to the negative carboxyl groups (see below)⁶⁷. During the simulations, most Ca^{2+} ions remained practically immobile, in contact with carboxyl groups. For the smaller number of 145 Ca^{2+} ions, indeed only a very small fraction of Ca^{2+} ions was mobile and their contribution to the total ion current was negligible, as shown in Fig. 7c and Table 1. With Ca^{2+} ions linked to carboxyl groups, the system is effectively neutralized (simulations 7 and 8). Differences between cationic and anionic currents are within the standard error of the simulations, indicating that there is no selectivity of ion current in this case.

Addition of 291 Ca^{2+} ions (simulations 9 and 10) resulted in a further change of the ionic conduction behavior. The currents carried by Cl^- are now larger than the combined K^+ and Ca^{2+} currents (Table 1 and Fig. 7d). This suggests that the nanopore in the latter system has

changed selectivity, possibly due to charge inversion in the nanopores. To analyze the reason underlying the changed ionic currents, we determined the ionic concentration profile in the pore as well as the electrostatic potential along the Z axis of the nanopore.

An analysis of the ion densities in the nanopore shows that Ca^{2+} outcompeted K^+ in the region close to the pore walls, the K^+ concentration being significantly less than in the situation without Ca^{2+} (compare Fig. 8b with 8d and 8e). However, the Ca^{2+} concentration at the pore walls increased only slightly when the overall concentration was changed from 145 to 291 ions. This indicates that the fraction of the carboxyl groups with an adsorbed Ca^{2+} did not change much for the higher Ca^{2+} concentrations, *i.e.*, the pore walls remained roughly electroneutral. But there arose an increase of the total Ca^{2+} concentration in the pore, accompanied by a corresponding increase in the amount of chloride ions. The distribution of the Cl^- ions, however, does not show any maximum in the vicinity of the position with the increased Ca^{2+} concentration. Such maximum of Cl^- concentration near the pore wall is typically indicative of charge inversion⁶⁸. Since one does not see such a maximum here, one can rule out overcharging of the nanopore walls as the cause for increased anionic currents (see Table 1). We suggest then that the slight increase of the adsorbed Ca^{2+} causes changes in the electrostatic potentials. These changes, together with the increased concentration of Cl^- ions, can explain the increased anionic current. Our results are in agreement with experimental data^{40,67} and previous modeling⁶⁹, which showed that the charge inversion and ion selectivity switch do not occur if a system contains a high concentration of monovalent cations. This effect, called *salting-out*, is explained by the competition of K^+ and Ca^{2+} ions for the negative charges at the walls. The K^+ ions concentration at the wall remains high enough so that surface overcharging does not occur.

To study how the adsorbed ions affect the electrostatic properties of the nanopore channel, we computed the electrostatic potential along the pore Z-axis, $V_{\text{system}}(Z)$. The procedure used has been described in detail before³³. Briefly, the averaged three-dimensional electrostatic potential was computed for the entire system using the *PMEpot* plugin²⁹ available in VMD⁴⁶ for the last 5 ns of each trajectory. From the three-dimensional electrostatic potentials, we extracted the electrostatic potential across the pore Z-axis at +1 V and -1 V biases, denoted as $V_{+1V}(Z)$ and $V_{-1V}(Z)$, respectively. Then, $V_{\text{system}}(Z)$ was calculated using:

$$V_{\text{system}}(Z) = \frac{V_{+1V}(Z) + V_{-1V}(Z)}{2}. \quad (5)$$

Adding $V_{+1V}(Z)$ and $V_{-1V}(Z)$ cancels out the influence of the external applied voltage biases +1 V and -1 V, leaving only the electrostatic contributions from all charged species in the system. Therefore, V_{system} describes the electrostatic potential of the system itself acting on a line coincident with the pore Z-axis.

Figure 9 shows V_{system} for all systems. There is a significant change in V_{system} at different pH conditions. At pH 4, the PET surface is not charged, there is no ion adsorption, and the resulting V_{system} is small and positive (Fig. 9a and 9c). However, at pH 7, the PET surface becomes negatively charged and in the presence of 1 M KCl, V_{system} becomes negative (Fig. 9b), which implies cation selectivity of the pore. After adding Ca^{2+} , the negatively charged surface binds the Ca^{2+} ions, V_{system} becomes positive again as shown in Fig. 9d and 9e. The reversal of the sign of V_{system} after Ca^{2+} binding suggests that charge inversion has occurred; however, we do not see selectivity for Cl^- ions, a characteristic feature of charge inversion. The absence of Cl^- selectivity can not be observed in our simulations due to the high ionic

concentration assumed; only at a sufficiently low ionic concentration would the effect of charge inversion and Cl^- selectivity arise.

4 Conclusions

In this article, we have reported the first all-atom MD simulations of PET polymer nanopores. The study presents several methodological and scientific accomplishments and opens an avenue for future research. First, we have presented a collapsing-annealing procedure to produce polymeric PET bulk structures. This procedure overcomes the difficulties identified for the growing-chain methodology⁶⁰ and can be easily used to build other polymeric bulk structures. Secondly, we have built a PET nanopore model that accurately reproduces geometry and surface charge density of the experimental systems. Third, we have built an MD model based on the CHARMM force field, which permits extension for future simulations, for instance, to study functionalized PET nanopores^{20,70}. Our all-atom MD simulations give insight into transport properties of these pores. We have described the ion dynamics inside PET nanopores immersed in KCl solution at different pH conditions, which correspond to different surface charge properties of the pore walls. Our results reproduced the cation selectivity observed at neutral pH conditions, at which the PET surface is negatively charged. Furthermore, we have calculated the ionic current carried by each ion species separately as well as the ionic distribution inside the pore. We have shown a very high affinity of Ca^{2+} ions to the surface deprotonated carboxyl groups, which is important for understanding the effect of charge inversion. Our simulations showed that mobility of Ca^{2+} ions in the pore is very low and that Ca^{2+} ions close to the carboxyl groups are practically immobile. Since our simulations were performed in the presence of a high concentration of KCl, charge inversion could not be observed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1. Atomic model of a polymer nanopore. The figure shows a polyethylene terephthalate (PET) nanopore immersed in electrolyte solution. The nanopore bulk material is shown in gray color. PET residues with deprotonated carboxyl groups are colored in purple. K^+ , Cl^- , and Ca^{2+} ions are pictured as blue, red and green beads, respectively. Water molecules are shown in white. A single PET polymer chain is highlighted, colored in cyan (carbon atoms), red (oxygen atoms), and white (hydrogen atoms).

Fig. 2. PET chemical structure. Shown are the chemical structure of a PET monomer in (a) *trans* and (b) *cis* isomeric forms. Also shown are the terminal PET monomers with (c) protonated and (d) deprotonated carboxyl groups, respectively.

Fig. 3.

Building bulk PET. The figure illustrates the collapsing/annealing procedure used to build amorphous PET. The first stage of the procedure involved collapsing a grid of PET 9-mers. (a) Model of a PET 9-mer. (b) Initial conformation of the PET grid. Ten different 9-mers were randomly located on a grid of $7 \times 7 \times 5$ points. Each 9-mer is presented in a different color. Subsequently, the grid was collapsed into a rectangular box. The snapshots at (c), (d) and (e) present the collapsing simulation after 0.4, 0.7 and 2 ns, respectively. (f) Enlarged view of the collapsed PET structure. The second stage of the procedure involved annealing the PET structure, in order to convert it into a periodic, amorphous box of homogeneous density. (g) Collapsed PET structure, colored in red, placed in a periodic box. The periodic images are colored in blue. The first step of the annealing cycle consisted of equilibration at 1000 K. Snapshots (h) and (i) show the simulation after 1 and 5 ns, respectively. The system was then cooled until reaching room temperature. The last frame of the annealing cycle is shown in (j); the PET polymers are seen to be tightly braided across the periodic cells.

Fig. 4.

Nanopore radius. Panel (a) shows a snapshot of a solvated PET nanopore. The PET structure is pictured as gray beads and water as a white surface. Panel (b) shows the radius of the PET nanopore along the Z-axis at two different stages of creation and after solvation. Circles denote the radius after the initial cut and patching of terminal residues. Squares denote the radius after rearrangement of the surface in vacuum. The solid line denotes the radius after solvation. The radius values were computed using the program HOLE⁶¹. Solid line and square symbols represent the average values over the last 2 ns of MD simulation at each stage.

Fig. 5.

Analysis of the annealing cycle for periodic bulk PET. Panel (a) shows the variation of temperature during the annealing cycle and the respective variation in density (b), characteristic ratio (c) and percentage of glycol dihedral in *trans* conformation (d). Vertical black guidelines divide each panel into three regions: the first region corresponds to 5 ns of equilibration at 1000 K, the second region to 1.2 ns when cooling from 900 K to 400 K, and the third region to 5 ns of equilibration at 300 K. In panel (b), the density values shown were computed for two cubic regions of equal volume (see text), an inner cube (x marks) and an outer cube (solid line). The inset in panel (b) shows a closer view of the density variation during cooling.

Fig. 6.

Pair distribution function, $g(r)$, of carbon-carbon pairs separated by a distance r . $g(r)$ was computed over the last 2 ns of a 5 ns MD equilibration at 300 K. The inset shows the $g(r)$ for carbon-carbon pairs, each carbon belonging to different PET 9-mers.

Fig. 7.

Instantaneous ionic currents through PET nanopores. The figure shows the ionic currents computed using Equation 4, each point representing an average over 0.5 ns. The ionic currents were calculated for each ionic species, K^+ (blue), Cl^- (red) and Ca^{2+} (green). Two different voltages are used: +1 V (positive currents) and -1 V (negative currents): (a) shows simulations 1 and 2, (b) shows simulations 3 and 4, (c) shows simulation 5 and 6, (d) shows simulations 7 and 8, (e) shows simulations 9 and 10. Simulation conditions are listed in Table 1.

Fig. 8.

Ionic concentrations as a function of radial distance from the nanopore center.

Concentrations are averaged over an 8 nm $[-40; 40 \text{ Å}]$ compartment along the Z-axis. The figures show the ion concentration inside the pores for each MD simulation at +1 V bias: (a) simulation 1, (b) simulation 3, (c) simulation 5, (d) simulation 7, (e) simulation 9. K^+ , Cl^- and Ca^{2+} concentrations are depicted in blue, red and green, respectively. Simulation conditions are listed in Table 1.

Fig. 9.

Electrostatic potential of the system $V_{system}(Z)$. $V_{system}(Z)$ is defined in Equation 5. Figures show $V_{system}(Z)$ for the systems at: (a) pH 4 and 1 M KCl, (b) pH 7 and 1 M KCl, (c) pH 4 and 1 M KCl and 145 Ca^{2+} ions, (d) pH 7 and 1 M KCl and 145 Ca^{2+} ions, (e) pH 7 and 1 M KCl and 291 Ca^{2+} ions. Lower solvent compartment, nanopore region, and upper solvent compartment are located in the intervals $[-150; 50 \text{ \AA}]$, $[-50; 50 \text{ \AA}]$, and $[50; 150 \text{ \AA}]$ along the Z axis, respectively.

Table 1

Ionic current simulations of PET nanopores. The table shows the conditions for the various simulations. The number of K^+ ions was 994 for all simulations. The number of Ca^{2+} ions in simulations 5–8 is sufficient to saturate half of the carboxyl groups, and sufficient to saturate all carboxyl groups in simulations 9 and 10. Cl^- were added in order to obtain charge neutrality in each of the simulations. MD simulations were performed under constant volume conditions. For pH 4, the simulations were performed for 10 ns (simulations 1, 2, 5 and 6); for pH 7, the simulations were performed for 20 ns (simulations 3–4 and 7–10). Averaged ionic currents and their standard error were calculated using Equation 4 for the last 5 ns for each simulation.

Index	pH	ϕ (V)	Ca^{2+} (# ions)	Cl^- (# ions)	K^+ current (nA)	Cl^- current (nA)	Ca^{2+} current (nA)	Total current (nA)
1	4	+1	0	994	2.02 ± 0.19	1.79 ± 0.18	0	3.81
2	4	-1	0	994	-1.60 ± 0.18	-1.85 ± 0.18	0	-3.45
3	7	+1	0	703	3.09 ± 0.17	0.83 ± 0.15	0	3.92
4	7	-1	0	703	-3.09 ± 0.17	-0.80 ± 0.15	0	-3.89
5	4	+1	145	1285	1.33 ± 0.18	2.24 ± 0.21	0.50 ± 0.08	4.07
6	4	-1	145	1285	-1.34 ± 0.18	-2.27 ± 0.21	-0.42 ± 0.08	-4.03
7	7	+1	145	995	1.62 ± 0.18	1.44 ± 0.18	0.06 ± 0.07	3.12
8	7	-1	145	995	-1.70 ± 0.18	-1.56 ± 0.18	-0.05 ± 0.07	-3.31
9	7	+1	291	1286	1.24 ± 0.18	1.98 ± 0.21	0.12 ± 0.10	3.34
10	7	-1	291	1286	-1.04 ± 0.18	-1.71 ± 0.21	-0.22 ± 0.10	-2.97