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Ion hydration in nanopores and the molecular basis of selectivity

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Abstract

Using a simple model, it is shown that the cost of constraining a hydrated potassium ion inside a narrow pore is smaller than the cost of constraining hydrated sodium or lithium ions in pores of radius around 1.5 Å. The opposite is true for pores of radius around 2.5 Å. The reason for the selectivity in the first region is that the potassium ion allows for a greater distortion of its hydration shell and can therefore maintain a better coordination, and the reason for the reverse selectivity in the second region is that the smaller ions retain their hydration shells in these pores. This is relevant to the molecular basis of ion selective channels, and since this mechanism does not depend on the molecular details of the pore, it could also operate in all sorts of nanotubes.

Keywords: Selectivity to ions; Numerical simulations; Polarizability; Transferable analytical potentials

Understanding the molecular basis of physicochemical processes has always been a powerful tool for advancing the knowledge about various phenomena occurring in the aqueous phase. Being able to extract physicochemical behavior from simpler systems, behavior that would be occurring in the complex case, is always convenient. There has been a great deal of interest in understanding the molecular basis for currents of different ionic species through biological membranes since Hodgkin and Huxley [1] proposed the cell excitability model based on an electric circuit with different ionic paths. This has led to the discovery of membrane proteins that work as selective ion channels and have multiple functions in the biological cell. The high selectivity these proteins have for particular ions is one of their most important properties and understanding its molecular basis remains a goal. Several X-ray structures of these molecular arrangements have been published [2–7], leading to considerable progress in our understanding of this phenomenon. Subsequent to the determination of these structures, multiple molecular dynamics simulations have been performed [8–20], yielding some information on how the selectivity could be operating. It is now clear that there is a narrow pore that acts as the selectivity filter and it is well conserved in all reported structures [7]. Subtle differences in the interaction of the walls and the semi-hydrated ion within this passage must make the difference that, for example, leads to a greater potassium (K^+) over sodium (Na^+) current when a similar electrochemical gradient is applied to a K^+ selective channel. Biological channels are not the only pores that convey ions in an aqueous environment; nanopores made in artificial membranes have been studied recently and it has been shown that ion selectivity and rectification can occur in these simple pores [21–24]. Furthermore, numerical simulations [25–27] and experimental observations [27] have made clear that water can enter into narrow pores and cavities and that in this environment a very particular behavior of water is observed. Hence, understanding the behavior of water molecules and ions in this environment is needed for the description of ion passage.

It seems clear, from the simulations and the experimental structures showing the ions inside the narrow pore, that pore

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flexibility and the coupled passage of several ions is behind the discrimination. It is also clear that the differences in the interactions between the channel walls and Na^+ or K^+ are small; both ions have a similar behavior, which indicates that there must be subtle distinctions behind the molecular basis of selectivity. Indeed, it has been reported recently that changes in the potential between chemical groups forming the pore, and thus affecting its flexibility, alter its ionic selectivity [28]. It has also been reported that changes in the water-pore potential inside a hydrophobic nanotube alter the water behavior [25]. This poses a paradox, since interaction potentials that are not refined must be used to treat the complex macromolecular structure. These interaction potentials consequently lack polarizability in a surrounding environment with multiple charges at close distances. They also lack nonadditive effects in structures that are closely packed, and, as a result, with small three-body distances. Finally, they lack intramolecular relaxation of water in a medium with strong inhomogeneities that could easily distort the molecule. While these effects have been acknowledged as potentially relevant to accurately simulate ionic solutions [29–31] and subtle features of proteins [32,33], and some properties have only been reproduced with polarizable models [34–36], there is no compelling evidence as yet that the lack of flexibility and polarizability seriously compromises the accuracy of the results obtained from simulations with simple standard models.

With this in mind, a previous work [37] looked into the ionic selectivity of pores to Na^+ vs. K^+ using the simplest possible model, i.e., a minimalist model that would be able to discriminate between both ions. In this way, it was feasible to use very refined force fields, which adequately reproduce the subtle differences between the hydration of the ions. The model also focused where the differences matter; that is, the coordinating properties of the ions. There, it was shown that constraining a water droplet containing Na^+ or K^+ inside a narrow pore constructed with a hard wall resulted in a thermodynamic advantage for K^+ over Na^+. This counterintuitive behavior, given that the latter is smaller than the former either as a bare ion or with its hydration spheres, was due to the coordination properties of the ions. The greater flexibility of the K^+ first hydration shell produced a less costly effect of constraining the ion. These results were in agreement with the experimental observation that Na^+ channels are wider than K^+ channels [38], a fact that was in contradiction with the ‘snug fit’ model either in its original form [39] or in the more recent version [3], requiring that a different process should be thought for Na^+ selectivity. Furthermore, it has been shown that the flexibility of the molecular pore is enough to accommodate both ions [28].

Here the minimalist model is used to determine if selectivity also appears under other thermodynamic conditions, i.e., rather than squeezing a droplet in vacuo, constraining the system in a pore with density of 1.0 g/cm^3. It is now clear that constrained water can undergo a phase transition at standard temperature and pressure [40] with large fluctuations in the density of the liquid as a function of the radius of constriction, so care must be taken in the definition of the thermodynamic conditions of the system. A perturbative method is used in this work to estimate the free energy [41] that is more accurate than the method used previously [42] and will be useful to further validate the results. The idea that the flexibility of the ions hydration shells is behind ionic selectivity is tested by considering now Li^+, a smaller ion than Na^+, whose passage through K^+ channels is also less favored [38].

1. Methods

The MCDHO model potentials for water [43], for the Na^+ and K^+ ions [34] and for the Li^+ ion [35] were used. This model has proved useful in yielding an accurate description of the solvation of these ions [34,35]: the predictions of the hydration numbers and radii, and of the hydration enthalpies were in full agreement with experiment for the three ions.

The simplest system that could be found to differentiate between the ions inside a pore is as follows. The ion surrounded by 70 water molecules (including up to the third hydration shell) was placed inside a cylindrical pore, of radius R_c , built by a repulsive wall with a hard core rejection (Fig. 1). This “drop” of water has a single ion, either Na^+, K^+, or Li^+, at the center of the pore, but with the liberty to move in the plane perpendicular to the pore’s axis. This system was used in Monte Carlo simulations in order to find the structural and thermodynamical behavior of each ion.

A series of Monte Carlo simulations were done on an NVT ensemble at 298 K without periodic conditions in a pore of dimensions such that the density was kept at $\rho = 1.0$ g/cm^3. The initial pore radius was 6.75 Å, where 70 water molecules were contained at the required density. The radius was decreased to a final value of 1.00 Å in 0.25 Å size step diminutions, thus squeezing the droplet but keeping the density. The starting point for each simulation was the final configuration of the system at the previous pore radius. A very large number of configurations (1 billion) were considered for each point (radius). This number of configurations is greater than the one required to ensure a statistical sampling longer than the correlation time (70 million) as estimated [37] with the method of Flyvbjerg and Petersen [44]. In fact, in the previous work [37], there was a limit in the number of configurations used since the water droplet would

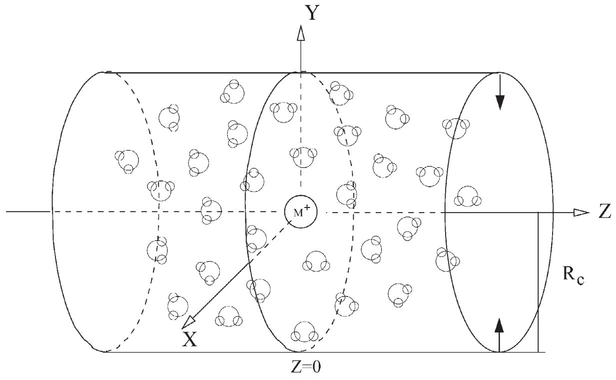

Fig. 1. Model cylinder with hard walls closed at both ends. The length was fixed to yield a density of $\rho = 1.0$ g/cm^3 for each radius and each hydrated ion.

eventually evaporate. However, all points in the series of simulations had the same number of configurations for both ions, and since the interest lies in the relative behavior between them, the partial evaporation that might occur did not pose a problem. In addition, it has been shown [45] that ions tend to keep the structural and dynamical properties of their first hydration shell intact as they are moved into the liquid–vapor interface. Since a fixed volume is used here, fragmentation of the hydrogen bond network appears at small radii as a consequence of a reduced surface tension. This was also found in the hydration of nanopores [25]. A large number of configurations is thus required to allow for proper sampling.

The last 800 million configurations were used for computing statistical properties such as the potential energy (E) and the structure functions. The Helmoltz free energy (A) was obtained using the free energy perturbation method [41] considering four λ steps of 0.1 and two of 0.05. For each step, 45 million configurations were done and the last 30 million were used to compute $\langle \mathrm{e}^{H(\lambda+\delta\lambda)-H(\lambda)}\rangle_{\lambda}$. The relative free energy was computed by converting Na^{+} into K^{+} and Na^{+} into Li^{+}.

Other average values, such as the distribution functions of the r_{OH} bond length, the HOH bond angle and the water dipole moment magnitude ($|\mu|$) for the first hydration shell were computed for the different pore radii.

2. Results

In a previous work [37] with systems of pure water and highly diluted solutions of Na^{+} and K^{+} confined within cylinders, it was shown that, as expected, the average enthalpies and free energies increased as the pore radius was decreased. A particular behavior for the pure water system was also found that consisted of a sharp decrease in the enthalpy at a pore radius of 2.75 Å. This decrement was due to the onset of a very ordered arrangement of the water molecules in a pore this size. This singularity was also reflected in the free energy, albeit reduced because of the entropic contribution of such a structured arrangement.

This behavior is now well established as a phase transition by constriction [25,40], and it also occurred in the present constant-density simulations. Even if the ion frustrated the formation of the ordered phase all along the pore, in some configurations, water in segments of the pore appeared with such an ordered structure as shown in Fig. 2. As a matter of fact, in the range of radii from 2.5 Å to 2.75 Å attaining convergence of the average properties became more difficult because more fluctuations appeared. This phase transition also occurred in simulations at constant pressure, where pressure was applied by a piston to the pore. In this case, the water density went from a low-density liquid to a high-density liquid, in agreement with the results of Zangi and Mark [40]. The density obtained from constant-pressure simulations is presented as a function of the pore radius in Fig. 3, where very large densities can be seen to occur. Hence, we decided to look into constant-density systems where the freedom to accommodate and even fragment the hydrogen bond network is something more likely to occur in short-length pores.

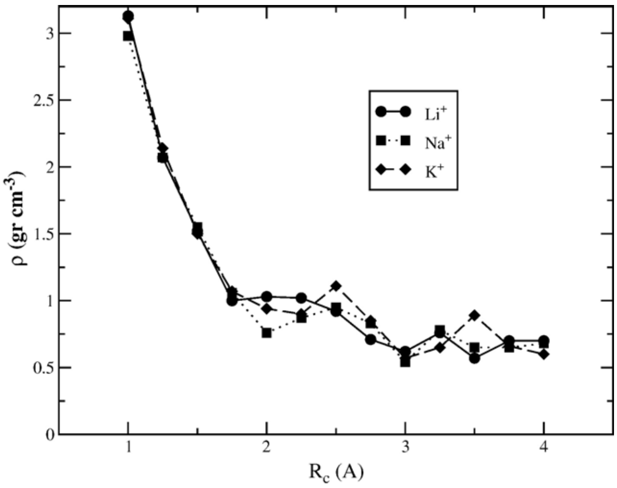

Fig. 3. Density of the hydrated ions in a system with 70 water molecules as a function of the radius of the pore. These results were obtained from simulations with the isobaric–isothermal ensemble at $T=298$ K and $p=1$ atm (=101325 Pa).

At the wider pore, the hydration enthalpies turned out to be −68 kcal/mol for K^{+}, −82 kcal/mol for Na^{+} and −109 kcal/mol for Li^{+}, that compare to −88, −98 and −128 kcal/mol, respectively, for the bulk values predicted by the same potential. It is clear that a reduction in the number of water molecules solvating the ion reduced the enthalpy in a similar manner for all ions. The difference in free energy obtained at $R_{\mathrm{c}}=6.75$ Å was 14.1 kcal/mol between Na^{+} and K^{+} and 39.5 kcal/mol between Li^{+} and K^{+}. These values compare rather well with their experimental counterparts of 17.2 and 42.4 kcal/mol, respectively [46,47]. It is worthwhile to remember that the single-ion solvation free energies are not directly accessible experimentally, whereas the differences between ions are consistently similar in different sets of data [48].

The energetic cost of constraining the ions (ΔE) was estimated by subtracting the total energy of the system at the radius of 6.75 Å from the total energy of the system at each radius. In this way, the relative cost of constraining each ion, and therefore, the selectivity of the pore, was computed from $\Delta\Delta E_{\mathrm{K-Na}}$ and from $\Delta\Delta E_{\mathrm{Li-Na}}$. These quantities are presented in the graph at the top of Fig. 4. For radii larger than 6 Å, there is no difference in the cost of constraining the ions. As the pore gets narrower, there is a clear advantage for K^{+} over Na^{+} and Li^{+}. At the onset of the region where the water ordered phase

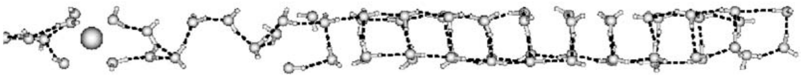

Fig. 2. A segment of the pore with $R_{\mathrm{c}}=2.5$ Å containing Na^{+} and showing the ordering of the water molecules induced by the confinement and frustration of this order by the ion.

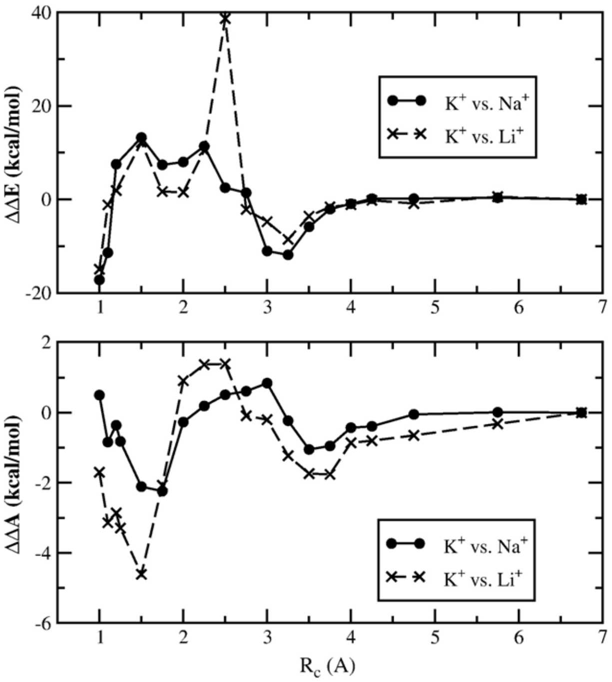

Fig. 4. Differences in the energetic cost of constraining the hydrated ions in successively narrower pores at constant density $\rho = 1.0$ g/cm^3. Top: potential energy. Bottom: free energy.

appears, there is a disadvantage for K^+, and as expected large fluctuations. Past this region, i.e., as pores become narrower, there is a selectivity for Na^+ and Li^+ over K^+, and finally, as the radius gets to 1.0 Å the pore selectivity to K^+ is recovered. There are several facts worth remarking in these results. First of all, even if not identical to the results for the squeezing of a droplet in vacuo, there is again a profile showing a counterintuitive behavior, the largest ion can be constrained into the smaller pores at a smaller cost. The relative behavior between Li^+ and K^+ mimics that between Na^+ and K^+, a pattern that agrees very well with the experimental observation that Li^+ mimics Na^+ with respect to the selectivity of the biological channels, i.e., it is as permeable as Na^+ trough the Na^+ channels and as impermeable trough the K^+ ones [38]. Also, a very interesting result is that in the range of biological channels, the smaller ones, $R_c \approx 1$ Å, are selective to K^+, whereas the larger ones, $R_c \approx 2.5$ Å, favor Na^+ and Li^+, again in very good agreement with the experimental observations.

The above results refer to the enthalpy and it is worth looking into the free energy cost of constraining the ions. In order to estimate this at each radius the relative free energy between ions was computed (ΔA). From this value the corresponding ΔA at 6.75 Å was subtracted resulting in $\Delta\Delta A_{\mathrm{K-Na}}$ and $\Delta\Delta A_{\mathrm{Li-Na}}$. These quantities are presented as a function of the pore radius in the graph at the bottom of Fig. 4. It is clear that, as expected, $\Delta\Delta A$ follows a profile similar to that of $\Delta\Delta E$, except in the region of the phase transition where fluctuations, and therefore statistical noise, are large. The $\Delta\Delta A$ profile shows again the three regions of selectivity, and now more clearly. Around $R_c = 1.5$ Å there are several pore radii where selectivity to K^+ appears. As a matter of fact some intermediate points were computed in this region in order to check that such a behavior was not fortuitous. Another interesting result is obtained from the comparison of the $\Delta\Delta A$ differences; the selectivity for K^+ seems to be greater than for Li^+ and Na^+, a finding in agreement with the experiment.

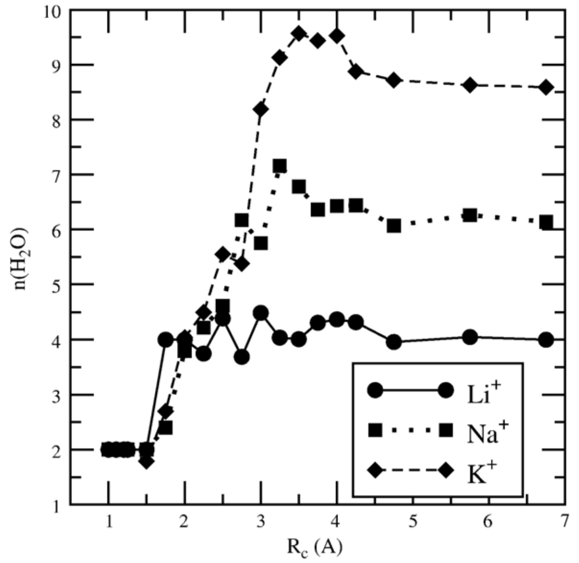

Fig. 5. Number of water molecules in the first hydration shell of the ion ($n(H_2O)$) as a function of the pore's radius.

Looking into the microscopic behavior of the hydration at the different pore radii, for the three ions, allows for an

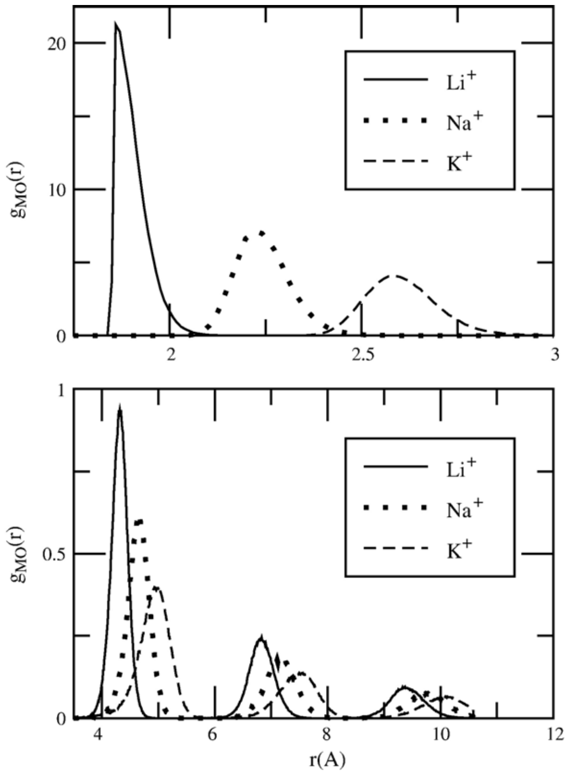

Fig. 6. Radial distribution function $g_{\mathrm{MO}}(r)$ at $R_c = 1.5$ Å. Top: from $r = 0$ Å to $r = 3$ Å. Bottom: from $r = 3.5$ Å to $r = 12$ Å.

understanding of the molecular basis of the selectivity shown. The ion–water radial distribution function (RDF) was calculated by building concentric spherical shells of width w centered on the ion and computing the average number of oxygen atoms inside them as a function of the shell radius (which is also the distance to the ion). By integrating this function up to the first minimum one gets the number of water molecules in the first hydration shell (n_{H_2O}). This is a definition equivalent to that for standard bulk values. The RDF shows clear maxima and minima for all pore radii even if excluded volume emerges as the pore narrows in this model. Fig. 5 presents the behavior of n_{H_2O} for the three ions as a function of the pore radius. It can be seen that for radii larger than 5 Å each ion has a n_{H_2O} equal to that observed in bulk [34,35]. As the pore narrows, n_{H_2O} for Li^+ fluctuates around the bulk value and then at $R_c = 1.5$ Å it switches to only two water molecules, one on each side. For Na^+, there is an increase of n_{H_2O} to 7 at $R_c = 3.25$ Å and then a continuous drop towards $n_{H_2O} = 2$ at $R_c = 1.5$ Å. For K^+ there is an increase up to $n_{H_2O} = 9.5$ with a plateau around $R_c = 4$ Å, and then a continuous decrease towards $n_{H_2O} = 2$ at $R_c = 1.5$ Å. The fact that for K^+, contrary to what could be expected, the number of neighboring waters increases considerably as the pore narrows was also encountered in the previous work [37]. At the region around $R_c = 2.5$ Å, it is clear that both Li^+ and Na^+ still have their first hydration shell complete and therefore explain their advantage over K^+. The increment of n_{H_2O} can be understood by the fact that the first hydration shell gets wider. It then becomes quite clear that constraining ions with their hydration shells into narrow pores leads to differences that are behind the observed selectivity. However, at $R_c = 1.5$ Å, all ions have two neighboring waters and the free energy clearly favors K^+, whereas the potential energy favors Na^+ and Li^+, as could be expected from a larger ion–water attractive interaction. There must be an entropic advantage when constraining K^+ in this region. This can be seen in Fig. 6 where the ion–oxygen radial distribution functions for the three ions at $R_c = 1.5$ Å are presented. It can be seen that the distribution is broad for K^+, less so for Na^+ and slender for Li^+. Further evidence of the difference in ordering can be seen in Fig. 7, where the histograms for the distribution of the number of neighboring waters at the same pore radius for the three ions are presented. It can be seen that whereas Na^+ and Li^+ have strictly two waters, K^+ has a distribution including one, two and three, hence showing more disorder.

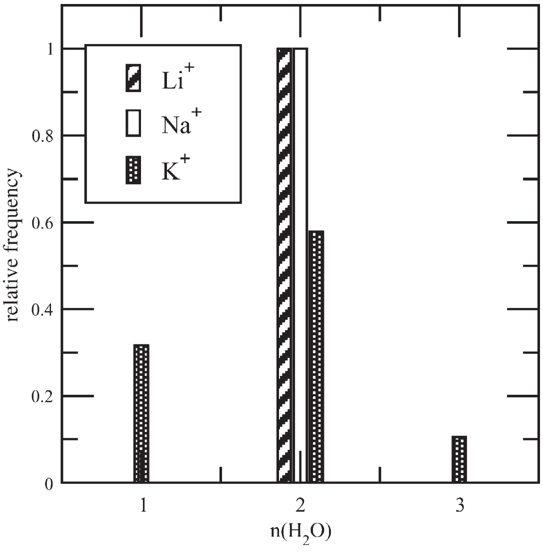

Fig. 7. Relative frequencies of the number of water molecules in the first hydration shell of each ion ($n(H_2O)$) obtained from the simulations with $R_c = 1.5$ Å.

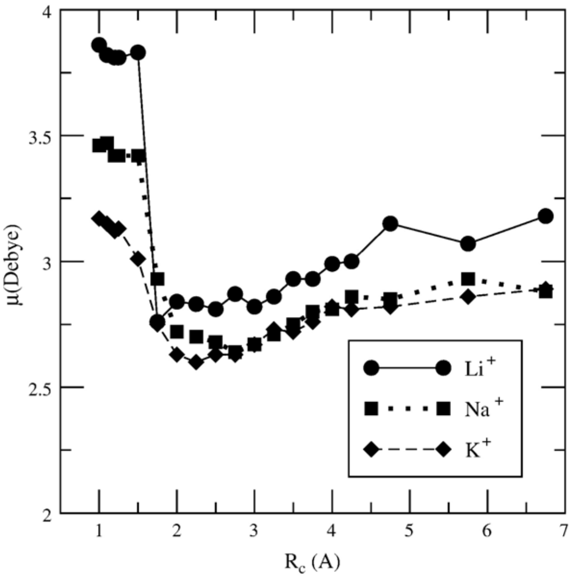

Fig. 8. Average dipole moment of the water molecules in the first hydration shells of the ions as a function of the pore's radius.

The effect that ions and constriction have on the properties of water molecules as a function of the radius of the pore for the first-neighbor waters was researched. The evolution of the water

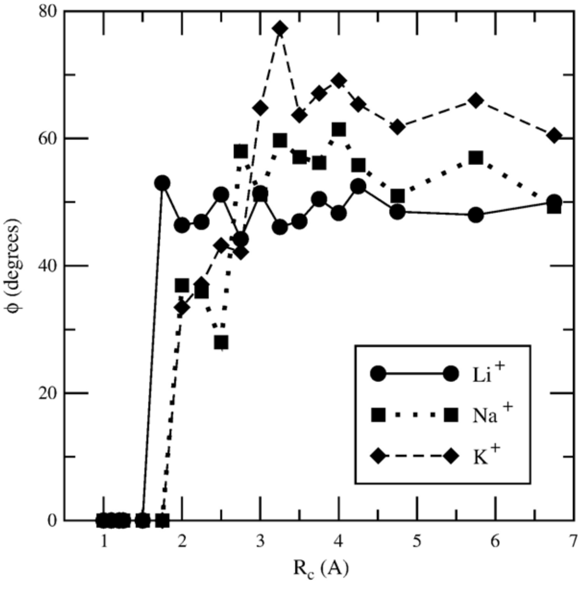

Fig. 9. Average angle between the dipole moment of the water molecules in the first hydration shells of the ions and the ion's electric field as a function of the pore's radius.

dipole moment is presented in Fig. 8. Considering that the bulk value of the model is 2.96 Debye [43,49], we can see a small reduction on the value for pores down to $R_c = 2$ Å, probably due to the reduction in solvation and, therefore, a move towards the vapor value (1.86 Debye [43]). However, for pores with smaller radii, the dipole moment presents a sharp rise, now responding to the field of the ion, being obviously more marked for Li^+. The angle (ϕ) between the water dipole and the ion field is reported in Fig. 9. Again, Li^+ keeps its bulk value all along the constriction and at $R_c = 1.75$ Å shifts to the optimal orientation. For Na^+, something similar occurs but less marked. K^+, in agreement with its more flexible hydration scheme [34], presents a dispersion of the orientation until turning towards the optimal.

Finally, the evolution of the molecular geometry of the neighboring waters as the hydrated ion is constrained is presented in Fig. 10. The HOH bond angle of water shows that for all ions the bulk value predicted by this model [43] is kept down to $R_c = 1.75$ Å where it starts decreasing. The OH bond distance (r_{O-H}) presents a bipolar behavior, similar to the dipole moment, first with a decrement and finally with an increment. It is clear that water responds to this special environment, both in its polarization and its geometry, and rises a point on the water models to be used in these conditions.

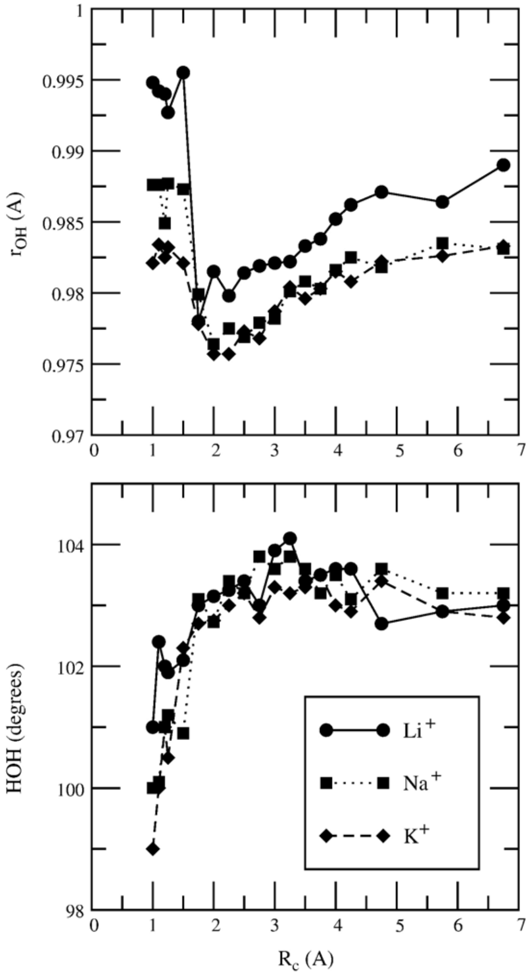

Fig. 10. Average geometric features (bond length and bond angle) of the water molecules in the first hydration shells of the ions as a function of the pore's radius.

3. Conclusions

This study was done with a potential that predicted the Li^+, Na^+ and K^+ hydration with great accuracy [34,35]. The model that was used also allowed Monte Carlo simulations with big enough sampling of the configurational space, and the minimalist system chosen was able to yield a reduced energetic cost for constraining K^+ over Na^+ and over Li^+ in a region of narrow pores. This is in agreement with a previous work on the advantage of K^+ over Na^+ [37]. The fact that Li^+, the smallest ion, is unfavored over K^+ is remarkable, but in full agreement with the experimental observations on the K^+ selectivity with respect to Li^+ and Na^+. The results show that the capability of K^+ for accommodating a distorted hydration shell leads to its advantage under a constrained environment and contributes to its selective passage through narrow pores. In this work, the selectivity to K^+ over Na^+ and Li^+ at pores with radii around 1.5 Å is confirmed, but also the reverse selectivity when the pore radius is increased at about 2.5 Å is now present. There is also a region, after the phase transition region, where K^+ is again favored, at $R_c = 3.5$ Å. This behavior is quite clear and it would be worth to search for an experimental confirmation of it.

The results also show that in these conditions the water molecules undergo changes in geometry and dipole moment with respect to bulk values, suggesting the need for the use of flexible potentials in the simulations of ion passage. Furthermore, the findings on the very peculiar properties of water under constriction [25,40] make it worth to check if such a behavior is reproduced by simpler potentials, which are commonly used in numerical simulations. This work is in progress and will be published elsewhere.

These results are relevant for biological and other pores, since the pore wall had no molecular detail, i.e., the results are due only to the relative responses of the ion–water systems to constriction. Of course the particular lining of the biological pore walls plays an important role in providing coordination sites for the ions and could add to the selectivity mechanism as well as other factors as the pore flexibility [28]. However, two recent works have presented experimental evidence that support the finding [37] that constriction by itself plays a role in the selectivity of nanopores: Vrouenraets et al. [50] have shown that pore modification of aquaporine OmpF with either charge variations or pore volume reduction affect the selectivity properties of the protein, whereas Shi et al. [51] have shown that a K^+- and Na^+-conducting channel has a selectivity pore quite similar to the KcsA channel but with a different setup of carbonyl oxygens, leading them to conclude that the electrostatic repulsion between the carbonyl oxygens is not the origin of the Na/K selectivity but that it should be due to geometrical constraints.

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