SIMULATION OF VOLTAGE-DRIVEN HYDRATED CATION TRANSPORT THROUGH NARROW TRANSMEMBRANE CHANNELS

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ABSTRACT Molecular dynamics studies for the voltage-driven transport of the alkali metal ions lithium, sodium, and potassium through gramicidin A–type channels filled with water molecules are presented. The number of water molecules in the channel is obtained from a previous study (Skerra, A., and J. Brickmann, 1987, *Biophys. J.*, 51:969–976). It is shown that the selectivity of the intrachannel ion diffusion through our model pore conforms to the experimentally observed selectivity of the gramicidin A channel. It is demonstrated that the number of water molecules in the channel plays a key role for the selectivity.

INTRODUCTION

Transmembrane transport is of special importance for all biological processes inside a living cell. In particular, the transmembrane transport of small ions, for which the lipid membrane is impermeable, plays an essential role. To provide a passageway for these ions through the lipid bilayer, a variety of integral membrane proteins and peptides exist and function as ion carriers, channels, and pumps (2). Ion transport through channels is also of great importance for signal conduction in nerve cells and is therefore of wide interest.

The gramicidin A ion channel has been subject to extended experimental studies (3–10). Gramicidin A is permeable for small univalent cations but completely impermeable for anions and polyvalent cations. Concerning the alkali metal ions, a selectivity sequence has been observed. Despite intense theoretical study, neither the molecular mechanism of ion transport nor the microscopic basis for ion selectivity is satisfactorily understood because of the complexity of the ion transport process.

The first theoretical approach done to describe the ion motion through gramicidin A used the rate theory analysis introduced by Eyring. Therein the energetics along the pathway of the ion through the channel is described as a sequence of potential barriers and minima in close analogy to a chemical reaction. From this model, kinetic equations are obtained that are fitted to the experimental results by variation of the number and heights of the potential barriers (5, 11–14). In this way the ion transport and, particularly, the role of water in the channel cannot be understood on a molecular level despite the introduction of microscopic parameters (15, 16), fluctuating potential barriers (17), or entropy effects (18) in more recent works.

A completely different approach to the understanding of the motion of hydrated ions through gramicidin A–type channels is based on the computation of energy profiles from microscopic potentials and the search for configurations associated with potential energy minima. In this respect the Monte Carlo technique is widely used. Studies were performed for the motion of the ion inside the channel in the presence (19–24) or absence of water (25, 26). However, the results obtained by this method are merely static (27) and of limited validity for the understanding of the dynamical processes involved in transmembrane ion transport.

To study the microscopic processes of ion motion, the molecular dynamics simulation technique is preferentially used (28).

In one of the first studies of this type, by Fischer et al. (29, 30), the presence of water molecules was completely neglected, and in one case the ion motion was restricted to the channel axis (29). Kappas et al. (31) considered the interactions between ions and water molecules inside the pore using an isotropic model of water; therefore, the important dipole properties were neglected. Aityan and Chizmadgev (32) merely investigated the motion of water molecules inside the channel in the absence of an ion. The molecular dynamics studies of Mackay et al. (33) and Kim et al. (34) are of special interest because they explicitly included the complete atomic structure of gramicidin A in their computations.

In a recent paper by us (1, later referred to as paper I), a microscopic model for the interior of a gramicidin A–type

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channel was presented. For this model, which is a refinement of the Fischer–Brickmann channel model (30), the water molecules in the pore are explicitly considered, and the number of water molecules accompanying the diffusion of the cation was determined. First results from this model, as the structure of the one-dimensional ionic solution in the channel, are in remarkable agreement with the findings of Mackay et al. (33) and Kim et al. (34), who both performed simulations with the complete structure of the gramicidin A dimer. However, the numerical effort for treating the ion–water dynamics in the simplified model approach is orders of magnitudes smaller than that required when treating the complete structure of gramicidin A. This allows simulations to be performed for periods on the order of nanoseconds instead of picoseconds. This advantage allows one to observe real ion transport steps in the numerical experiments.

In this study we present the results of our investigations of the mechanism of ion diffusion through narrow transmembrane channels (gramicidin A type). These investigations are based on our previous findings described in paper I. Here our interest is focused on the transport through the interior of an ion channel. As was shown in paper I this transport occurs in a quasi one-dimensional ionic solution. Here we describe how the interactions of this one-dimensional solution with the channel wall leads to a selectivity sequence in the diffusion of the Li^+, Na^+, and K^+ inside the channel.

METHODS AND MODEL APPROACH

Description of the Model

The great advantage of performing computer experiments (as opposed to real experiments) is different effects that may contribute to a particular approach can be studied independently by choosing model systems that can well mimic one effect but neglect the others. In this way one can learn step by step about the particular influences of the different effects.

The physical model on which these molecular dynamics simulations are based was already described in detail in paper I. The ion channel is represented in a simplified form by a helical arrangement of carbonyl groups according to the peptide carbonyl groups in the gramicidin channel.

We are interested in the intrachannel transport process, i.e., we completely neglect the processes of the association and dissociation of ion and channel by introducing periodic boundary conditions. Moreover, we do not consider either conformational changes of the gramicidin A channel dimer during the ion transport process or long-range electrostatic interactions with the amino acid side chains of gramicidin A or the liquid bilayer. From these model restrictions it is clear that our results cannot be directly compared with the experimental data obtained from the gramicidin A channel. Further investigations on other influences on the nondiffusion rates are in progress.

Here we chose the TIP4P model developed by Jorgensen et al. (35) as a model description for the water molecules. The ions of lithium, sodium, and potassium investigated here were represented as Lennard–Jones sphere bearing a charge of 1 e. The equations of motion were solved by the predictor corrector algorithm reported by Gear (36). To treat the rotations of the water molecules we used the quaternions introduced by Evans (37, 38) and applied the equations of motion formalism of Sonnenschein (39). The molecular dynamics simulations were performed with a time step length of $1.0 \cdot 10^{-15}$ s and a system temperature of 298 ± 10 K.

Calculation of the Permeability of Coefficients

Two different mechanisms for the ion diffusion process inside the channel must be considered.

The first one is a hopping mechanism, necessitating distinct binding positions with well defined potential minima for the ion. The ion performs thermally activated jumps between these binding sites. The duration of the hopping process is small compared with the mean time period the ion stays at one binding position. In this case the diffusion coefficient D can be calculated from the separation a of adjacent binding sites and the one-sided hopping ν frequency as follows (29):

$$D = a\nu^2.$$

If there are no binding sites for the ion or if the potential barriers are low compared with the mean kinetic energy of the ion, then we observe a continuous diffusion process. Under these conditions, Fick's laws are valid. We may then calculate the diffusion constant D from the mean square displacement $\langle x^2(t) \rangle$ with time t as:

$$D = \frac{1}{2} \frac{\langle x^2(t) \rangle}{t}.$$

Both mechanisms require much statistical data for the calculation of the diffusion coefficient. However, at room temperature with no applied field there are too few hopping events for a statistical analysis within a simulation period of 100 ps.

There are in principle two methods to enhance the ion migration rate. First, the temperature (as calculated from the average kinetic energy of the particles in the system) can be raised. Second, the ions can be driven by an external electrical field.

The first method was applied by Fischer et al. (29, 30). These authors could show that in the case of an ion without water in the channel, the high temperature diffusion data (T = 1,000 K) from the simulations can be well extrapolated to room temperature. For the present model such an extrapolation is a priori not justified. At high temperatures the water molecules would lose their dipole properties because their rotations would become much too fast.

In contrast, the use of an electrical field as a driving force for the particles is more realistic from an experimental point of view. Such fields occur in experimental investigations concerning the ion conductivity of biological membranes as well as in native systems, e.g., nerve cells. The voltages across the membranes amount to several hundred millivolts in these cases (9).

In our computer simulations the electrical field was only applied to the particles inside the pore (ion and water molecules). Since we cannot consider the polarization effects of the whole gramicidin A channel structure, it is of no use to subject the carbonyl groups to the electrical forces.

The molecular dynamics simulations were performed with a voltage of 1.0 V across the channel according to an electrical field of $4.37 \cdot 10^8$ V/m. This is the voltage at which the electrical resistance of lipid bilayers breaks down (40). In our theoretical approach this effect can be disregarded, since we explicitly ignore the properties of the lipid membrane.

Under these conditions the ion mobility is even too low for a statistical analysis of the ion transport. Therefore, we try to obtain semiquantitative measurements of the ion selectivity in the following way. We draw the position of the ion in the direction of the channel axis against the time and approximate the so obtained trajectory by a straight line applying the least square fit method of Gauss. The slope of this line gives the mean velocity v for the ion motion, which is so treated as approximately linear,

under the influence of an electrical field E. The mobility B is then calculated as follows:

$$B = v/E.$$

RESULTS AND DISCUSSION

Comparison of the Transport Mechanisms for Li^+, Na^+, and K^+

Taking the number of water molecules as a basis, which was determined in paper I, we investigated the transport mechanism of the alkali metal ions inside the pore. For this purpose zero field molecular dynamics simulations were first performed for Li^+ and Na^+ with eight water molecules each and for K^+ with seven water molecules. The trajectories for these systems are given in Figs. 1–3. From the diagrams it becomes apparent that the movements of the particles inside the pore are strongly correlated. Saltatory motions proceed through the whole row of particles. This means that the channel interior possesses a highly ordered relative structure, despite the permanent movement of all particles. This also becomes obvious in the well defined appearance of the probability density maxima, discussed in paper I.

It is obvious from the form of the trajectories that the transport mechanism of Li^+, Na^+, and K^+ shows characteristic differences for Li^+, Na^+, and K^+.

Li^+ stays at one binding position during the whole simulation period, performing oscillations with small amplitude. This behavior is due to the small ionic radius of lithium, which leads to extraordinarily strong interactions between Li^+ and the carbonyl oxygen atoms.

The simulated time period of 100 ps is not long enough to observe significant motions of Li^+. This is changed when an electrical field gradient along the channel axis is applied. Now Li^+ is forced to perform jumps in field direction (Fig. 4). Between the jumps the ion oscillates on its binding positions. This shows that Li^+ transport inside the channel definitely follows the hopping mechanism described above. It can be concluded from the observed step height that there are three binding sites per single turn of the carbonyl helix.

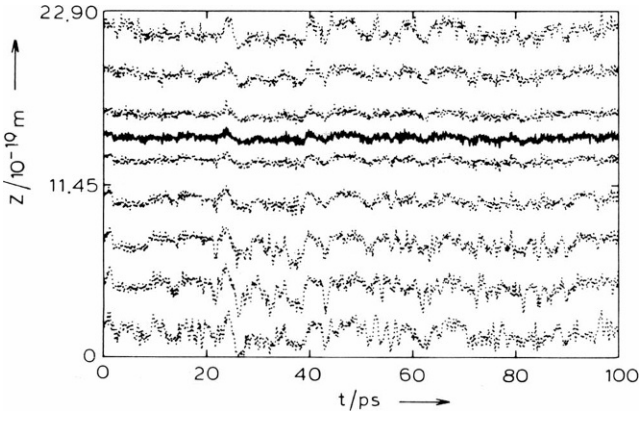

FIGURE 1 Projections onto the channel axis of the trajectories of a lithium ion and eight water molecules in the channel with no external voltage. *Solid line*, ion; *dotted line*, water molecules.

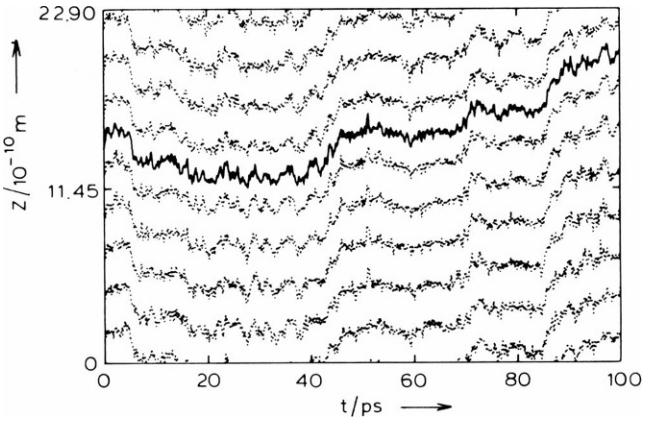

FIGURE 2 Projections of the trajectories of a sodium ion with eight water molecules (as in Fig. 1).

In contrast to Li^+, the Na^+ is quite mobile even in the absence of an external field. This is because Na^+ has a larger ionic radius than Li^+, resulting in much weaker electrostatic interactions between Na^+ and the carbonyl oxygens. The amplitude of Na^+ oscillations is considerably larger than that of Li^+. Therefore, steps can hardly be detected in the trajectory of Na^+. It is evident that Na^+ motion cannot be described as a mere hopping mechanism, but rather resembles an erratic diffusion process.

The mobility of K^+ is comparable to that of Na^+. However, the shape of the K^+ trajectory is similar to that of Li^+. Thus, K^+ moves according to a hopping mechanism. As in the case of Li^+, there are three binding sites per single turn of the carbonyl helix.

Obviously, the transport mechanism does not change continuously when passing from Li^+ to Na^+ to K^+. Whereas the trajectories of Li^+ and K^+ are in close resemblance (disregarding the greater transport rate of

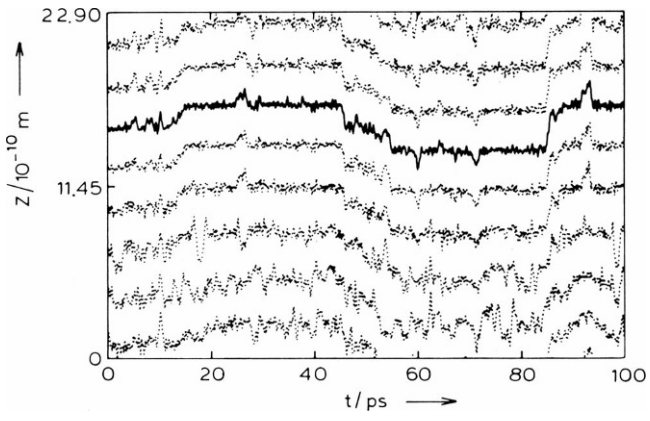

FIGURE 3 Projections of the trajectories of a potassium ion with seven water molecules (as in Fig. 1).

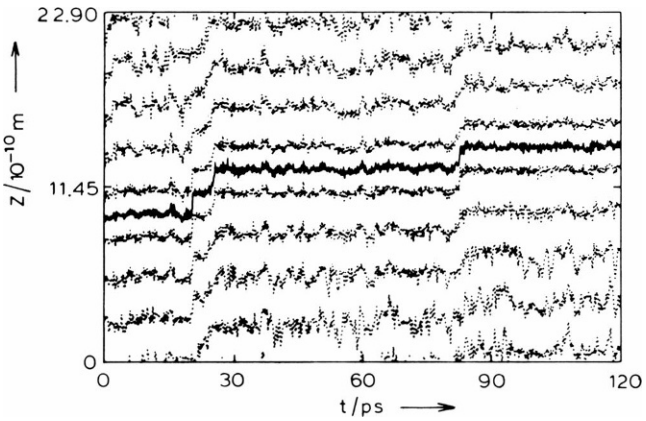

FIGURE 4 Projections of the trajectories of a lithium ion and eight water molecules (as in Fig. 1) but with an external voltage in the positive Z direction.

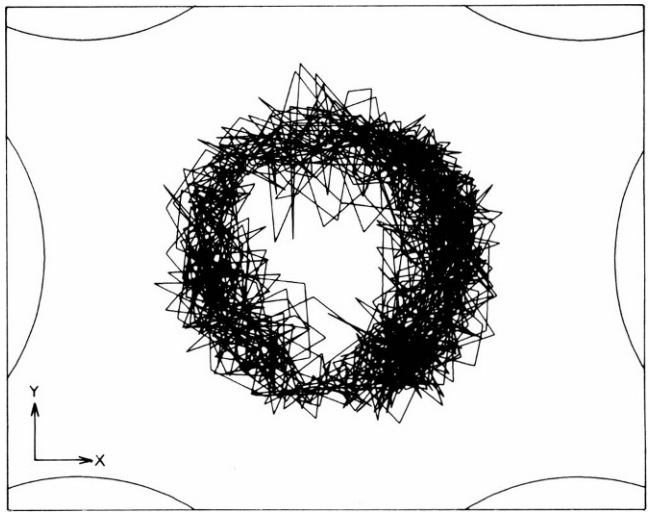

FIGURE 6 Projection of the Na^+ trajectory onto a plane perpendicular to the channel axis.

K^+), Na^+ shows an abnormally high mobility on its binding sites.

The anomalous behavior of Na^+ is further investigated by the Fast-Fourier-Transform analysis (41). Using this method we obtain a value of 73.5 cm^{-1} and 75.0 cm^{-1}, respectively, for the oscillation frequency of Li^+ and K^+. In contrast, the oscillations of Na^+ occur at a frequency of 15.2 cm^{-1}. Obviously the oscillations of Na^+ have not only a larger amplitude but also show a significantly lower frequency.

To ascertain the positions of the binding sites for the different ions, the ion trajectories projected onto a plane perpendicular to the channel axis are mapped (Figs. 5–7).

It is seen that K^+ binding sites are trigonally arranged around the channel axis (Fig. 7). The number of three binding sites per single turn is in accordance with the threefold screw axis as symmetry element of the helical arrangement of the carbonyl groups.

The binding sites of Li^+ are more pronounced than those of K^+. Due to the smaller ionic radius of Li^+ they are located further away from the channel axis. Although there is only one binding site to be seen in Fig. 5, there are three for Li^+, as is shown in Fig. 8. An important feature is that these sites are twisted about 60° against the binding sites of K^+. The different locations of the binding sites for Li^+ and K^+ also become obvious from a planar view through the channel axis in Fig. 9.

As opposed to Li^+ and K^+, the trajectory of Na^+ shows no obvious binding sites for Na^+ (Fig. 6). The trajectory runs within a circular band nearly symmetrical with respect to the channel axis. The mean distance of the Na^+ trajectory from the channel axis ranges between that observed for Li^+ and that for K^+. The analysis of the trajectory of Na^+ projected onto a plane containing the channel axis (Fig. 10) shows that there are no binding sites to be recognized either. From this figure it can be seen that

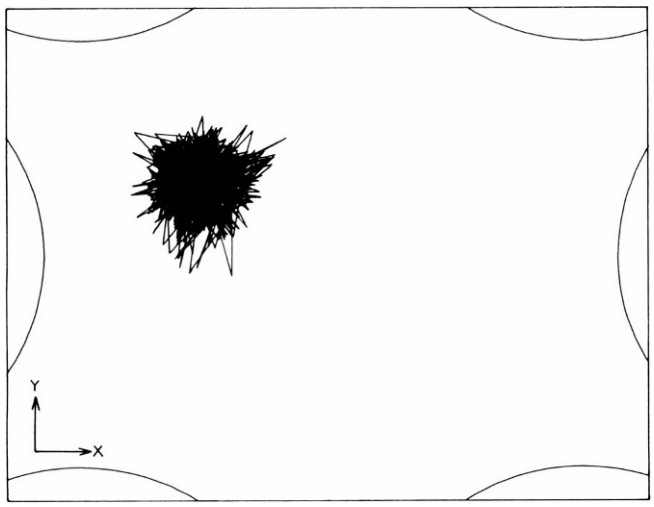

FIGURE 5 Projection of the Li^+ trajectory onto a plane perpendicular to the channel axis.

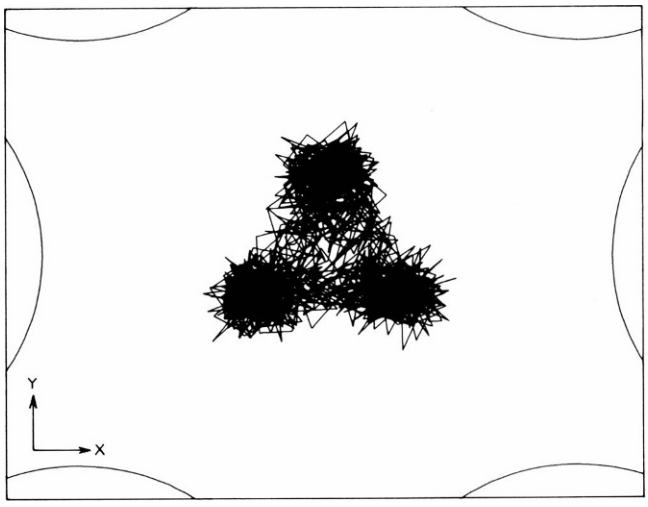

FIGURE 7 Projection of the K^+ trajectory onto a plane perpendicular to the channel axis.

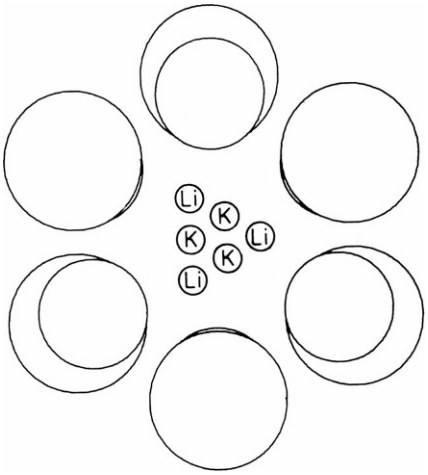

FIGURE 8 Projections of the equilibrium positions of Li^+ and K^+ onto a plane perpendicular to the channel axis.

Na^+ follows a spiral pathway around the channel axis, as was proposed by Kim and Clementi (27).

Why does Na^+ show a behavior so different from its alkali neighbors above and below it in the periodic table?

The potential minima, which do certainly exist for Na^+, are hidden by the large amplitudes of the thermal oscillations at 300 K. To circumvent this effect an additional simulation was performed with a system temperature of 100 K. The trajectories of Na^+ and eight water molecules at this temperature are shown in Fig. 11. A step mechanism for the ion movement is clearly indicated. The step height is remarkably smaller than that observed in the case of Li^+ and K^+ at 300 K. Moreover, the ion only performs jumps between the same two binding sites over the whole simulation period, which indicates that the potential barrier between these two sites is rather low.

On the basis of these observations, the following explanation for the abnormally high mobility of Na^+ can be deduced. There are two types of potential minima — three of each type per single turn of the channel helix. One type of potential minima is especially deep for Li^+, whereas it is the other type for K^+. For Na^+ both types of potential

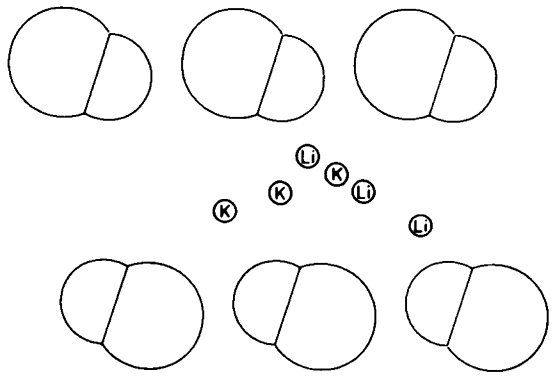

FIGURE 9 Projections of the equilibrium positions of Li^+ and K^+ onto a plane containing the channel axis.

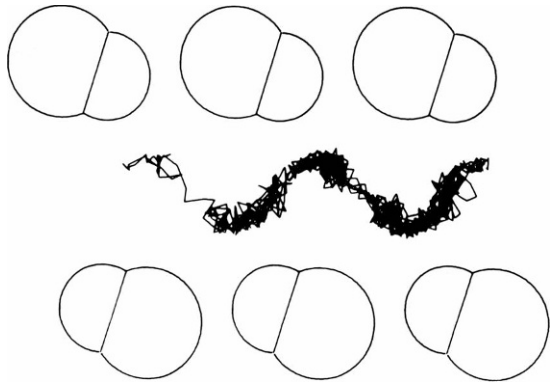

FIGURE 10 Projection of the trajectories of Na^+ onto a plane containing the channel axis.

minima are of comparable energy, leading to a double-well potential with a low barrier in between.

Selectivity of the Ion Transport Process

Molecular dynamics simulations without an external field could give insight into the relative position of quasiequilibrium sites but not the transport selectivity within the ion channel. We could observe that Li^+ is practically immobile, whereas Na^+ and K^+ exhibit a transport rate of comparable magnitude.

To obtain semiquantitative data on the relative migration rate of the ions, an electrical field was applied across the channel, as described above, and simulations were performed for a period of 120 ps. The corresponding trajectories of Li^+, Na^+, and K^+ are depicted in Fig. 12. The comparison of these trajectories with those obtained from simulations without an electrical field (Figs. 1–3) gives evidence that the transport mechanism is not significantly influenced by the applied voltage.

It becomes obvious from the trajectories shown in Fig. 12 that the transport rate increases from Li^+ to Na^+ to K^+. It is an interesting result that this selectivity sequence of the ion transport inside the pore is identical to the experi-

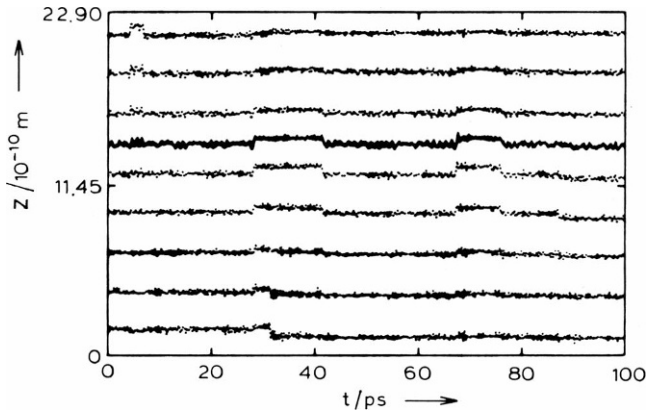

FIGURE 11 Projections of the trajectories of a sodium ion with eight water molecules at T = 100 K (as in Fig. 1).

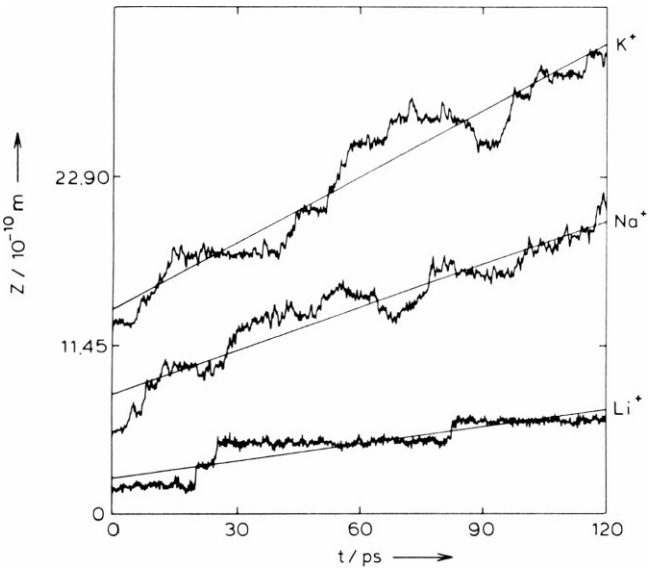

FIGURE 12 Projections of the trajectories of Li^+, Na^+, and K^+ onto the channel axis with an external field in the positive Z direction. The trajectories of the water molecules are omitted. The lines indicate the average drift positions of the ions.

mentally observed selectivity for the entire transmembrane transport process through the gramicidin A channel (4, 9, 10). The values determined for the ion mobility B, as described above, are given in Table I. They are compared with the experimentally obtained ion conductivities of gramicidin A (4, 10). Even though some authors suggest that the association between ion and channel is the rate-limiting transport step, it becomes evident that the selectivity of the ion transport inside the pore may significantly contribute to the experimentally observed selectivity of the whole transmembrane transport process.

To investigate the influence of the one-dimensional solvation structure inside the pore on the ion mobility, a molecular dynamics simulation was performed with one Na^+ and seven water molecules. As a result, we obtain a value for the transport rate that is 1.83 times higher than that determined for Na^+ and eight water molecules. Provided that the number of water molecules is the same, the ion transport rate of Na^+ becomes even larger than that of K^+.

The decrease in the transport rate when the number of water molecules inside the pore is raised is because (*a*) the mass of the moving particles is augmented, and (*b*) the number of interactions between the single file and the ion channel increases.

TABLE I
CATION MOBILITIES B IN THE GRAMICIDIN A DIMER CHANNEL

	Li^+	Na^+	K^+
$B(10^{-8}\,m^2 \cdot V^{-1} \cdot s^{-1})$	0.90	2.24	3.44
B_M/B_{Na}	0.40	1.0	1.53
M^+/Na^+ (exp.)	0.35	1.0	2.6

On the basis of the observations described above, we conclude that there are two factors that are essentially responsible for the determined transport selectivity inside the channel. The abnormally high mobility of the sodium ion leads to the higher transport rate of Na^+ relative to Li^+ and K^+, provided that the number of water molecules is identical. On the contrary, the large ionic radius of K^+ results in a decrease of water molecules in the channel. A consequence of this is that the selectivity ratio of Na^+ and K^+ is inverted.

The influence of ion size, which takes effect through the number of water molecules occupying the ion channel, was not studied explicitly until now. The results clearly indicate that effective mass and effective size of the migrating ions must be used in microscopic transport models (as the Fischer–Brickmann model [18]) when the water molecules are not explicitly being considered in the simulations.

CONCLUSIONS

Using the molecular dynamics simulation technique, we could show that there are different binding sites for Li^+, Na^+, and K^+ inside the gramicidin A ion channel. This leads to different transport mechanisms for these ions as well as an abnormally high mobility of Na^+. The high mobility of Na^+ is overcompensated by the fact that in the case of K^+ there is one less water molecule in the channel. This shows that the number of water molecules occupying the channel, which is determined by the ion size, is of essential importance for the intrachannel ion transport rate. Finally, we could show that the selectivity of the ion transport inside the pore is identical with the experimentally observed selectivity for the entire transmembrane transport process. It will be a task of future theoretical research to investigate the influence of the association and the dissociation step on the overall transport rate.

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