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Selectivity against proton in cation permeable hybrid solid state membrane

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ABSTRACT

Theoretical investigations based principally on Monte Carlo calculations were conducted to interpret the hindered mobility of protons which was experimentally observed in a hybrid biological/artificial nanopore constituted of the ion bio-channel gramicidin A confined inside an artificial solid-state nanopore. We show that this experimental outcome may result from the high concentration of gramicidin A that progressively diminishes the transfer of proton from one side to the other of the nanopore. More, using molecular dynamic simulations data we demonstrate that the water molecules are repelled from the gramicidin structure outside the nanopore, leading to a strong decrease of the proton transfer.

1. Introduction

The translocation of protons through biological channel [1] such as voltage gate proton channel is involved in bioenergetic or enzymatic processes [2]. As an example, the photosynthesis or CO_2 hydrolysis are based on long range proton transfer passing through ion channels [3–5]. Even if proton diffusion was widely investigated in the past decades, the mechanism is still not completely understood and remains under debate. More astonishing is the anomalous mobility of proton in water due to specific structural diffusion [6]. Indeed, the transport of the proton electrical charge can take place without any diffusion of atomic or molecular species since it necessitates only the chemical exchange of protons between successive hydrogen bond donor and acceptor groups. This phenomenon is well described by the so-called Grotthuss mechanism [6,7]. In this case, the hopping step consists in a proton transfer between the adjacent $(H_3O)^+$ and H_2O molecule, along the orientation of the water dipolar moment. The existence of an extended and relatively "soft" (or relatively mobile) network of hydrogen bonds is thus required to allow such a translocation leading to a long range electrical charge transfer.

In biological ion channels the nature of the water/proton selectivity is of fundamental importance. However, the kinetics of the reaction for proton diffusion is still heavily discussed, i.e. the question being whether the kinetics is governed either by the rotation of the water molecule or the proton hopping between two water molecules [8]. Thanks to its simple structure, the ion channel gramicidin A (gA) was used as a reference case to investigate proton transfer. In biological membranes, gA usually transports proton much faster than the monovalent cations. However this feature is strongly dependent on the membrane composition (typically phospholipid head groups) and the resulting structure of the water molecule sub-network, i.e. 1D chain, inside the protein channel [9,10]. The influence of the head groups has been reported by Chernyshev and Cukierman [11] who have shown that the proton transfer strongly decreases when the membrane is composed of phosphoethanolamine (PE) or is made of ceramide (NODS) [12,13]. More recently proton blockage was reported from experiments when gA proteins were confined inside a synthetic nanopore. To make it short, it was shown that this hybrid nanopore was impermeable to H^+ until pH was equal to 2 while it remained permeable to the other ions [14]. Indeed, we have shown experimentally [14] and theoretically [15] that two specific regimes could be extracted for the hybrid membrane depending on the gA concentration. At low gA concentration, the proteins are denaturated on the pore wall and a specific positive electrostatic channel due to water molecules and proteins promote the anions (i.e. Cl^-) diffusion with no selectivity for cation. At higher gA concentration, the proteins occupied the nanopore center and kept their biological helical structure while ejecting water from nanopore center. The electric properties of the hybrid membrane were inverted with a

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strong negative electrostatic potential channel near the pore center due to the β-helical gA conformation. In this configuration, cations could diffuse mainly through the inner channel of the proteins to compensate their dehydration allowing thus an ionic selectivity to appear.

The emergence of high performing computational simulations allows us to study model systems in biological environment. For instance gramicidin with high proton transfer rate or aquaporin with efficient permeation of water while excluding protons were investigated, using quantum coupled to classical simulations, in order to get insights into the proton conduction pathways [8,16]. The evaluation of the free energy profile of a proton transfer along the channel revealed the relative importance of the solvation free energy of protons combined to the Grotthuss-mechanism [17] and thus explained the blockage of protons through the aquaporin channels. The same studies were conducted on gramicidin to elucidate its high permeability to proton, depending on the organization of the confined water molecule subnetwork. It was shown that the probability for protons diffusion was directly connected to the electrostatic barrier and the relative position of the protons inside the gA [18]. Some other theoretical studies have been carried out to calculate the proton flux across gA as a function of the membrane potential. The dynamical Monte Carlo developed in Still et al. [19], led to results in accordance with the experimental ones and thus provided a possible microscopic explanation for the observed phenomenon.

The main purpose of the present work is to theoretically investigate the particular behavior of gA confined inside a synthetic cylindrical nanopore so-called hybrid nanopore. Although the simulation of the proton transfer between several adjacent water molecules can be performed using quantum mechanics based calculations, the long range proton translocation throughout the hybrid nanopore investigated here is not reasonable in terms of computer time consuming using a full quantum description. However, data such as activation barriers determined from quantum mechanics based computation on smaller systems can be used as input in Monte Carlo (MC) calculation so that computation of larger systems is made possible.

Because of the large size and complexity of the hybrid system investigated in this paper, the MC study appears to be the most convenient tool to get a deeper insight into the proton transport mechanism inside the nanopore from the gramicidin structure to interpret the experimental outcome. This will be reinforced by molecular dynamics (MD) data. The MD method used here is based on classical arguments and will give us some supplementary arguments to interpret the proton hopping blockage.

The MC calculations allow us to perform statistical determinations of proton transport through an idealized hybrid system. They only concern the mobility of protons since they do not account for the displacement of the other atoms of the system. This simplified system considers that gA helices are aligned on a rigid vertical axis and are therefore "frozen". The probabilities of proton hopping are based on the theoretical results obtained in Ref. [19] (which uses quantum mechanics) and will be discussed according to the structural informations gained from our MD results obtained on the complete confined system.

2. Theoretical methods

2.1. Monte Carlo (MC) method

In these calculations, the model system is certainly idealized compared to experiments. Indeed to complete the nanopore, all the successive gA helices adsorbed in the pore center were aligned on a same vertical axis, from one side to the other of the nanopore and were assumed to be fully filled by perfect water 1D wire. Note that we aware on the gA disorder in the nanopore, i.e. the absence of perfect alignment of the monomers. We can thus assume that the blocking of the proton transport calculated in the perfectly ordered system is even more pronounced in the disordered one. The MC model [20] was developed to take into account the two different classes of events which are related to the proton transport through the nanopore filled with several gA proteins. The first one corresponds to the elementary proton translocation between two adjacent water molecules in accordance with the Grotthuss mechanism. The probability for translocation is based on the length and the angle of the O–H···H bond. It is then strongly correlated to the organization of the water molecules sub-network, i.e. the 1D chain in our case, while it is independent on the membrane potential. The second class of events considers the long range proton transfer between two equivalent positions located in two neighboring gA [19]. This event takes into account all the paths, independently on the considered elementary process, for a protonic charge to be transferred from one gA to its neighbors. This long range transfer strongly depends on the membrane potential while it is independent on the organization of the water molecule sub-network inside the gA helix. The membrane potential difference can be viewed as an electrical field but also as any force, i.e. ionic or pH gradient, between the two reservoirs.

With this simplified model, protons can either directly access the previous or successive gA helix or be ejected to the entrance or the exit reservoirs of the nanopore as shown in Fig. 1.

2.1.1. The translocation elementary process

The protons were introduced through the first gramicidin, depending on the pH of the entrance reservoir and the membrane potential. The probability $P_{0\to1}$ (respectively $P_{1\to0}$) to uptake (respectively release) the proton from the reservoir inside the gA system is dependent on the energy barrier at the entrance (respectively exit). Several values were tested from 10 to 0 kcal/mol (simulating a "free" entrance) to reproduce the influence of pH for the proton uptake. However, one of the main outcomes of our study is that this parameter shows no influence on the overall proton diffusion process. In the following, we fixed the barrier at the entrance (exit) equals to 4.6 kcal/mol as calculated in Ref. [19]. We limited this study to incomplete protons filling of the gA and hence disregarded the formation of perfect proton wires in the system to keep at least one neutral water molecule between each proton. This seems to be reasonable if we assume that protons can rapidly reach the reservoirs.

The translocation probability based on the transition state theory was modeled by a hopping process from one stable water site k to an adjacent one $k \pm 1$ in a given gA. It depends on the energetic barrier [19] and on the temperature T according to:

$$P_{k\to k\pm1} = \frac{\exp(-\Delta E_{k\to k\pm1}/k_BT)}{\sum_0^{11}\exp(-\Delta E_{k\to k\pm1}/k_BT) + \sum_1^{11} q_{k\to k} + \sum_1^{11} q'_{k\to k}}$$

where k_B represents the Boltzmann constant, T is the temperature. The different energy barriers $\Delta E_{k\to k\pm1}$ responsible for translocation are summarized in Table A1. $q_{k\to k}$ and $q'_{k\to k}$ correspond to the long-range transport processes probabilities given in Table A2.

2.1.2. The long range transport phenomenon

The probability $Q_{k\to k}$, event number $i = 24$–34, of direct transfer across a gramicidin to the following one (or to the previous one, respectively the probability $Q'_{k\to k}$ for event number $i = 35$–45) is calculated according to values given in Table A2 [19] and depends on the membrane potential. It describes the transfer of a proton to the neighboring gA via all the existing paths in the channel and is defined as: