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Simulation of Proton Transport in the Gramicidin A Channel

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Abstract—The free energy profiles for proton transfer along the oriented water file inside the gramicidin A channel were calculated. An original implementation of the rigid-body molecular dynamics method was used for describing the peptide groups of the channel and outer water molecules. The inner water wire was simulated using the PM6 force field parameters, which adequately describe the formation and cleavage of chemical and hydrogen bonds in water molecules. Different mechanisms of proton transfer through the gramicidin A channel were considered, namely, proton H^+ translocation, transfer of the anion defect OH^-, and reorientation of the water file inside the channel. To facilitate parallel calculations of trajectories, the reaction coordinate was divided into segments, and the results were combined by the weighted histogram analysis method. The first two processes, H^+ and OH^- transfers, were shown to be barrierless. Only the stage of reorientation of the water file inside the channel has an energy barrier.

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Gramicidin A is a pentadecapeptide consisting of L and D amino acids (formyl L-Val L-Gly L-Ala D-Leu L-Ala D-Val L-Val D-Val L-Trp D-Leu L-Trp D-Leu L-Trp D-Leu L-Trp ethanolamine) forming a right-handed helix. The size of the gramicidin A molecule is insufficient to form a channel in a membrane; therefore, a transmembrane ion channel is formed by the gramicidin dimer. Due to its small size, gramicidin is a conve-

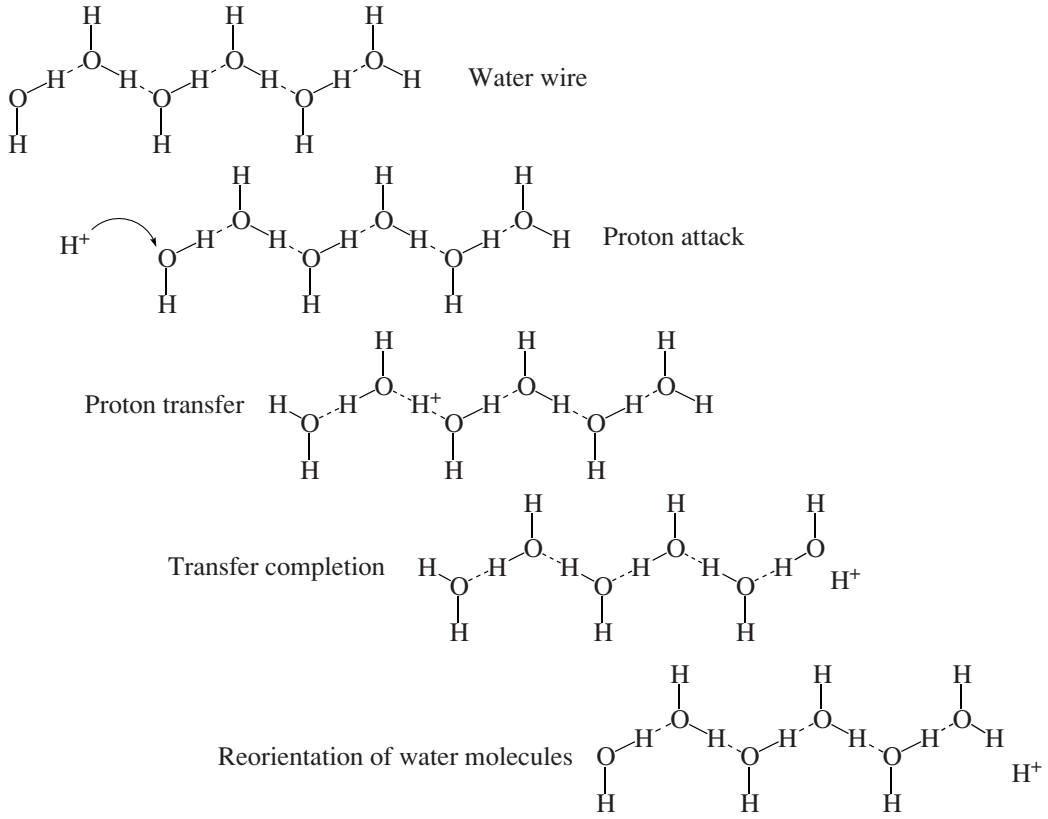

Fig. 1. Classical scheme of proton transfer along the water wire.

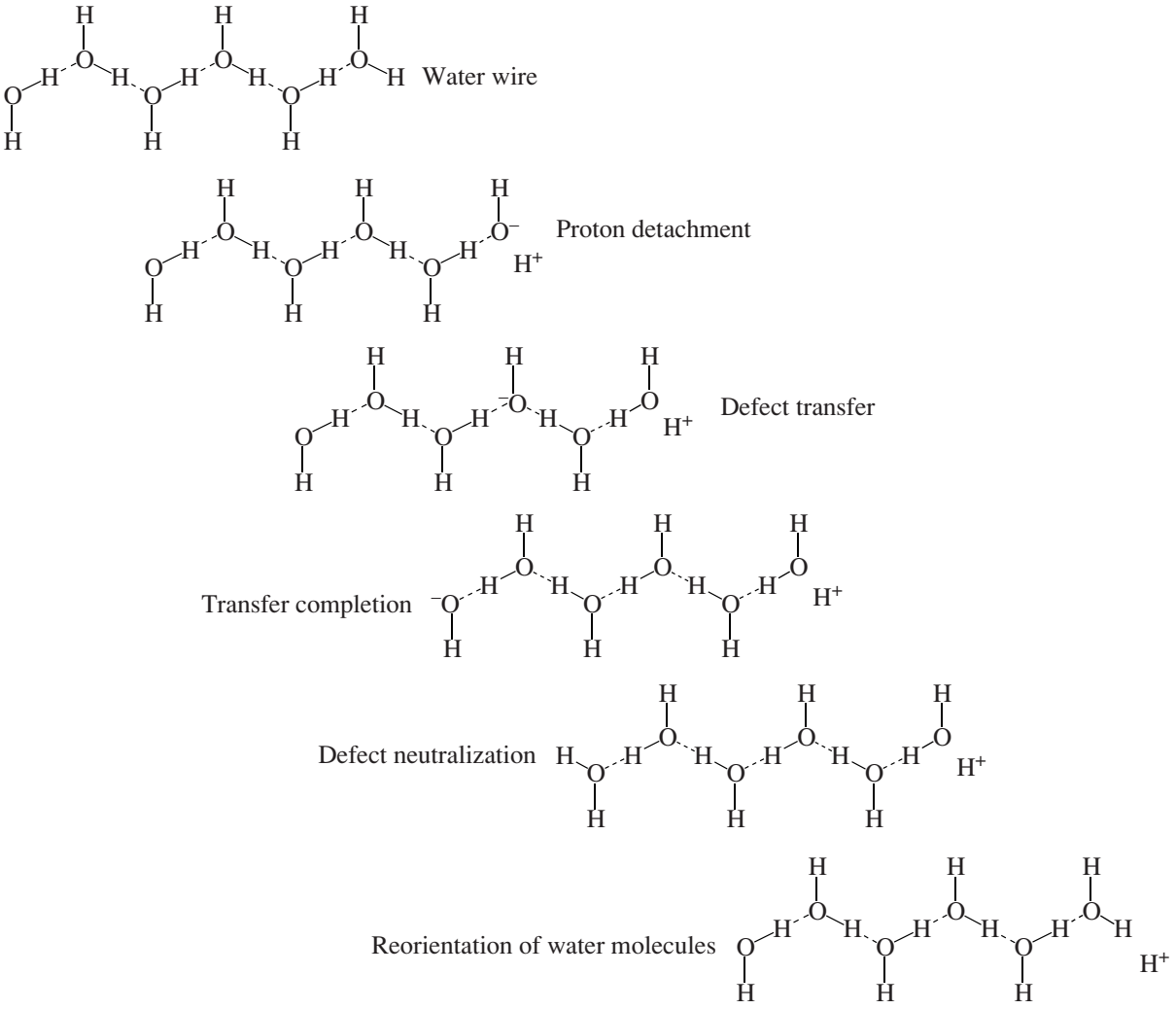

Fig. 2. Scheme of anion defect transfer.

nient system for simulation of proton transfer along oriented chains of water molecules, which are often referred to as proton wires [1–4] (Fig. 1). Notwithstanding the popularity of this model, the mechanism of water-wire proton transport remains debatable. In particular, an original scheme of proton conductance through the gramicidin channel was suggested in [5]. This scheme implies that the process can be described by the movement of the anionic defect OH^- (Fig. 2). The result of both processes is proton transfer from one end of the channel to the other. After each transfer event, the water file inside the channel must rotate to the original configuration to prepare for the next event.

In this work, we compared the calculated free energy profiles for proton transfer along the oriented water file in the gramicidin A channel assuming the existence of both proton and anion transfer. In addition, the stage of reorientation of the water file inside the channel was considered.

Figure 3 shows the molecular model used in trajectory calculations. The water file inside the channel comprises nine water molecules. At both ends of the channel, clusters of 20 water molecules (outer water molecules) are located. The channel walls are formed by peptide groups (hydrogen atoms are omitted for clarity). The starting coordinates of heavy atoms were constructed on the basis of the 1JNO structure [6] from the protein data bank.

A new implementation of the rigid-body molecular dynamics method was used for describing the motion of peptide groups of the channel and outer water molecules [7, 8]. Peptide groups are subdivided into rather small rigid fragments, and their motion in peptide chains is described by rigid-body dynamics. In this case, the channel walls are formed by 144 rigid fragments. The outer water molecules are also treated as rigid bodies. The forces acting on these rigid fragments are calculated using the CHARMM27 force field parameters [9]. The water wire with the proton or

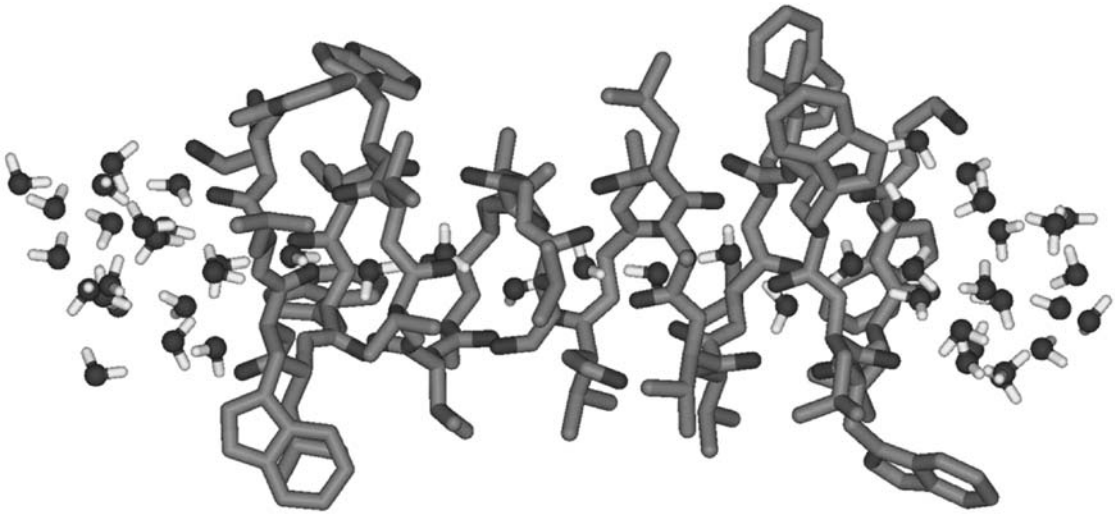

Fig. 3. Model system consisting of the gramicidin dimer (rod show only heavy atoms) with the water wire inside the channel and outer water molecules.

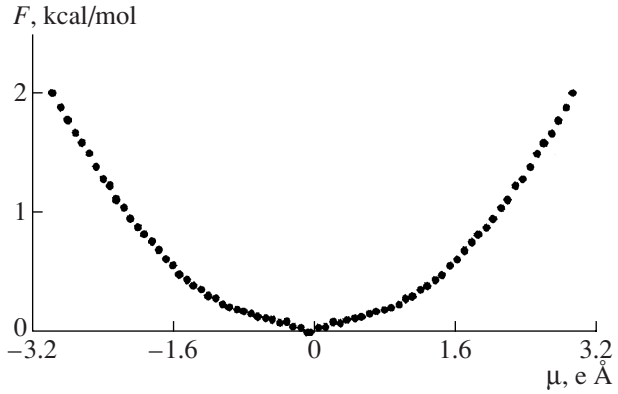

Fig. 4. Free energy profile for the proton transfer stage.

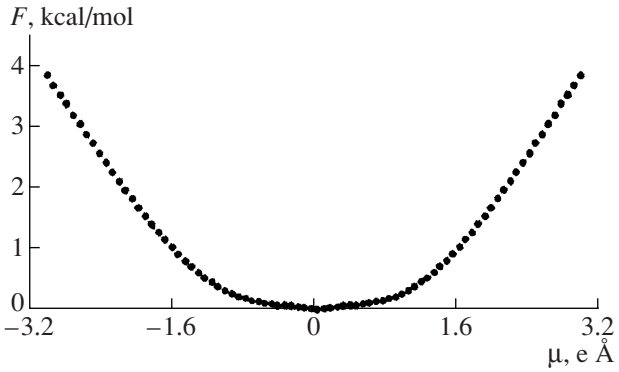

Fig. 5. Free energy profile for the OH^- transfer stage.

hydroxide anion was modeled with PM6 force field parameters [10], which makes it possible to describe cleavages and formations of chemical and hydrogen bonds in water molecules.

The integration of molecular dynamics equations was performed in the canonical (NVT) ensemble with the Nose–Poincaré thermostat [11]. The integration of equations of motion was performed using original software. As recommended in [2], the projection of the dipole moment onto the channel axis was used as the reaction coordinate. The dipole moment was calculated for the atoms of the water molecule file. Trajectories were calculated for a temperature of 300 K with an integration step of 0.5 fs. To implement the parallel trajectory calculations, the reaction coordinate was subdivided into six segments (windows) according to the umbrella sampling scheme [12]. In each window, 60000 configurations were analyzed at an interval of 2.5 fs. The results were recombined by the weighted histogram analysis method [13]. The free energy was calculated by statistical thermodynamics formulas through the probability distribution along the reaction coordinate. The computational results are shown in Figs. 4–6.

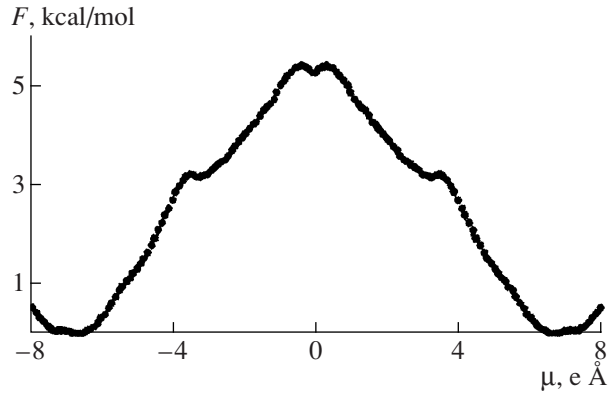

Fig. 6. Free energy profile for the water file reorientation stage.

Our calculations allow us to conclude that proton and OH^- transfers are barrierless processes. It is worth noting that the potential well corresponding to the location of a charged particle in the center of the channel is deeper for OH^- (~4 kcal/mol) than for a proton (~2 kcal/mol). The stage of reorientation of the water file inside the channel has an energy barrier, and so this stage is the rate-limiting one.

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