Artificial Water Channels

Mihail Barboiu*

Water is fundamental to life, playing a variety of functions related to its complex dynamic behavior at the supramolecular level.[1] Most of the physiological processes depend on the selective exchange of ions or molecules between a cell and its environment, with water playing a crucial role in their translocation events.[2] Artificial ion channels have been extensively studied with the hope of facilitating ionic conduction in bilayer membranes.[3] However, there has been less progress in the area of synthetic water channels.

In contrast to spherical ions, dipolar water molecules shed light on the inherent multiple interactions with biological environments through the combination of weak reversible bonds, namely hydrogen bonding, salt bridges, dipolar, and coordinative interactions. Moreover, the overall dipolar orientation of assembled water dipoles is of tremendous importance in the regulation of the selective transport of charged components across the cell membrane. For example, encapsulated water wires of opposite dipolar orientation control the electrochemical potential selectively along the aquaporin pore Aqp channel, thereby allowing the rapid diffusion of water, while protons and ions are excluded.[4] The water permeability of Aqp-incorporated polymeric vesicles has been at least an order of magnitude larger than values obtained for classical polymeric membranes.[4c] Moreover, it has been shown that about five water molecules may flow per nanosecond through carbon nanotube membranes under an osmotic gradient comparable to those measured for biological water channels.[4d] Finally, the one-dimensional water wires have attracted a lot interest, and selective proton gating is the key function of the influenza A M2 proton channel.[5] Different water clusters have been entrapped within complex superstructures. They have attracted a lot interest in terms of a variety of fundamental processes such as water structuration and also in the context of special aspects of water–cluster interactions with the host matrix or diffusional phenomena under confined conditions.[6] Despite such an impressive development, only a few artificial hydrophobic,[7] hydrophilic,[8] and hybrid amphiphilic pores[9] have been designed to selectively transport water very efficiently through bilayer membranes. Water transport across phospholipid vesicles can be monitored using optical microscopy or dynamic light scattering.[7–9] The molecular-scale hydrodynamics of water through the channel will depend on channel–water and water–water interactions as well as on the in-pore electrostatic dipolar profile of the water within the channel.

The diffusion of water and facilitated transport of protons with exclusion of the transport of other cations and anions through bilayer membranes were reported for the first time by Percec et al.[7] The dendritic dipeptides **1** (Figure 1 a) self-assemble through enhanced peripheral π stacking to form stable helical pores in bilayers. These pores, envisioned as "primitive aquaporins", transport water but do not exclude protons. The ion-exclusion phenomena are based on hydrophobic effects which appear to be very important.

Later, Barboiu and co-workers reported that imidazole (I) quartets can be mutually stabilized by inner dipolar water wires, reminiscent of G-quartets stabilized by cation templating.[8] The I-quartets are stable in solution, in the solid state, and within bilayers, leading to the tubular channel-type chiral superstructures. These systems have provided excellent reasons to consider that the supramolecular chirality of I-quartets and water-induced polarization within the channels may be strongly associated. The confined water wires, similar to the situation in aquaporin channels, form one hydrogen bond with the inner wall of the I-quartet and one hydrogen bond with an adjacent water molecule. Moreover, the water molecules adopt a unique dipolar orientation and preserve the overall electrochemical dipolar potential along the channel. These results strongly indicate that water molecules and protons can permeate the bilayer membranes through I-quartet channels. The ion-exclusion phenomena are based on dimensional steric effects, whereas hydrophobic and hydrodynamic effects appear to be less important. The water-free "off form" superstructure of the I-quartet is reminiscent of the closed conformation of the proton gate of the influenza A M2 protein.[5] The slight conformational adjustments allow formation of the water-templated I-quartet, through which protons can diffuse along a dipolar oriented water wire in the open-state pore–gate region. These artificial I-quartet superstructures obtained by using a simple chemical approach are in excellent agreement with structural X-ray and NMR spectroscopic results as well as theoretical results that might provide accurate mechanistic explanations for water/proton conductance through the influenza A M2 proton channel.

In a very recent report Hou and co-workers proposed a very elegant artificial system that functions exclusively as single-molecular water channels.[9] Polydrazide-substituted pillar[5]arenes were used to form tubular hydrogen-bonded

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[*] Dr. M. Barboiu
Adaptive Supramolecular Nanosystems Group
Institut Europeen des Membranes, ENSCM-UMII-UMR CNRS 5635
Place Eugene Bataillon CC047, 34095 Montpellier (France)
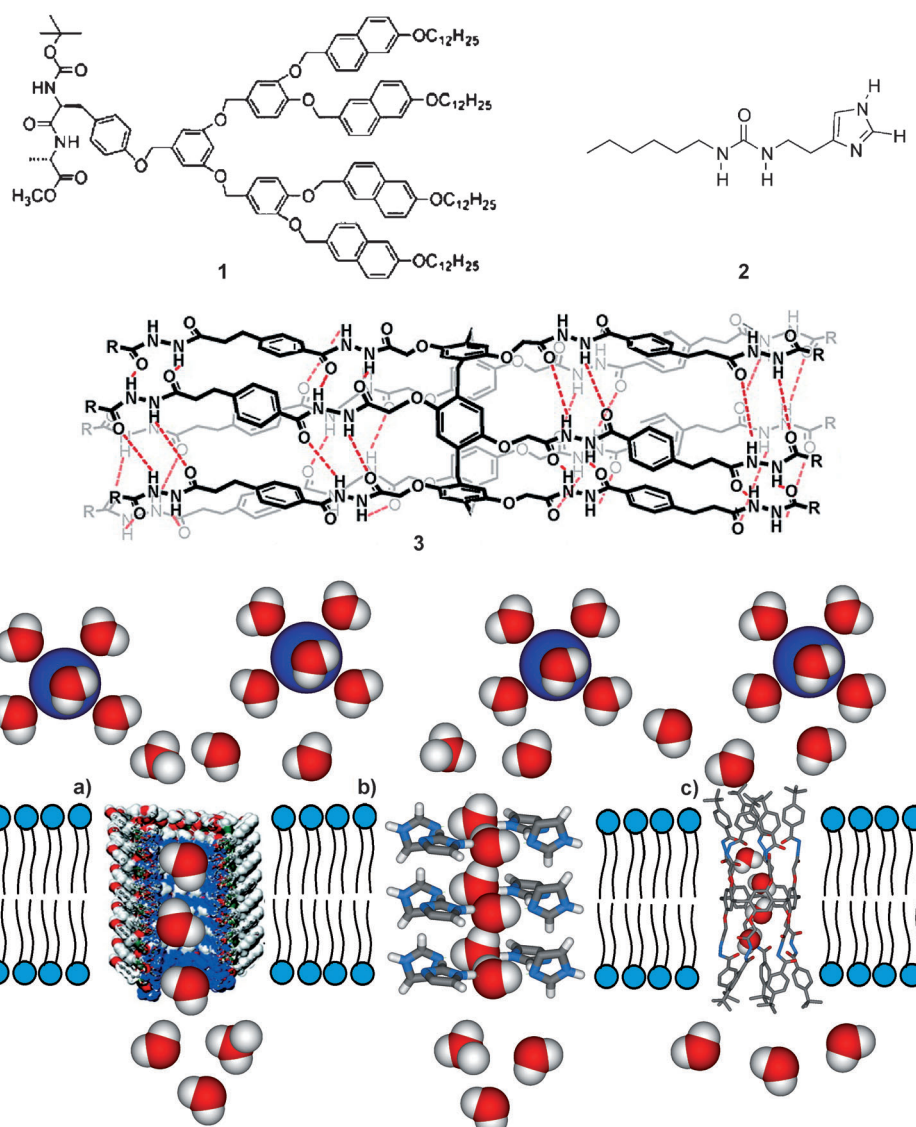E-mail: mihai.barboiu@iemm.univ-montp2.fr

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Figure 1. Water channel systems: a) Cross-section of the helical pore assembled from dendritic dipeptides **1**[7] and b) oriented dipolar water wires within a chiral supramolecular I-quartet assembled from lipophilic ureidoimidazole **2**[8] that selectively transport water and protons against ions; c) hydrazide-functionalized pillar[5]arene **3**[9] that functions exclusively as highly selective single-molecular water channels. Water molecules and protonated water molecules are represented by red and white CPK models. Violet spheres represent hydrated cations that do not penetrate the bilayer membrane.

superstructures which are robust when embedded in bilayer membranes. The water-transport mechanism is strongly dependent on the length of the tubular assemblies: the pillar[5]arene tetraester, which is the shortest in the series, induces the formation of water wires in stacked molecular cylinders, which can be used successfully to translocate protons through bilayer membranes.[10] The introduction of polyhydrazide-appended arms on the pillar[5]arene core platform results in the formation of alternative hydrophobic/hydrophilic regions which disrupt the formation of the water wires and thus block the proton flux (Figure 1c) The crystal structures show the water is hydrogen bonded and forms dimers near to the hydrophilic regions of the channel, while other disordered water molecules are evident in the hydrophobic region.[9] The medium-length hydrazide-substituted pillar[5]arene may transport water only if two molecules

are pillared in the bilayer, and the activity depends on the concentration.[10] The longest hydrazide-substituted pillar[5]-arene with a length of 3.5 nm perfectly fits the thickness of the bilayer and shows excellent activity for the transport of water and OH^- ions by a single-molecular transport mechanism.[9] Moreover, this unimolecular system, similar to the aquaporins, does not transport protons. In contrast to aquaporins, which control the water/proton selectivity on the basis of the opposite dipolar profiles of the water within the channel, the unimolecular channels control their selectivity by the disrupted water wires within the channels.

With all these factors in mind, the artificial water-channels adventure is just starting. Powerful synthetic scaffolds that mimic the natural protein functions generate water/proton translocation pathways in bilayer membranes. The ion-exclusion behaviors of all the systems presented here are

based on hydrophobic[7] or dimensional steric effects,[8–10] whereas hydrodynamic effects appear to be less important. The results on the water channel are interpreted as arising from discreet arrangements of membrane-spanning architectures, where the transport of water would occur.[8,9] The activities for water transport (3.6×10^{-5} s^{-1} [8] or 3.6×10^{-5} s^{-1} [9]) corresponding to vesicle swelling phenomena are strongly dependent on the ratio of the active water-channel component and the lipid. More importantly, the asymmetrical chiral superstructures of I-quartets can orient the dissymmetric dipolar water wires within the channels, a very important aspect for proton pumping across the membrane[8] that is probably related to the proton-gating mechanism in the influenza A M2 proton channel.[6] Finally, straightforward synthetic access to amphiphilic tubular superstructures that disrupt the formation of water wires[9] give rise to novel strategies to constitutionally build up very selective water/ proton transport devices such as those found in the aquaporins.[4] All of these examples unlock the door to the novel interactive world of water channels that parallels that of biomolecular systems.

Received: July 23, 2012
Published online: ■■ ■■, ■■■■

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Highlights

M. Barboiu* ———————— ▮▮▮▮–▮▮▮▮

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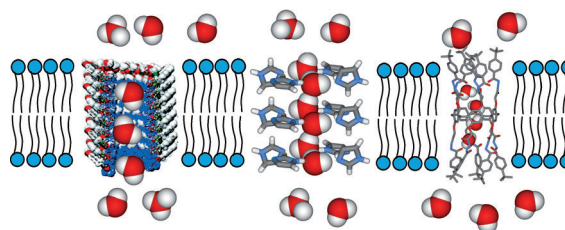
Going through the channels: Synthetic scaffolds mimicking natural protein functions have been developed that allow water/proton or only water translocation pathways in bilayer membranes (see picture). The ion-exclusion behaviors of the synthetic systems are based on hydrophobic or dimensional steric effects, while hydrodynamic effects appear to be less important.

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