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Artificial water channels—deconvolution of natural Aquaporins through synthetic design

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Artificial Water Channels (AWCs) have been developed during the last decade with the hope to construct artificial analogues of Aquaporin (AQP) proteins. Their osmotic water permeability are in the range of natural transporters, making them suitable candidates that can potentially transport water at lower energy and operating cost. Compared to AQPs, AWCs would have several potential advantages, such as improved stability, simple and scalable fabrication and higher functional density when confined in 2D membrane arrays. The first knowledge gap between AWCs and AQPs is in the mimicry of the complete set of functionality, in terms of obtaining systems capable of simultaneous water permeation and salt rejection, while not forfeiting the advantage of simplicity. Despite incipient developments, major problems still remain unsolved, such as their up-scaling preparation procedures from laboratory studies to square meters needed for large industrial membrane applications. However, the flow of structural information from molecular level through nanoscale dimensions, towards highly ordered ultradense macroscopic arrays of AWCs is conceptually possible. Successfully transitioning from synthetic molecules to functional channels and materials could lead to a new generation of membranes for water purification. Moving AWCs into products in the commercial arena is now the main objective of research in this new-born field.

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INTRODUCTION

Water scarcity and the problems associated with the lack of the clean water are well known.[1] Treated as a lack of essential resource; it is becoming increasingly urgent in the context of simultaneous growth of population and economic activities. Maintaining the demand and supply balance is foreseen to have a noteworthy impact on climate change due to production generated emissions. To address the increasing demand for water supply, several cutting edge technologies have been explored during the last decades.[2] For clean water, the most abundant source by far is represented by the Oceans, as they hold 97.5% of the total amount of water on the globe.[3] Today, about 100 million m^3/day of desalinated water is being produced, with an annual increase of more than 10%. Current technologies are based on thermal processes (multi effect desalination, MED and multi stage flash, MSF) and membrane processes (pressure driven reverse osmosis, RO; voltage driven electrodyalisis, ED; membrane distillation, MD and forward osmosis, FO), with RO being the dominant process used for seawater or brackish water desalination.[4] Energy use has dropped, but is still about twice the thermodynamic minimum. Even at maximal thermodynamic efficiency of about 60%, desalination costs are considerably higher than the costs of using fresh surface or ground water. Desalination will always be relatively expensive. Efficiency may increase in the coming years by changing the process conditions, or by changing the membranes. According to Elimelech et al.[5] the minimum energy required when operating at 60% recovery, is around 1.2 kWh/m^3 and this value increase above 1.5 kWh/m^3 at 80% recovery. Closed-circuit reverse osmosis will soon allow operating at these high recovery regimes but with higher minimum energy requirements and probably much higher effective energy requirements. The target of the future membrane is to increase both the water permeability by 3–5-folds of the currently best TFC membranes while achieving 99.9% rejection. As pointed out recently by the same in many cases selectivity matters as much if not more than permeability. There is need for membrane innovation.[6] The RO desalination, using thin-film composite membranes, has evolved over the years bringing down the costs significantly.[7] More than half of a century has passed since the first functional RO membrane was designed.[8] Despite this, the low resolution of the molecular structure and the morphological variability of the active polyamide layer are still not perfectly determined.[4,5,9] In general, this is impacting the transport mechanism and performances to separate water and ions trough the membrane. Fundamental knowledge of the material structure understanding is highly important for the up-scale of the materials from the laboratory toward membranes, modules and further process designs. New materials bearing promise for higher productivity in desalination have been developed in recent years, consequentially leading to the emerging research fields of thin-film nanocomposites[10] and biomimetic[11,12] membranes. In both cases significant performance enhancement has been achieved in comparison to traditional RO membranes.

The transport of water across the cell membrane is specifically occurring along aquaporins (AQPs), known for their high osmotic water permeability and perfect rejection of ions. These properties have inspired the incorporation of AQPs into membrane materials for the design of *bio-assisted membranes* for desalination. However

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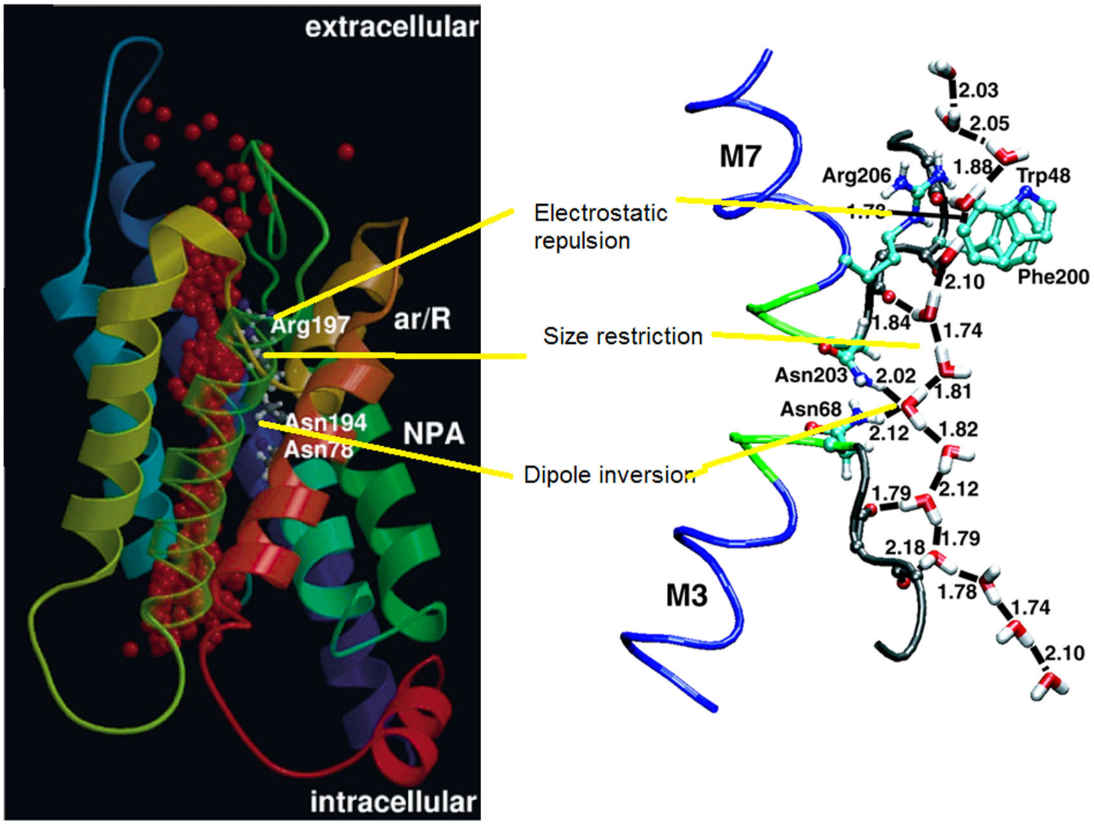

Fig. 1 Structure of the AQP pore region: highlights of key features of the water channel performances (adapted with permission from ref. [20,22], copyright Elsevier 2003 and AAAS 2002, respectively)

the large scale applications of such bio-assisted systems are still suffering from high costs of the AQPs production, low stability, and fabrication constraints of the membrane and desalination operating conditions. Artificial water channels—AWCs have been recently proposed as the *biomimetic membranes* alternatives of biological AQPs and the interest in these completely synthetic channels has considerably grown during the last years. Currently, the research on AWCs is focused mainly on the design and synthesis of novel conducting channels with improved water transport performances and solute rejection properties. Donnan steric pore and dielectric exclusion effects have to be taken into account when discussing the ion rejection capabilities of the membranes, especially when considering that it was showed that for closed geometry pores (cylinders) the dielectric exclusion is enhanced.[13]

This review article will focus on recent accomplishments on artificial water channels, the simplest synthetic biomimetic analogues, replicating the high water-channel performance of natural AQPs in lipid bilayer membranes.

INSPIRATION FROM NATURAL WATER TRANSPORTERS-AQUAPORINS

Natural systems have evolved for millions of years to adopt highly efficient functional structures.[14] Nature inspired technology is plentiful in our current society, and most of these relate to the macroscopic scale.[15] Having dug deeper into the microscopic layers, scientists became concerned with uncovering how biological machineries work, in hopes to regulate and replicate their functions. As a relevant example, the molecular features of biological pores are very important for the future design of artificial systems allowing modulation of pore functionality (e.g., pumping, gating) under ionic gradients across the lipid membrane.

Aquaporins

One representative class of these biological machineries are those of the proteins belonging to the AQP family.[16] The main function of the natural AQP is that of selectively transporting water with extreme efficiency across lipid bilayers (~10^8–10^9 water /s/ channel) with perfect rejection of ions and protons (Fig. 1).[17] An attempt to compare the permeability of a polymeric membrane incorporating aquaporin (AqpZ-ABA) was made by Kumar et al.[18] The typical RO membrane and the polymer ABA without Apq show a productivity of 2 and less than 1 µm/s/bar while the modified AqpZ-ABA exhibited a productivity of 167 µm/s/bar.[18] Indeed an improvement in membranes permeability of ~2 orders of magnitude will not yield to a decrease in energy consumption by the same factor.

Although the main role of the AQPs proteins is to transport water through the membrane of cells, only a handful of AQPs are specific water transporters, other members being able to transport small solutes such as ammonia, carbon dioxide, urea or glycerol.[19] There are several features which are important for the AQPs efficient transport mechanism:

Selectivity filter. AQPs are self-assembled from multiple subunits within trans-membrane domains.[19–22] They have an hourglass structure with a narrowest central NPA (asparagine-proline-alanine) pore of ~3 Å offering size restriction, selectivity against cations being reinforced through electrostatic repulsion by arginine residue found in the region known as the aromatic arginine (ar/R) constriction. (Fig. 1)

Water in the selectivity filter is H-bonded to the protein and to other adjacent waters, allowing the passage of only a single file of molecules. The narrowest diameter of the pore itself is large enough for the water molecules to pass having themselves a diameter of ~2.8 Å, but theoretically not restrictive enough to block the passage of dehydrated Na^+ or Mg^{2+} cations, with ionic radii of about 2 and 1.6 Å. There are two mechanisms that prohibit the passage of cations. One is related to the water-solute pair interaction. Both Na^+ and Mg^{2+} have >3 Å hydration shells in water solutions but the structure of the pore itself doesn't favor the dehydration of the cations, leaving them too large to pass through the pore.

Dipolar orientation of water wires: water/proton selectivity. An interesting collective structuration of water is taking place in the narrowest pore region of the protein, the interconnected water molecules adopting a dipole orientation outwards from the center of the pore. The point where the dipole inversion takes place is next to Asp 203 and Asp 68: here a water molecule is sitting perpendicular to the pore axis with the two aspartate moieties acting as hydrogen donors for the oxygen of this central water. This is preventing the water molecule from receiving any extra proton from adjacent molecules. Although protons can pass from one water molecule to another through a Grotthuss mechanism,[23] the inversion center breaks the water wire dipole and prohibits the proton translocation. More recent studies[24] confirm bidirectional dipolar alignment of water wires controlling the water vs. proton transport selectivity of AQPs. The conclusion is that water moves pairwise in concerted fashion through the selectivity filter. The precise dynamic clustering of four water molecules is strongly favored via donor-acceptor H-bonding, excluding other small molecules, including the hydroxide anions, as they are not able to form a stable H-bonding within the selectivity filter.

Water transport evaluation

To be able to characterize more easily the proteins in vivo functions, scientists have developed synthetic vesicles that mimic biological cells. Using simple techniques, unilamelar lipid vesicles can be created that are much less complex than the natural membranes,[25] but keep the advantages offered by a lipid bilayer barrier. In order to quantify the water transport, a scattering modulation method of a vesicle suspension is used exploiting the shrinking/swelling properties of vesicles under osmotic pressure. Synthetic vesicles are made with and without AQPs incorporated and subjected to an osmotic shock.[26] It is important to note that vesicles composed of only lipids have also a significant permeability due to the passive diffusion of water, mainly caused by the flipping motion of lipids. By comparing the permeability of the vesicles with and without AQPs inserted into the bilayer, one can determine the water transport specific to the proteins. Using this method several members of the AQP family were studied in vesicles to determine their water permeability which can be as high as 0.3 cm/s compared to the permeability of the passive water diffusion of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) vesicles which have a permeability of ~0.01 cm/s.[27]

In an effort to standardize water transport performances, vesicle osmotic water permeability values are converted into number of water molecules/channels/s. Thus the unit permeability of AQPs are in the range of 10^8–10^9 molecules of water per second.

This vesicle based water transport experiment has been generally adopted for determining the water transport capabilities of AWCs also.

BIO-ASSISTED DESALINATION TECHNOLOGIES

Due to its energy efficiency, membrane materials dominate the water purification technologies and are expected to do so in the near future.[28] The high permeability and selectivity of AQPs inspired their incorporation into membranes for desalination and water-purification. A new branch of membrane technologies for water purification called AQP biomimetic membranes (ABMs) was developed.[29] In the simplest fashion these membranes consisted of three main components: (i) AQP proteins (ii) liposomes in which the AQPs are embedded for protection, and (iii) a polymeric support. The choice for the liposomes is argued for by the fact that the AQPs are transmembrane proteins and their native environment is the hydrophobic region of the cellular membranes. As such, a first reasonable strategy was to fabricate membranes having an active barrier a lipid bilayer containing AQP for the enhanced water permeation. Freger et al. showed that the supported lipid bilayer (SLBs) membranes are suitable impermeable platforms for incorporation of AQPs for water filtration. However no steady results have been obtained with such AQP/SLBs.[30] Ding et al. demonstrated the fabrication of covalently bounded SLBs on a polymeric supports that can yield membranes with higher stability.[31] This was achieved through the covalent attachment of SLBs to a polydopamine coated porous polyethersulfone support. The covalent bonding between the bilayer and the support prevents the easy desorption of the lipid matrix, offering stability to the active layer of the membrane. Nevertheless the SLB is still prone to degradation when in contact with solutions containing detergents, which can readily disrupt the lipid bilayer. The performances of these SLB membranes are remarkable in water filtration, although the reliability of these remains an issue for long term applications and scalability. To tackle this problem a different approach was needed for the matrix hosting the AQPs. In terms of flexibility and stability the block copolymers offered a good solution. The first work by Kumar et al. presents the incorporation of a bacterial type protein AQPZ into polymeric vesicles, *polymersomes*, made of a block copolymer with poly-(2-methyloxazoline)-poly-dimethylsiloxane)-poly-(2-methyloxazoline) (PMOXA-PDMS-PMOXA) units.[18,32] It has been shown that the otherwise impermeable polymersomes undergo an increase of up to 800 times in water permeability when the AQPZ is incorporated. The activation energy for water was comparable for that obtained in the case of the native protein.

In a compromise to obtain high stability and relatively high performance biomimetic membranes, a different strategy was applied through the use of a mixed matrix approach. Zhao et al.[33] managed to trap bilayer vesicles incorporating AQPs into traditional polyamide thin films. This way the AQPs can achieve high efficiency having a basically native environment and at the same time keeping the composite membrane stable through the robustness of the polyamide matrix. The hybrid AQP-based membranes proved to be more permeable than their simple thin film composites (TFC) counterparts, meanwhile being stable for periods relevant for industrial applications.[34] However, production of AQP proteins is a non-trivial task, since biological protocols and reagents are used, as well as the purification setup still represents an expensive and time-consuming obstacle. A possible way to further improve biomimetic membranes is to replace AQPs with synthetic channels.[35]

ARTIFICIAL WATER CHANNELS

New innovative technologies are needed to tackle the increasing need of clean water. A promising strategy for this is to develop completely synthetic artificial water channels AWCs that are capable of selective water transport across a membrane barrier.[35] Using artificial systems is attractive, as they can offer increased stability, scalability and easier fabrication process than their protein counterparts. But in order to achieve similar efficiency using artificial systems, it is important that they are able to imitate the protein's key structural features and functions using a simple as possible synthetic fabrication approach. The design of the synthetic AWCs is highly versatile as their synthetic strategies can be directed towards targeted properties. Their incorporation into

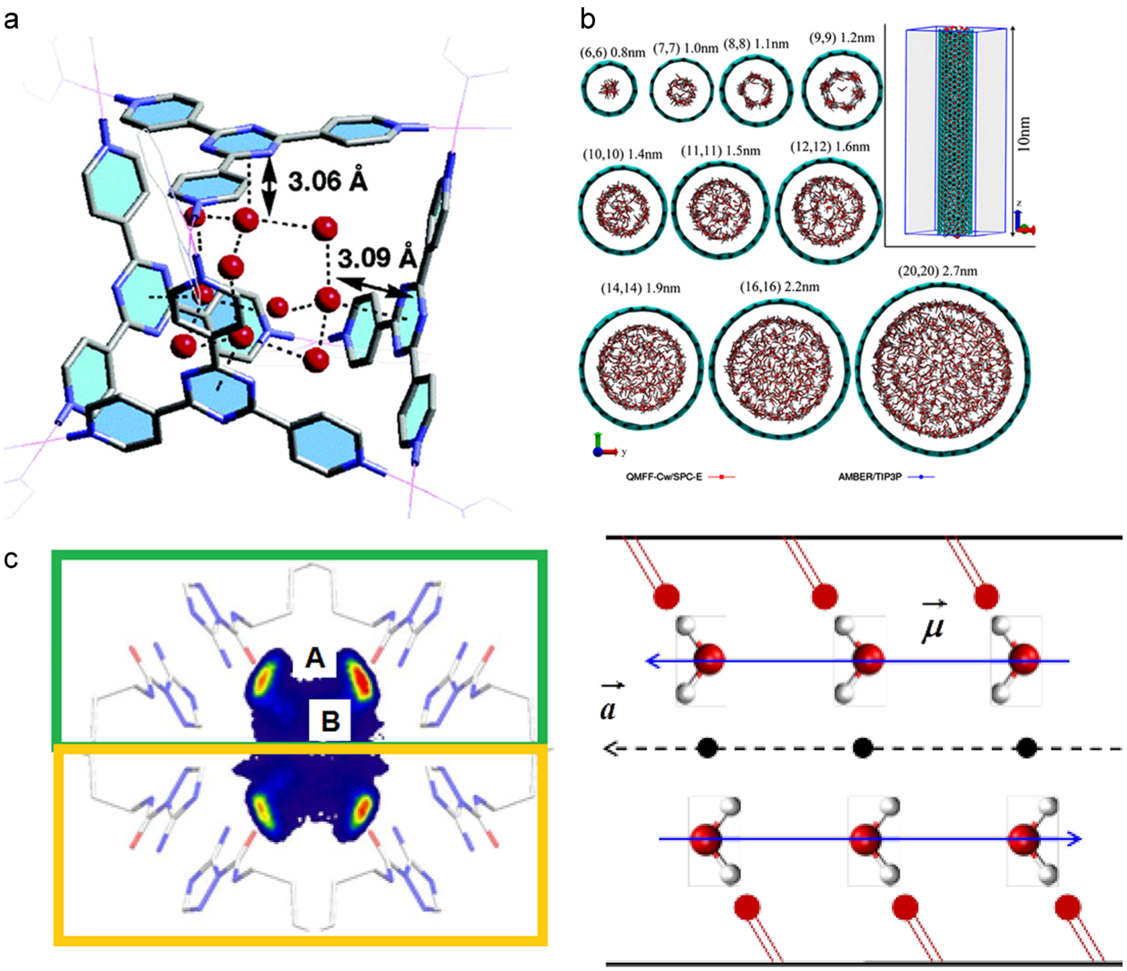

Fig. 2 **a** "Molecular ice" in the confinement of a self-assembled organometallic cage (adapted with permission from ref. 37, copyright American Chemical Society 2005) and **b** Water structuration in a 10 nm long CNT with varying pore sizes obtained through equilibrium molecular dynamics. size (adapted with permission from ref. 38, copyright Royal Society of Chemistry 2014) The radial density contour plot of dipolar oriented water molecules confined in an artificial channel (left) with calculated water molecule alignment along the walls of the channel (right) (adapted from ref. 39)

materials should be in principle more easy and reproducible as the channel structures can be adapted to be compatible with up-scale engineering methods, in contrast to biological components.

Water clusters under confinement

Molecular encapsulation, meaning the confinement of molecular species in a closed space, offers possibilities to explore the collective behaviors of water in conditions very close to confined biological water[15] or water in biology,[14] meaning the waters in interaction with natural biomolecules at the limit between solid and liquid states.[36] A water cluster is a discrete hydrogen bonded self-assembly of several molecules of water, spontaneously evolving under confined conditions, have been entrapped within complex structures providing useful information for better describing a variety of fundamental processes such as water structuration under confined conditions[37,38] (Fig. 2a, b) and dynamic diffusion phenomena (Fig. 2c).[39]

Clusters of water may also self-organize in special forms of "higher and lower density" assemblies, depending on their positions and relative interactions under confinement.[40] Among different water clusters, the one-dimensional water-wires have attracted a lot of interest with a special emphasis on their structural features similar to biological water-clusters, present inside the protein channels or cavities.[13,14] In order to make progress towards highly selective biomimetic membranes operating close to natural AQPs performance, studying the molecular interactions and the dynamic nature of water clusters under confined conditions is of tremendous importance.

Subnanometer water dynamics in carbon nanotubes

At the molecular-level, liquids can exhibit substantially different physical behaviour as compared to the classical Newtonian fluid mechanics. A rather distinctive type of synthetic porous systems, which may be considered as highly permeable water channels, are the carbon nanotubes (CNTs).

Known for their wide applications in nanotechnology, they have recently attracted more attention for applications in nanofluidic devices for translocation and separation.[41–43] With the narrowing of the pore sizes of CNTs, a new discovery was made regarding the mass-transfer behaviour across CNTs with pore sizes approaching the nanoscale. Simple diffusion or Newtonian flow doesn't apply when water cluster are broken down on entering the nanotubes (Fig. 2b). Between 1.25 and 1.39 nm the water suffers a transition from bulk phase water into solid-like organized water. Under 0.9 nm, water adopts a single file structure very similar to the one found in the AQPs. The change in structuration in the confinement of the pore causes water molecules to pass through with enhanced speed due to a boundary slip mechanism.[43,44] CNTs

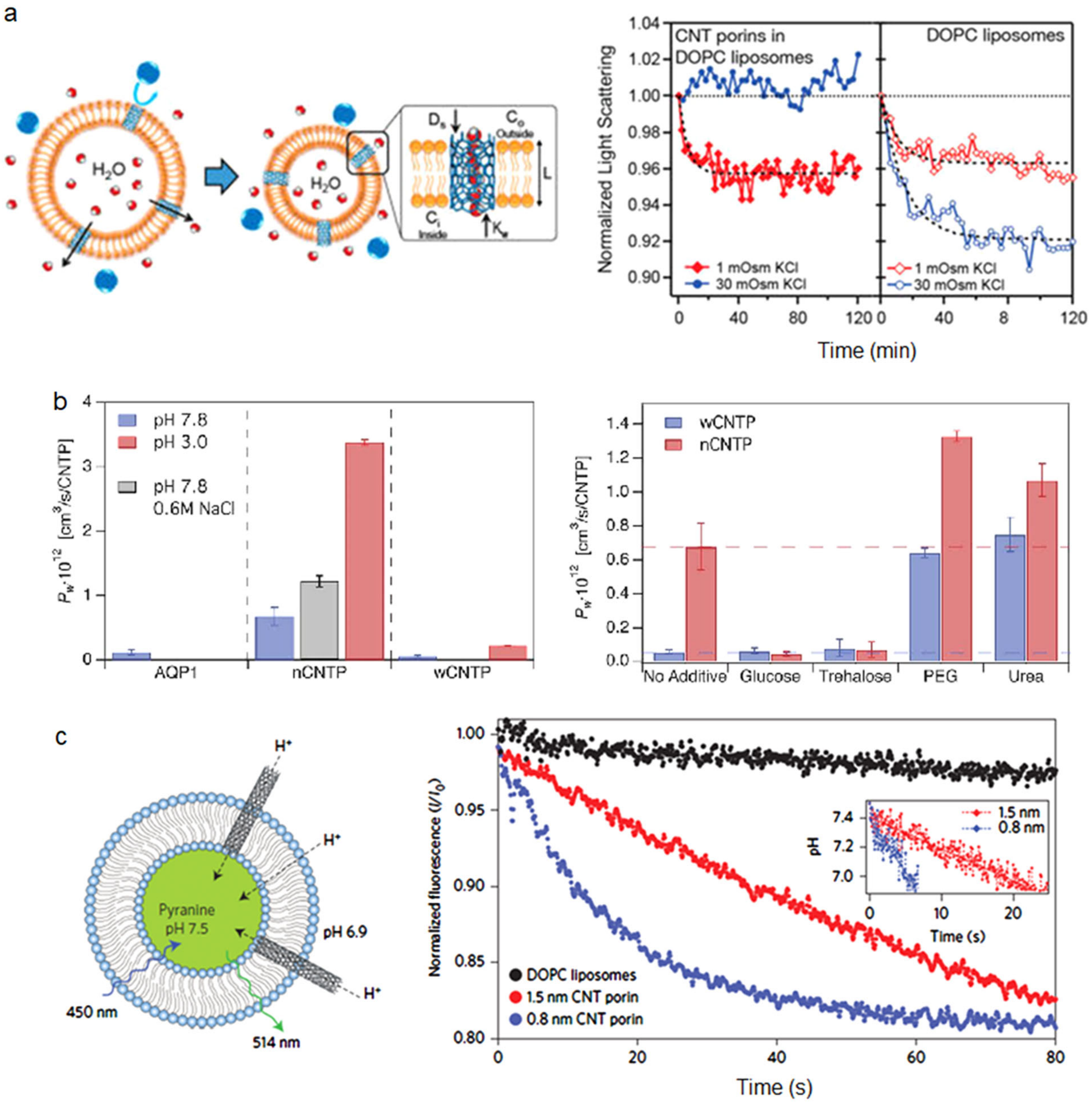

Fig. 3 **a** Water and ion transport through a 1.5 nm CNTs in bilayer membranes **b** Water permeabilities compared with AQPs and **c** proton transport through 0.8 and 1.5 nm CNTs (adapted with permission from refs. [47,49,50], copyright American Chemical Society 2014, AAAS 2017, and Springer Nature 2016, respectively)

have been proved to easily self-insert themselves into both biological and synthetic lipid bilayer membranes.[45,46] Noy et al. conducted several studies on the permeability and selectivity of subnanometric CNTs, when inserted into lipid environments.[47–50] Vesicles containing short CNTs (5–20 nm length) were prepared and it was demonstrated that the ion transport rates are strongly related to the level of ionic strength of the solutions and the hydration radii of the cations (Fig. 3a). Special behaviours towards water and proton transport were observed when the diameter of the tubes is in the range of 0.8 nm. The rate of the water transport within 0,8 nm CNTs exceeds that of biological AQP water transporters and of wider 1.5 nm CNTs by an order of magnitude (Fig. 4b).[49] Similarly, the proton transport rate is directed by the organization of the water molecules into a single-file chain, reaching values of one order of magnitude higher than for bulk water (Fig. 3c).[50–52] CNTs exhibit significant ion exclusion that can be as high as 98% under certain conditions, supporting a Donnan-type rejection mechanism, dominated by electrostatic interactions between fixed membrane charges and mobile ions, whereas steric and hydrodynamic effects appear to be less important.[53] So far functional membranes have been prepared using aligned CNTs with a diameter of 6–10[54] or 1.3–2 nm.[55] The ~1.6 nm CNTs reveal a flow enhancement that is more than three orders of magnitude faster than the no-slip, hydrodynamic flow as calculated from the Hagen-Poiseuille equation.[55]

Although impressive in performance, there is still the issue of producing low poly-dispersity of open CNTs, high rejection performance under increased salt concentration, practical alignment procedure and further up-scaling of the technology for affordable desalination applications. Nonetheless, CNTs represent a very attractive tool for obtaining robust filtration membranes.

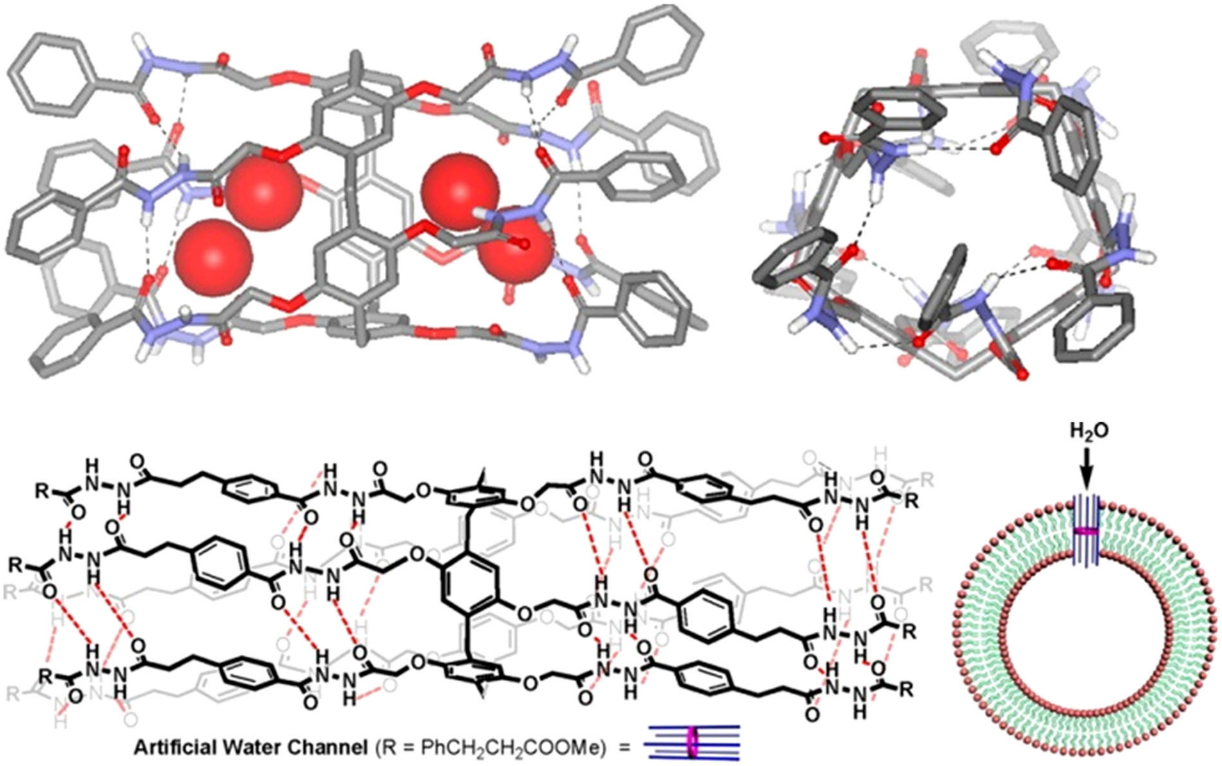

Fig. 4 **a** Single molecular Pillar[5]arene PAP1 water channels (adapted with permission from ref. 59, copyright American Chemical Society 2012)

Artificial water channels

We know that the AQPs are the representative proteins for the water transport across lipid bilayers, but their structures are tremendously complicated. Simpler molecular architectures encapsulating water may provide excellent and valuable models for understanding/designing novel biomimetic water channel systems.[56] Although there is a rich inventory when it comes to molecular encapsulation of water,[37–39] in most cases the host systems are highly polar which prohibits them to be used in conditions similar to the one offered by the hydrophobic bilayer of the membrane to AQPs. As so, the development of the AWCs is highly important. The first synthetic water transporting systems have been reported recently[57] and the term of Artificial water channels has been coined practically at the same time.[58]

The common features of the AWCs are the presence of a central pore, which is a confining hydrophilic or hydrophobic region that allows the passage of water, and a hydrophobic shell that permits the insertion into the lipid membranes and subsequent analysis for water transport. There are two main approaches towards designing these systems, when considering the structure of channels:

- *single molecular channels*, as one molecular entity that can span the length of the bilayer;
- *supramolecular channels* that can self-assemble from multiple molecular components into AWC architectures spanning the bilayer.

Single molecular channels. The pillar[5]arenes, PAP1 developed by Hou et al.[59–61] behave as single molecular channels (Fig. 4). Intramolecular H-bonds between the hydrazide arms confer robustness, keeping the membrane spanning channels intact, when inserted into a lipid bilayer. The X-ray single crystal diffraction and cryo-SEM prove the tubular conformation of the PAP1 channels, including discontinuous water dimers in the pore.

PAP1 have a relatively low water transport rate of up to 40 molecules of water/s/channel. Although there is no selectivity against cations, PAP1 are impermeable to protons. Like in AQPs they display high water selectivity against H^+ and OH^-ions. The explanation for this is the impeded proton hoping *via* the Grotthuss mechanism through a broken, discontinuous water wire in the structure of PAP1 channel, while the cation transport can be attributed to carrier transport mechanism.[59] Following up on these results a second generation of more hydrophobic pillar[5]arenes, PAP2 containing peptidic poly-phenylalanine arms were designed. PAP2 have been proved to also efficiently mediate the transport of amino acids.[60] Moreover, the average single channels osmotic water permeability for PAP2 was determined to 3.5×10^8 water/s/channel, being in the range of AQPs and CTNs.[61] Nevertheless, PAP2 channels present a drawback when it comes to ionic selectivity. Having an inner pore size of ~5 Å, they allow the passage of cations according to their hydration energy. Molecular dynamics simulations show an oscillation between an empty and water filled states for the PAP2, with some protruding of lipid chains into the channels. More interestingly, PAP2 channels are most likely densely packed in a hexagonal arrangement in 2D membranes, thus the fabrication of active flat thin-layers is possible.[61]

Self-assembled supramolecular channels. The second category of AWCs use a non-covalent self-assembly strategy, that often confer the supramolecular channels properties that are not predictable and differ completely from that of their monomeric building blocks.[62] Based on this concept Barboiu et al. have reported AWCs based on alkylureido-imidazoles that can be used for the self-assembly of tubular imidazole I-quartet channels, mutually stabilized by water wires (Fig. 5).[57] They show similar structural features as found in the AQP pores, with a central pore size of ~2.6 Å, close to the 3 Å provided by the AQP channel. The water molecules form a single molecular wire adopting a unique dipolar orientation inside the chiral I-quartets. The I-quartet channels are

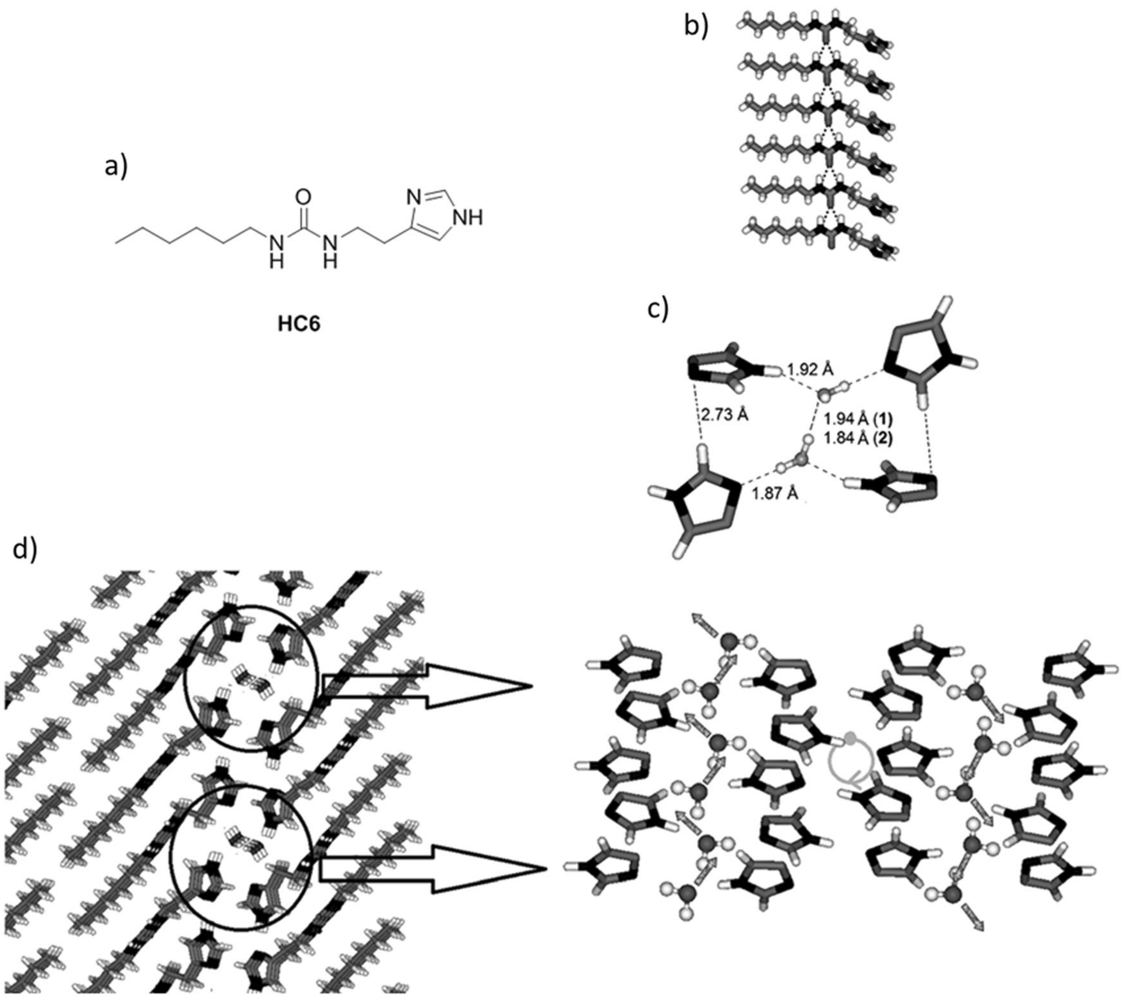

Fig. 5 Single crystal structure of **a** hexyl-ureidoethylimidazole and its related **b** urea H-bonding ribbons and of **c** I-quartets containing water molecules that present **d** dipolar orientation (adapted with permission from ref. [57], copyright Wiley, 2011)

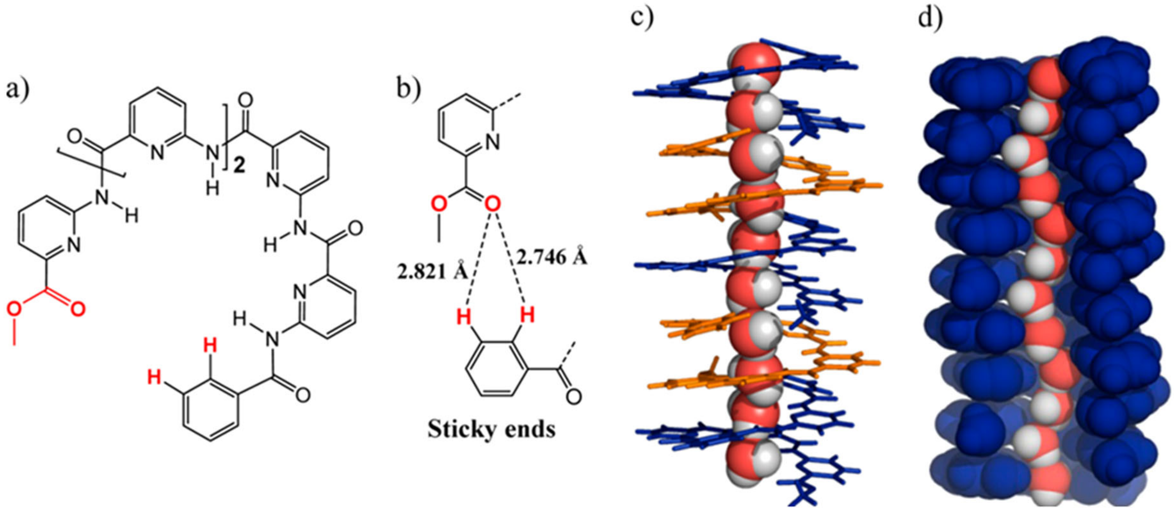

Fig. 6 **a** Aquafoldamers; **b** "sticky ends" motifs for self-assembly; **c** X-ray single crystal structure and **d** representation of a single water file (adapted with permission from ref. [65], copyright American Chemical Society 2016)

able to transport ~1.5×10^6 water/s/channel, which is within two orders of magnitude of AQPs' rates but most important, reject all ions except protons.[63] This total ion-exclusion selectivity is timely important and unique for the AWCs. It is based on dimensional steric reasons, whereas hydrophobic and hydrodynamic effects appear to be less important. The proton conductance through I-quartets is ~ 5 H^+ per second per channel and approximately half that of the natural M2 influenza protein.[64]

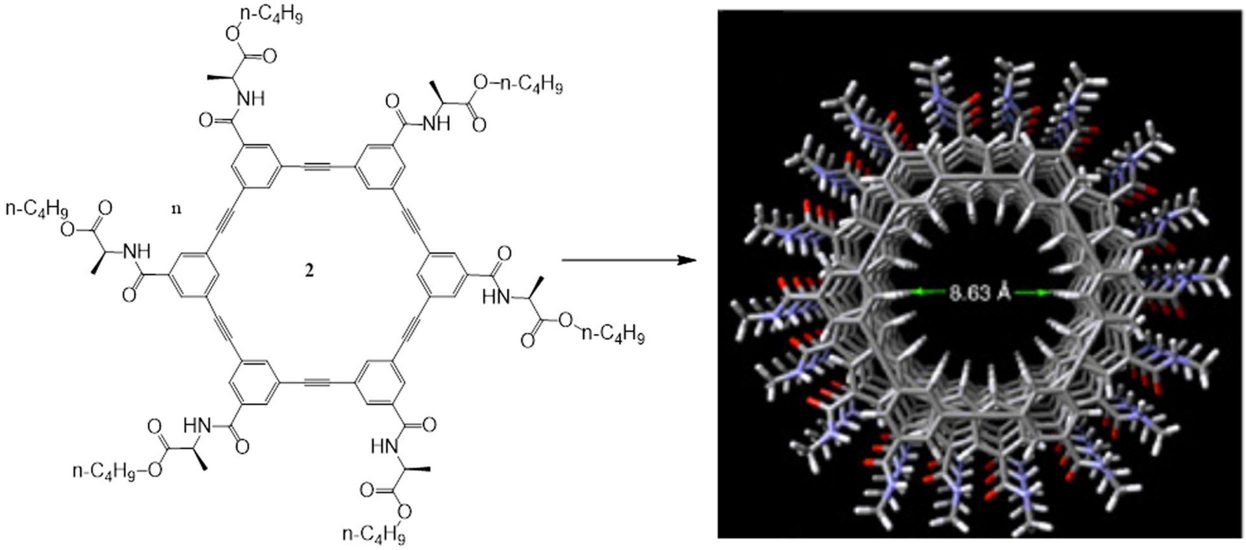

Fig. 7 Simulated structure of macrocyclic channels (adapted from ref. [66])

Table 1. Performance overview of artificial water channels and pores reported until now[58]

Water channels	Net permeability for water/single channel permeability	Selectivity	Ref.
Aquaporins—AQPs. hourglass structure with a narrowest constriction of 2.8 Å	167 µm/s/bar 4×10^9 water molecules/s/channel	High selectivity for water, perfect rejection of ions and protons	17
Carbon nanotubes- CTNs Estimated diameter = 15 Å	300 µm/s/bar, 1.9×10^9 water molecules/s/channel	–	49
Carbon nanotubes- CTNs Estimated diameter = 8 Å	520 µm/s/bar, 2.3×10^{10} water molecules/s/channel	Ion rejection in dilute solutions	49
Hydrophilic I-quartets, channel (2.6 Å)	3–4 µm/s/bar 1.5×10^6 water molecules/s/channel	High selectivity for water, reject all ions except protons	63
Aquafoldamers, hydrophilic channel (2.8 Å)	No permeability reported	High selectivity for water, reject all ions except protons	65
Hydropobic tubular macrocyclic pores (6.4 Å) with peptide appended arms	51 µm/s/bar 4.9×10^7 water molecules/s/channel	No selectivity for water, high conduction for K^+ and H^+	66
Hydrazide appended Pillar[5]arene, **PAP1** unimolecular channel (6.5 Å)	8.6 × 10–6 µm/s/bar 40 molecules/s/channel	No selectivity for water conduction for alkali cations no conduction for H^+	59
Peptide appended Pillar[5]arenes, **PAP2** unimolecular channel (5 Å)	swelling: 30 µm/s/bar or 3.5 10^8 molecules/s/channel shrinking: 1 µm/s/bar or 3.7×10^6 molecules/s/channel	No selectivity for water, good conduction for alkali cations	60, 61
Double helical water T-channels (~2.5–4 Å)	No permeability reported	Enhanced conduction states for cations and for H^+	39
RO membrane	2 µm/s/bar	99.8% rejection of salts versus water	31
FO membrane	2.5 µm/s	–	4, 5
RO membrane	5.3 µm/s		

The I-quartets have been found to efficiently transport protons when an osmotic pressure is applied, in the absence of any pH gradient. This highlights the importance of oriented dipolar water-wires inside the channels, allowing polarization and synergetic *antiport* proton translocation through the bilayer membrane.

In another example, Zeng et al. designed small olygopyridine molecules that are able to self-assemble into helical *Aquafoldamers* with a pore of ~2.8 Å, close to the size of narrowest region in AQPs (Fig. 6).[65] The supramolecular nanopore contains a single file of water molecules. Water transport experiments were run using a simple dynamic light scattering (DLS) setup. Interestingly, when water permeability tests were performed the channels showed no osmotic pressure induced water transport, but when under proton gradient was applied, they presented observable water transport.

This underlines the dependence between the chain-like confinement of the water inside the pore and translocation capabilities of the channel, however a standardized value for channel permeability needs to be determined in order to properly assess water transport performances. The channels showed no transport of Na^+ and K^+ cations, making them a viable option for desalination applications.

With a similar approach Gong et al. have synthesized macrocycles, able of self-assembly into tubular channels *via* stacking and H-bonding interactions (Fig. 7).[66] Although the size of the pore of 4–5 Å would normally offer little selectivity, remarkably the channels can selectively transport K^+ against both Li^+ and Na^+ cations.

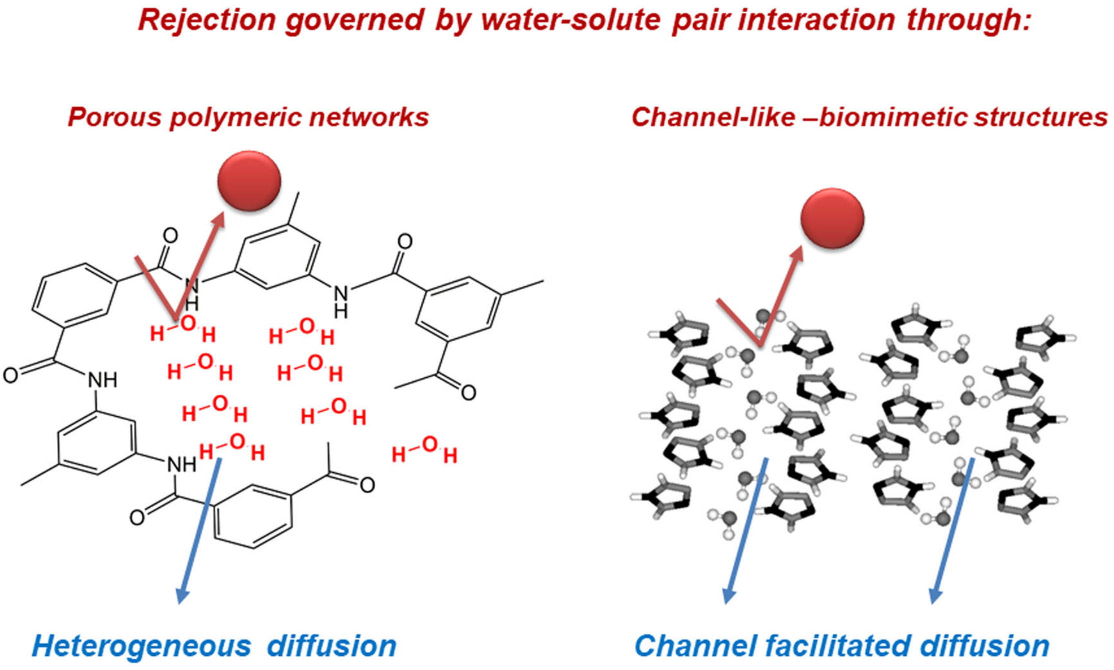

Fig. 8 Novel approach for desalination-artificial water channels

The transport of water occurs in a similar fashion as the one observed in the case of CNTs, a hoping of water molecules between voids having no specific binding to the walls of the pore. The determined osmotic water permeability of these hydrophobic channels is ~4.9×10^7 water/s/channel.

OUTLOOK

The current research on AWCs is focused on their synthesis, molecular simulations and transport properties in lipid bilayer membranes. The osmotic water permeability of several artificial systems ranges from one[61] to two orders[63] of magnitude lower than that of AQP1, with similar or even better values for CTNs[49] (Table 1).[58] The large cross-sectional area of AQPs (9.0 nm^2) is somewhat disproportionate in regards with the size of its active water pore. It is important to note that the effective cross-sectional area of the AWCs channels in 2D layers will take up significantly less space than proteins. From an engineering point of view, this could potentially increase by orders of magnitude the permeability of AWCs per surface area when compared with AQPs.

The two main challenges for AWCs are (i) to make tailored channels that reject salt but allow the easy passage of water molecules and ii) the transfer of the AWCs from the nanomolecular level to that of large scale membrane materials. Although this has been achieved using AQPs,[29] no studies have been reported yet on integrating the AWCs within active layers casted onto polymeric membrane supports. Designing stable polymer matrixes capable of keeping AWCs in their active state will prove crucial for future hybrid membranes. The use of lipidbilayers or hydrophobic polymers as host matrixes, which certainly can be affected by the presence of organic solutes or surfactants in water, is not a necessary option. They have been used until now to compare the AWC with AQP One strategy to obtain modified active layer is to incorporate the AWC networks while forming the Polyamide PA layer of RO membrane or to imagine new cross-liked polymers in order to obtain networks of AWC within the thin layers. If AWC are covalently attached to TFC, there is no degradation of layer, only temporary channel destabilization. This way the nanometric AWCs are dense and highly robust, would be encapsulated in the dense part of the membrane while the PA matrix should be responsible for the rejections of organics.

To compete with polymeric reverse osmosis membranes, the current gold standard for desalinating seawater, water flux and rejection rates for artificial water channels need to be very close to that of AQPs. While having even higher flux values will not have a substantial impact on membrane filtration performances, highly water specific membranes will improve the quality of water produced as well as remove unnecessary pretreatment processes.[67] An optimal bonding of water clusters within the channel is needed for selectivity, while less friction/interaction with the channel structure is desired to increase the water permeability. These key features must be combined in order to exploit both the selectivity of hydrophilic H-bonding channels like I-quartets[63] and the high permeability of hydrophobic carbon nanotubes.[49] Shorter channels lengths, more dense channels per unit area of surface will play an important role in developing efficient water filtration systems based on AWC technology. Given the importance of developing even more efficient membranes for desalination, this will be an exciting and challenging project, potentially redefining the paradigms of desalination (Fig. 8).

CONCLUSIONS

Considering the potential of AWCs to provide 100% water specificity against any other solute, membranes based on hybrid water channel/polymer technology can contribute to reduce the cost of water desalination mainly by removing post-treatment processes. With the current state of development, it is clear that the AWCs still have room for improvement. Related research in the field of AWCs is fundamental in nature and should allow the development of a new base of knowledge regarding water transport at the molecular level. The first identification of AWCs in 2011 has opened the door to new applicative desalination processes.[57] We speculate that biomimetic AWCs might have timely impact on increasing water filtration efficiency by using natural principles to change the desalination paradigms. AWCs will present robust and compact structures that would support better mechanical pressure which seems to not impair the restructuration of AQP biomimetic membranes[29] Mimicking the complex functions of channel proteins is an important challenge. Different scientific accomplishments may complement each other for a more comprehensive understanding of the structure and mechanisms used by proteins to effectively transport water in biological systems. Straightforward synthetic availability of Artificial Water Channels- *the artificial Aquaporins* –give rise to novel strategies towards the design of highly selective water transport devices. The result of the *fast biomimetic transport of water through the AWCs* might have important practical applications other than *advanced desalination*, such as the production of ultrapure water for biomedical use or one-step purification of highly diluted solutions. We believe that AWCs hold the potential to become integral part of cutting edge water treatment technologies.

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AUTHOR CONTRIBUTIONS

I.K., Y.M.L., Z.S. researched data for the article, made substantial contributions to discussions of the content, MB wrote the article and reviewed and/or edited the manuscript before submission and was responsible for communication with the editor and preparation of the final version of the manuscript.

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