Beyond aquaporins: Recent developments in artificial water channels

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Abstract

A molecular scale understanding of the fast and selective water transport in biological water channels, aquaporins (AQPs), has inspired attempts to mimic its performance in synthetic structures. These synthetic structures, referred to as artificial water channels (AWCs), present several advantages over AQPs in applications. After over a decade of efforts, the unique transport properties of AQPs have been reproduced in AWCs. Further, recent developments have shown that the performance of benchmark AQP channels can be exceeded by new AWC designs using novel features not seen in biology. In this article, we provide a brief overview of recent AWC developments, and share our perspective on forward-looking AWC research.

1. Introduction

Aquaporin (AQP) water channels are cellular membrane proteins that modulate water transport across cell membranes. Classical AQPs can translocate water at permeation rates greater than 10^9 molecules per second ($H_2O \cdot s^{-1}$), under a standard one osmolar osmotic gradient, while excluding all ions including protons.[1, 2] A ~3 Å constriction near the channel entrance and a collocated presence of a positively charged Arginine residue is proposed to prevent ion entry.[3, 4] Further, a set of two conserved asparagine-proline-alanine (NPA) amino acid residue motifs near the mid plane of the channel force a water dipole reorientation that interrupts the continuously bonded water-wire leading to exclusion of protons (**Figure 1A**)[3]. Proton transport generally occurs in hydrogen bonded (H-bonded) water by the Grotthuss mechanism and requires the presence of continuous H-bonding. Given the extraordinary water permeability and water/ion selectivity of AQPs, it is not a surprise that it inspired a new research area of bioinspired membranes for aqueous separations in the mid 2000s.[5, 6] Further, in the early 2010s, the area of artificial water channels (AWCs) developed. AWCs are synthetic surrogates of AQPs that are proposed to circumvent the disadvantages of purely biological components.[7] In this perspective, we present a short overview of recent progress in AWCs, along with a commentary on the latest developments where AWCs have been reported to achieve transport performance exceeding those of AQPs while utilizing alternate water transport and ion exclusion strategies.

2. Recent developments in AWC design

The primary thrust of AWC development over the last decade has been to reproduce the essential functional features of AQPs by approximating its overall structure. Early attempts[8, 9] demonstrated water permeation though formation of unitary water-wires (or water-ion 1D complex observed in ion channels) (**Figure 1A**).[3] These attempts were followed by demonstration of fast AQP-like water transport in these channels by elimination of water-pore wall interactions while still maintaining 1D water-wires. However, recent studies showed that it may not be necessary to rely on this approach to achieve efficient and selective water transport relevant to practical applications. In this work, we have classified AWC research trends into three phases (I ~ III) based on the key channel design ideas and their evolution in recent years. Attempts to create macro-scale membranes around these channels are excluded from this perspective.

2.1. Phase I: Elementary mimicking of AQP channels

AQPs and many other biological pore-forming molecules such as potassium channels (for e.g. the bacterial KcsA)[10] or gramicidin A (gA)[11] enable water transport through a single file configuration of water molecules, which is known to energetically favor water permeation.[12, 13] Therefore, in the first phase of

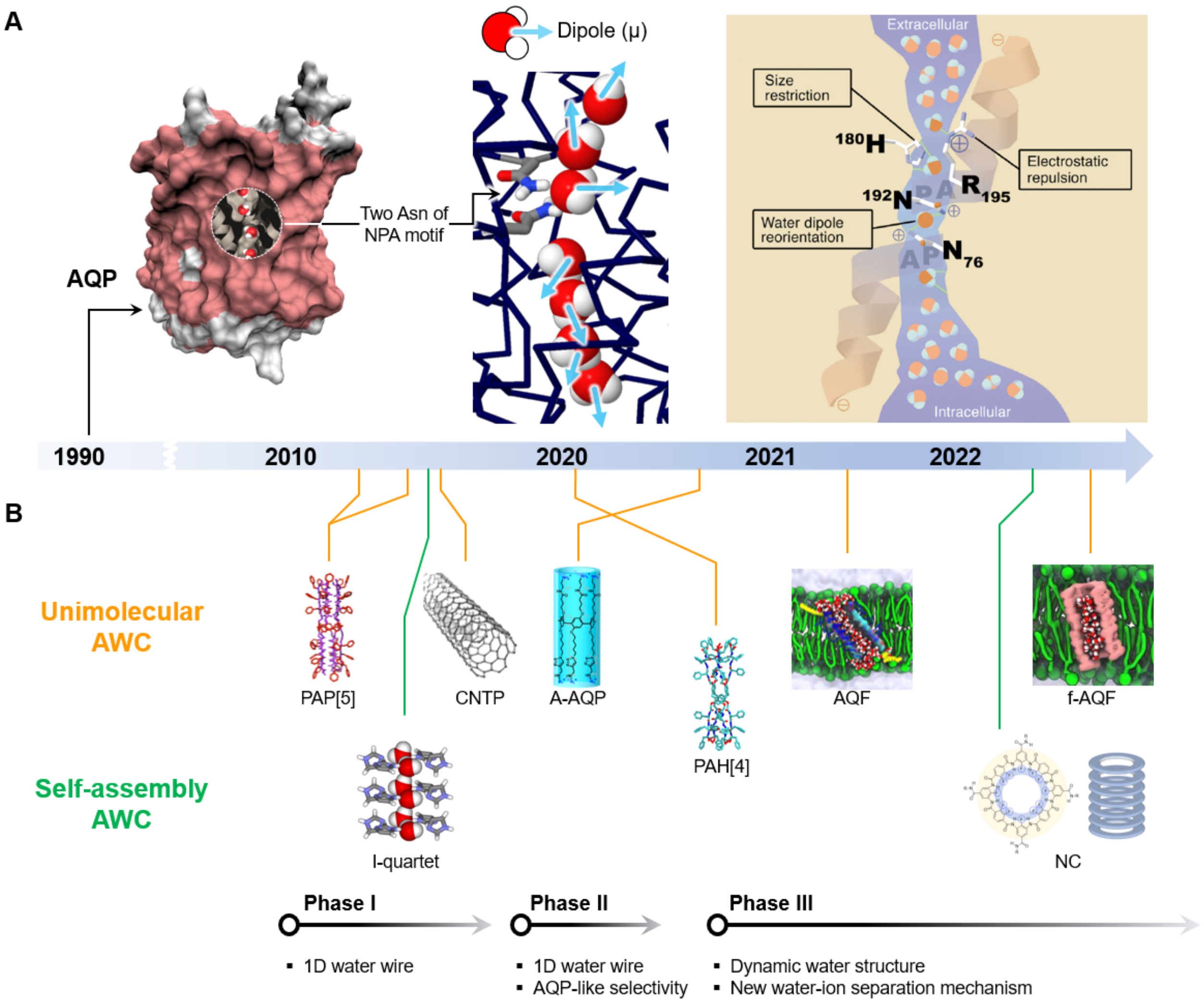

Figure 1. AQP and recent developments of AWCs as synthetic transport elements of biomimetic and bioinspired membranes. (A) AQP water channel. The direction of dipole (μ) orientation of water (sky blue arrows) is presented, which also shows single-file water configuration in the pore. On the right panel, representative water transport properties of AQPs are highlighted; size restriction, electrostatic repulsion, and water dipole reorientation. Reproduced with permission from ref[4]. Copyright 2002 American Society for Clinical Investigation. (B) Recent developments of representative AWCs in chronological order, classified by structural (unimolecular and self-assembly) and water configuration (unitary water-wire and dynamic arrangements). Reproduced from ref[19]. Copyright 2019 American Chemical Society (peptide-appended pillar[5]arene, PAP[5]). Reproduced from ref[16]. Copyright 2013 American Chemical Society (I-quartet). Reproduced from ref[21]. Copyright 2020 American Chemical Society (A-AQP). Reproduced with permission from ref[25]. Copyright 2019 Springer Nature Limited (PAH[4]). Reproduced with permission from ref[26]. Copyright 2021 Springer Nature Limited (AQF). Reproduced from ref[27]. Copyright 2022 American Chemical Society (f-AQF).

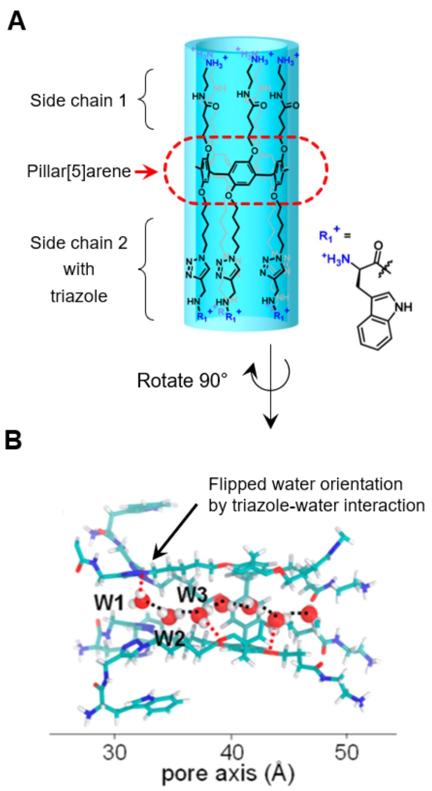

Figure 2. A-AQP is designed by appending two different types of side chains (side chain 1 and side chain 2 with triazole moieties) on both sides of pillar[5]arene macrocycle. (A) Cationic functional groups at channel entrances are presented with blue. (B) 1D water-wire presentation in the channel. **W1** water molecule interacts with triazole moiety (N atom, blue) and dipolar orientation is flipped, likely observed in AQP. Reproduced from ref[21]. Copyright 2020 American Chemical Society

research in this field, AWC designs focused on mimicking this 1-D water wire configuration within channels by building tubular shaped transmembrane nanostructures (**Figure 1A** and **B**). Efforts focused on limiting pore sizes to the 3 – 5 Å range to just barely fit one water molecule.[14-16] However, first generation channels such as Imidazole-quartets (I-quartet, **Figure 1B**)[9] and hydrazide appended pillar[5]arenes[8] had extensive H-bond interactions between pore wall and the diffusing water-wire, which led to lower permeabilities. Inspired by work on water transport in biological channels and the importance of minimizing water-pore wall interactions, subsequent generations of channels have opted to utilize hydrophobic pore lining groups. Additionally, pore-lining functional groups have been introduced to confer local charges on the structures. Two major synthetic strategies to implement these concepts: (1) building unimolecular transmembrane structures (including truncated single-wall carbon nanotubes, CNTs[17]) and (2) forming self-assembled supramolecular structures in the membranes using small building blocks (**Figure 1B**). Apart from their pros and cons, such as difficulty of synthesis, scalability, and structure tunability, a few designs with water transport abilities were proven to be as effective as AQPs with single channel permeability values as high as 10^8 – 10^{10} $H_2O \cdot s^{-1}$. These efforts successfully demonstrated the potential of AWCs as synthetic transport elements for biomimetic and bioinspired membranes.[18-20] However, high water over ion selectivity while maintaining high water permeability and proton exclusion was not achieved until very recently.

2.2. Phase II: Recapitulating AQP structure, function, and performance

It has been recently demonstrated that it is possible to recapitulate classical AQP structure and function and demonstrate the resulting high permeability and water over ion selectivity in AWCs. Hou and coworkers developed a pillar[5]arene based molecule that they termed Artificial Aquaporin (A-AQP). This molecule was synthesized by appending two different side-chains on each end of a pillar[5]arene macrocycle, with both chains containing positively charged terminal groups (**Figure 2A**).[21] These cationic functional groups at the periphery of channel entrances not only help exclude ions but also reduce the energy barrier for water entry that may have led to increased water permeability. This boost in permeability is in line with what has been proposed for AQPs with similar charges at pore entrances.[22] More interestingly, the N atoms of triazole moieties on appended side chains on one side of the channel function as H-bond acceptor, which in coordination with H-binding of water with oxygen atoms towards the center of the channel, leads to flipping of the dipole orientation of permeating water molecules. This water dipole reorientation leads to truncation of proton-wires in the middle of channel pores reminiscent of that seen in AQPs. Similar to AQPs, this truncation leads to proton exclusion by eliminating continuously H-bonded water wires, which are seen in other non-proton rejecting pillar[n]arene channels[14, 23, 24] (**Figure 2B**). This work is an elegant recapitulation of the water dipole orientation that within AQPs channels, albeit with a much simpler structure. It is noteworthy that the A-AQP is the first synthetic structure that achieved (1) AQP-like permeability, (2) ion rejection, and (3) proton rejection with flipped dipolar orientation during water transport.

2.3. Phase III: Going beyond AQP structure and performance

Even though relying on 1D water-wires in single digit AWC pores has been successful, it seems that the following question has arisen in the field, “is single file water permeation profile really the most optimized for *practical* water transport?”. The word practical here could be interpreted differently, but here we use it to indicate channels achieving higher permeability than AQPs even if we compromise on some ion selectivity while still having “high-enough” selectivity for applications such as reverse-osmosis membrane applications for seawater desalination, brackish water treatment, and wastewater recycling. This recent change in perspective led development of more dynamic water molecule configurations in channels, and new molecular engineering ideas for channel design.

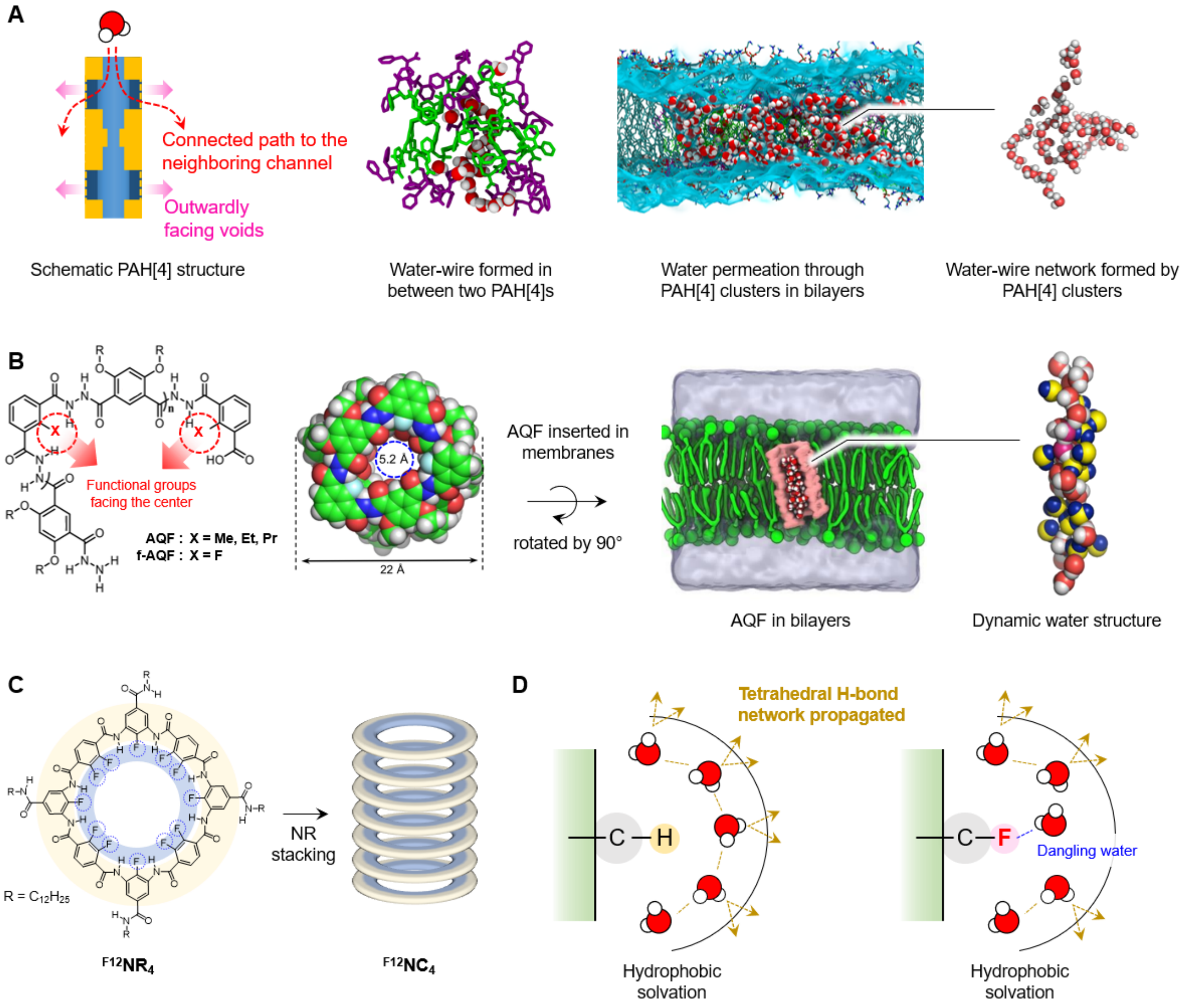

Figure 3. High performance AWCs with non-traditional single file or non-single water configurations as a new paradigm for AWCs. (A) Schematic illustration of PAH[4] structure that has micro-voids facing neighboring channels, which are synergistically interconnected in bilayer membranes forming water-wire networks. Reproduced with permission from ref[25]. Copyright 2019 Springer Nature Limited. (B) Chemical structure of f-AQF and molecular dynamics simulation snapshots to show dynamic water structures in f-AQFs during permeation. Reproduced from ref[27]. Copyright 2022 American Chemical Society. (C) NC formed by vertical stacking of NRs with fluorinated internal cavity structure. (D) Schematic comparison of hydrophobic solvation of hydrocarbon (C-H) and perfluorocarbon (C-F). Electrostatic interaction between fluorine and dangling water disrupts H-bond networks of surrounding water molecules, resulting in broken water clusters near the surface of internal channel wall.

2.3.1. Dynamic water-wires formed by transiently interconnected water permeation pathways. We recently reported on a new class of AWCs, termed as peptide-appended hybrid[4]arenes (PAH[4]) (**Figure 3A**).[25] Inspired by the lateral diffusion of biological membrane components in the bilayer matrix, PAH[4]s were designed to have angstrom-scale outwardly-facing "void windows" that can be interconnected in neighboring channels to provide interconnected paths for water diffusion. Consequently, we found that water molecules diffused through the connected micro void structures forming the branched water-wire networks in aggregated channels. Inside each string of this network, the number of H-bonds formed by water molecules is maintained at around two, lowering the energy barrier to water diffusion as observed in AQPs and carbon nanotube porins (CNTPs). In addition, the synergistically increased number of permeation paths within the given area of membranes resulted into the meaningful improvement of membranes' water permeability and water-NaCl selectivity, which could, if made into membranes, surpass conventional polymer-based desalination membranes in terms of quantitative measures of water-to-ion permselectivity.

2.3.2. Widening pore apertures while maintaining selectivity with alkyl and fluorinated intraluminal hydrophobic surfaces. A hydrophobic inner pore surface is now a generally accepted criterion for developing AWCs with high water permeability. Hydrophobic pore walls reduce interactions between permeating water molecules and their surroundings and, thereby, reduce the energy barrier of breaking those interactions that would hinder translocation of water molecules. A question that arises about such channels is, "are there designs where pore sizes larger than 3- 5 Å (corresponding to single water molecule occupancy) can lead to high water permeability and ion selectivity?" Three recent studies indicate that, along with the intraluminal surface modification using aliphatic hydrophobic and fluorinated groups, increased pore volume may provide sterically favorable environment for fast water permeation.

Aquafoldamers. Zeng and coworkers developed aquafoldamers (AQFs) using self-folding polymers as structural backbones (**Figure 3B**).[26] AQFs are designed to accommodate more than one water molecule within a plane normal to the direction of water transport, with pore lumen protruding alkyl chains (methyl, ethyl, and propyl) toward the center of the pores from the inner surface, resulting in effective pore sizes of 6.5 Å, 4.5 Å, and 3.0 Å, respectively. Abundance of saturated aliphatic groups prevent the entry of cations such as Na^+ as these groups are unable to strip waters of hydration from these ions. They also, surprisingly, break water-wires to restrict proton transport (as discussed in a later section). Remarkably, while the AQFs showed the same order of water permeability s AQP1, the activation energy of water diffusion was higher than 8 kcal/mol for all cases, which according to current understanding is indicative of less favorable water transport of f-AQFs compared to AQPs that have the values lower than 5 kcal/mol.

Fluoro-aquafoldamer. Inspired by the AQF structure, the same backbone structures with AQFs were further modified to have perfluoro compounds with sp^2 hybridized carbon to develop fluoro-aquafoldamer (f-AQF), but without alkyl chains (**Figure 3B**).[27] As a result, f-AQF has a 5.2 Å pore lumen, which is smaller than the size of first-shell hydrated Na^+ and K^+ ions (7.2 Å and 6.3 Å in diameters, respectively) and therefore restricts ion permeation. Also, f-AQF showed trends similar to AQFs with respect to the relationship between water permeability and activation energy. The activation energy of water diffusion was measured to be 7.1 kcal/mol, which is indicative of less favorable water transport of f-AQFs, compared to typical biological water channels that have the values lower than 5 kcal/mol but its water permeability was higher that the archetypal classical AQP, AQP1. The faster water transport of f-AQFs, may indicate the importance of increasing the pore size and having more dynamic configuration of water molecules to increase water permeability of AWCs.

Fluorous nanochannels (NCs). Another recent study on fluorous nanochannels (NCs) by Aida and coworkers also seems to support this new direction in channel design. They developed a series of nanochannels (NCs) with different pore sizes that are 9 Å ($^{F12}NC_4$), 14.6 Å ($^{F15}NC_5$), 17.6 Å ($^{F18}NC_6$), and 19 Å ($^{F12}NC_6$), by stacking polyamide-based nanorings (NRs) with perfluorinated functional groups (**Figure 3C**) within lipid bilayers.[28] All NCs reported showed significantly improved water permeability over AQP1 by a factor of up to ~10^3. The authors explain this very surprising result by invoking electrostatic interactions at molecular interface between fluorine and water that induces breakage of surrounding water clusters into "smaller pieces", dramatically reducing the shear hindrance of viscous fluid permeation through the nanochannels (**Figure 3D**). They further describe this phenomenon as being similar to the slip-flow model in carbon nanotubes. The water permeability of the NC channels was measured as 5.5×10^{-10} $cm^3 \cdot s^{-1}$ (1.8×10^{13} $H_2O \cdot s^{-1}$ for $^{F12}NC_4$) under a 0.25 osmolar gradient. Considering that the pore diameter of $^{F12}NC_4$ (9 Å), the linear velocity of water in this case can be estimated to be ~200 m/s. This high value seems to be close to the limit of what kinetic theory would predict for the velocity of non-interacting ideal molecules' diffusing at thermodynamic equilibrium[29]. Therefore, we suggest that the model proposed by this study remains to be validated further.

Perfluorinated compounds: polar H-bond acceptor but hydrophobic? The underlying principle of increasing water permeability of nanochannels still seems to be maintenance of hydrophobic inner surfaces to enable frictionless flow. In this regard, by far, the efforts have been focused on how to reduce interaction between channel wall and permeating fluid molecules, for example, between pore-lining lining groups and permeating water molecules. However, superhydrophobic fluorinated channels add more complexity to this line of thought, even though perfluoro compounds such as Teflon® have been already very well known as good water repelling materials. Further, fluorine is one of the strongest electronegative atoms that can electrostatically interact with water molecules. Therefore, the principle of increasing hydrophobicity by fluorination as proposed by Aida and co-workers seems to be to not to eliminate completely the interaction between the surface and local water molecules. Rather, F···H-O-H interaction disrupts tetrahedral H-bond networks of surrounding water molecules, breaking down water nanoclusters into even smaller aggregates (**Figure 3D**).[30, 31] Those small clusters are proposed to "slide through together"

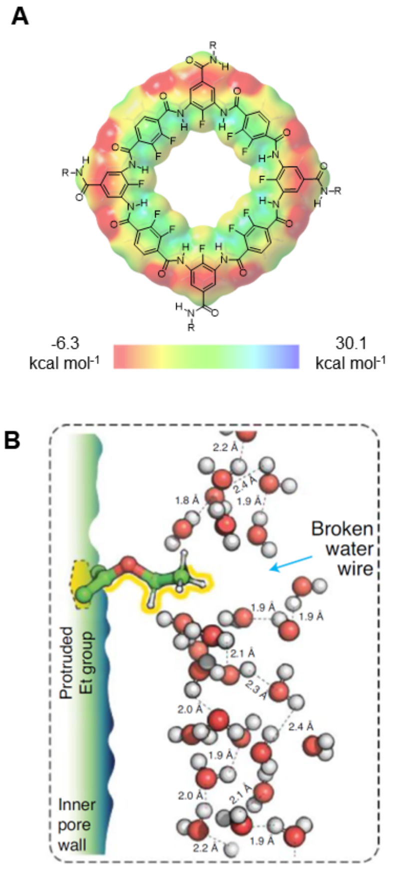

Figure 4. (A) Electrostatic potential maps of NCs calculated by density functional theory calculation. Reproduced with permission from ref[28]. Copyright 2022 The American Association for the Advancement of Science. (B) Breakage of H-bonds networks of water clusters in the pores by protruding alkyl (Et group) chains in the channels. Reproduced with permission from ref[26]. Copyright 2021 Springer Nature Limited.

with reduced viscous shear stresses. It is also interesting to note that, compared to the single-walled carbon nanotube that has 5 Å pore in diameter which transport water with 1D-wire configuration, carbon nanotubes with 8 Å (CNTP-8) pore diameter showed an order of lower water permeability[17] but fluorinated nanochannels with 9 Å diameter ($^{F12}NC_4$) showed three orders of higher permeability,[28] while both CNTP-8 and $^{F12}NC_4$ transport water as clusters, and not in the classical single-file profile.

3. Emerging strategies for improving ion selectivity of AWCs

Separating ions from water is also important property of AWCs. Among many possible ion species, a special interest is to remove monovalent ions such as Na^+ and Cl^-, as it is closely related to the applications of water purification and desalination. One straightforward strategy has been to constrict the channel pore size to smaller than the first-shell hydrated ions but to be larger than water molecules. Unless exceptional chemical potential is provided to the system to dehydrate ions (e.g., 50 ~ 80 kcal/mol for complete dehydration of K^+), this steric exclusion model has been demonstrated as sufficient to remove or separate ions from water to meet the requirements of desalination application.[21, 25, 32] The following ion separation mechanisms provide opportunities for new channel designs with larger pore sizes that have both high water permeability and selectivity.

Electrostatic repulsion. While electrostatic screening of charged species to introduce ion selectivity has been used previously in porous media, it has not been similarly emphasized in AWC design, particularly within channel pores. This is because pore lining functionalization with polar groups is directly opposite to the method of increasing hydrophobicity to improve water permeability. Therefore, beyond decorating the channel entrances with charged ligands, the major efforts to design AWCs have been to avoid any polar groups in the pores. However, polar-superhydrophobic perfluorinated compounds seems to open a new avenue of satisfying the twin goals of achieving hydrophobicity but maintaining an electrostatic potential barrier in the pores for ionic repulsion. This strategy was recently implements in fluorous NCs (**Figure 4A**)[28] that have negative potential distribution at the intraluminal surfaces, while maintaining hydrophobicity. The authors indicate that his is the reason for exceptional water-to-ion selectivity of $10^8 \sim 10^{13}$, which far exceeds the requirements of desalination applications ($\sim 10^4 - 10^5$), of these fluorous NCs.

Use of pore lining groups that prevent ion dehydration. As discussed earlier, AQFs are designed to accommodate more than one water molecule within a plane normal to the direction of water transport, with pore lumen protruding alkyl chains. This is particularly the case with channel design containing methyl and ethyl pore lining chains that result in effective pore sizes of 6.5 Å and 4.5 Å. These relatively open pore sizes that are larger than dehydrated monovalent ions were still shown to substantially exclude ions. The authors attribute this to the properties of saturated aliphatic groups as aliphatic hydrophobic group are unable to strip waters of hydration from these ions[26] in contrast to aromatic groups that can interact with cations through cation pi interactions which could result in ion dehydration.

Intermittent water-wire breakage during water permeation. As the ionic radii of proton is significantly smaller than other elements and they have very fast protonation-and-deprotonation turnover rates, AQPs adopt NPA motifs as selective filters to completely block proton transport.[3] The NPA motifs truncate the proton transport pathway in the middle, by interrupting the H-bond network (wire in this case) formed by water (**Figure 1**). As discussed earlier, A-AQPs adopted this classical strategy to exclude protons while allowing rapid water transport (**Figure 2**). A surprising and completely counterintuitive example is the intermittent breakage of H-bond networks in pores by fluctuating alkyl groups demonstrated by Zeng and coworkers in their recently reported AQFs[26]. These AQFs contained inwardly protruding alkyl chains that fluctuate in and out the plane of the pore, and dynamically disrupte and break H-bond networks of water clusters in the pores, resulting in significantly reduced H^+ transport rates (**Figure 4B**).[26] This was, to our best knowledge, the first demonstration of breaking H-bond networks of water clusters, and introducing proton rejection within nanochannels using an alternate mechanism that is not so far reported in biology.

4. Moving Forward

Synthetic water channel research has flourished during the last decade. This field was first motivated by AQPs and thus initial research efforts were naturally been focused on “fully” translating AQP functionality in synthetic models. However, this trend has evolved in recent years. Scientific maturation in synthetic, experimental and analytical methodologies have led to an increasing influx of new molecular engineering ideas into this field. There have been several efforts towards making synthetic channels more practically relevant than their natural counterparts. At the same time, there have some recent paradigm-shifting findings compared to what was seen and accepted in biological systems. For example, transport analysis in biological pores indicates that the determining factor of water transport is driven by enthalpic effects of confining water and reducing inter-water hydrogen bonding, and increasing the entropic properties such as increasing pore volume (widening pore size) should not lead to increase in water permeability.[33] However, three recent case studies,[26-28] independent but reported almost at the same time by separate research groups indicate that increased pore size could critically enhance water permeability while maintaining selectivity, when coupled with the introduction of new surface chemistry such as alkyl or fluorous modifications. Therefore, further research to reduce such gaps would help further establish new fundamentals needed to move this exciting field of AWCs forward.

5. Acknowledgements

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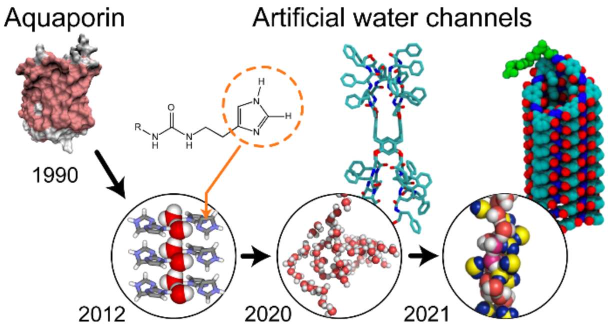
TOC Graphic



BIO

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Woochul Song is a Postdoctoral Scholar in the Department of Chemistry at the University of California, Berkeley. He received his bachelor's and master's degrees in Chemical Engineering at Sungkyunkwan University in South Korea in 2014 and 2015, respectively. After a one-year research internship at Korea Institute of Science and Technology, he moved to the U.S. for his Ph.D. He completed his Ph.D. in Chemical Engineering at The University of Texas at Austin in 2021, where he conducted research on artificial water channels and biomimetic membranes for water purification and separations. Currently, he works on metal-organic frameworks to expand scientific knowledge in organic/inorganic materials for sustainable molecular separations such as water harvesting and reduction of greenhouse gas emissions.

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