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Artificial Water Channels –incipient innovative developments

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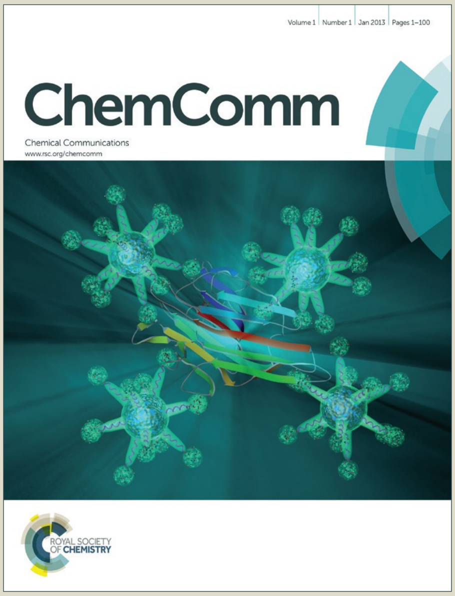

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Aquaporins (AQPs) are biological water channels known for fast water transport (~10^8-10^9 water molecules/s/channel), with complete proton/ion exclusion. Few synthetic channels have been designed to mimic this high water permeability and to reject ions at a significant level. This Feature Article will discuss the incipient developments of the first Artificial Water Channels systems.

Introduction

Natural protein channels are essential for the rapid and selective conduction of metabolites between the interior of the cell and its external environment.[1,2] They transport water, protons and ions over long distances and their structure helps to overcome the high energy barrier of the translocation through the cell bilayer membranes.[3] Understanding the dynamics of the transport through the confined space of protein channels is of crucial relevance for many biological scenarios or for areas of applications including separation, sensing and delivery processes.[4-6]

Mihail Barboiu received his PhD in 1998 from University of Montpellier before spending 2 years as post-doctoral researcher with Prof. Jean-Marie LEHN at University Louis Pasteur in Strasbourg. He is CNRS Research Leader at the Institut Européen des Membranes in Montpellier and Fellow of Royal Society of Chemistry. A major focus of his research is Dynamic Constitutional Chemistry toward Dynamic Interactive Systems: adaptive biomimetic membranes, delivery devices etc. Author of more than 180 scientific publications, 3 books and 20 chapters and 250 conferences and lectures, Dr. Barboiu has received in 2004 the EURYI Award in Chemistry and in 2015 the RSC Surfaces and Interfaces Award for the development of Artificial Water Channels.

Water is known to play a crucial role in such translocation processes, owing to its complex interactional behaviors at the molecular level, both with the protein channel structure and with the transported species.[7-8]

The highly selective transport of water in natural systems is occurring along Aquaporin (AQP) channels known for their fast transport rates (~10^8-10^9 water molecules/s/channel), and the perfect rejection of ions and protons (Fig. 1a).[3] Aquaporin water channels are composed of an hourglass structure with a narrowest constriction of 2.8 Å. Each water molecule in AQP water channels forms one H-bond with the inner-wall of the protein and one with an adjacent water molecule. Of particular interest, the dipolar alignment of water molecules imposed by the water-pore and water-water interactions, can control the water *vs.* proton transport selectivity of AQPs.[3] These discoveries have inspired the incorporation of AQPs into artificial membranes for desalination and water-purification applications.[9] However their large scale applications is not yet possible, lying to the high costs of the AQPs production, low stability and practical synthetic constraints of membrane fabrication processes.

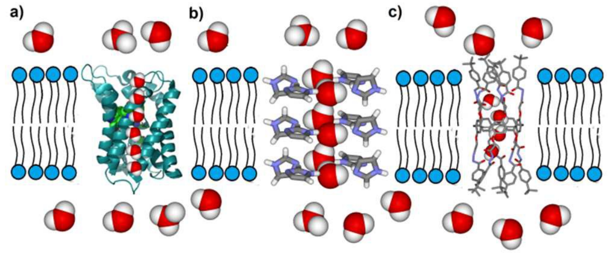

Figure 1. From a) Natural Aquaporins toward b) self-assembled and c) unimolecular Artificial Water Channel systems. Adapted from reference 12a

Artificial water channels - AWCs[10,11] constituted from a water-permeable central pore surrounded by an external hydrophobic shell accommodating the bilayer membrane environment, have been recently proposed as the biomimetic synthetic alternatives of highly selective biological AQPs. Increased interest in AWCs has considerably grown during the last five years, since they have been proposed to mimic natural AQPs.[10] Among the numerous investigations,[12] the most used

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strategy to construct the AWCs is the bottom-up supramolecular strategy, in which biomimetic architectures are constructed *via* the self-assembly of molecular precursors through non-covalent bonding (Fig. 1b). Another way is related to the use of tubular structures that can be used as single-molecular water channels spanning the bilayer membranes (Fig. 1c).

This Feature Article will focus on very recent accomplishments on Artificial Water Channels, the simplest synthetic biomimetic analogues, replicating water-channel conductance states of natural AQPs in lipid bilayer membranes.

Molecular encapsulation of water

Molecular encapsulation of water-clusters in artificial capsules or channel systems offers possibilities to explore the collective behaviors of water in conditions very close to confined biological water, at the limit between solid and liquid states.[13] Different water clusters have been entrapped within complex structures and they have attracted a lot of interest in a variety of fundamental processes such as water structuration related to water-water or water-host-matrix interactions under confined conditions[13a] and also in context of dynamic diffusion phenomena of water molecules across the channels.[13b,c] Among different water clusters the one-dimensional water-wires have attracted a lot interest with a special emphasis on their structural features similar to biological water-clusters, present inside the protein channels. Self-assembled tubular supramolecular architectures, mutually stabilized by strong non-covalent bonds and encapsulating inner water wires have provided excellent reasons to be considered as valuable models for biomimetic water/proton-channels systems.[13d-g] However, most of these structures are highly polar and their inclusion in hydrophobic bilayer membranes remains complicated to be achieved. Clusters of water may also self-organize in special forms of “higher and lower density” assemblies, depending on their positions and relative interactions under confined conditions. These systems are highly relevant for understanding the adaptive features of water clustering in biological systems, related to their interactions with other metabolites. All these non-exhaustive examples are relating specific features of the self-assembly behaviors of water clusters under confined conditions, toward systems of increasing functional complexity.

Within this context, understanding the molecular-scale dynamics of water clusters confined in such structurally simple artificial channels might be of crucial relevance for the next developments of functional AWCs. The mechanisms of water transport through aquapores are related to structural behaviors of water clusters entering the channels which lose or change part of the H-bonds connecting the water molecules, depending on the hydrophobic or hydrophilic nature of the channel. Spontaneous and continuous diffusion of one-dimensional ordered chain of water molecules in interaction or not with the surrounding aquapore is related to molecular interactions with the inner pore surface and diameter, dipolar water orientation.

Self-assembled Artificial water channels

Despite such impressive development of complex architectures for water encapsulation, only few artificial systems have been described to efficiently and selectively conduct water through bilayer membranes.

The water diffusion and facilitated transport of protons excluding cationic and anionic transport through bilayer membranes have been reported for the first time by Percec *et al*.[14] They used dendritic dipeptide, **1** (Fig. 2) that self-assemble *via* enhanced peripheral π-stacking of aromatic dendrons, to form stable helical pores of 14.5 Å average diameter and called them “primitive aquaporins” which are functional in bilayer membranes.[14b]

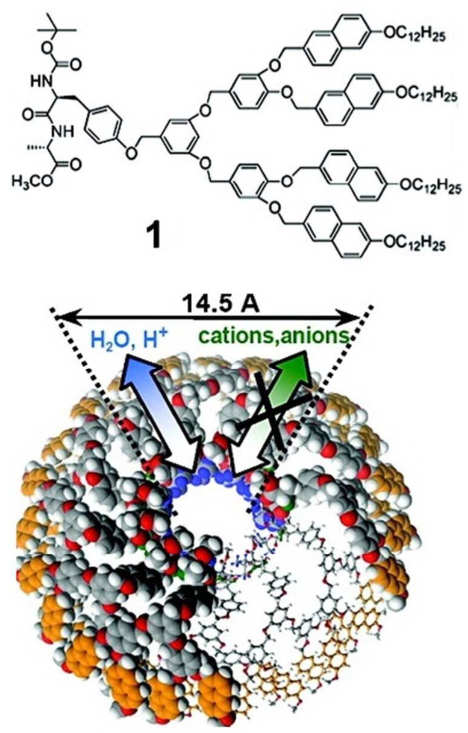

Figure 2. Cross section and top views of the Percec’ helical aquapores assembled from dendritic peptide **1.** Adapted from reference 14b.

These aquapores[14c] were envisioned transporting water, while excluding all ions except protons. The ion-exclusion phenomena are based on hydrophobic effects, which appear to be more important than sterical constraints.

These systems could be considered as self-assembled supramolecular congeners of Carbon Nanotubes – CTNs presenting similar pore openings that were estimated to have an average diameter of pore of 16 Å. The single channel permeability of CTNs (12, 12) is $9x10^8$ water molecules/s/ channel, with no ionic solutes rejection.[15]

Later in two successive papers,[10,11] our group introduced the term of Artificial Water Channels - AWCs, consisting of channel-type architectures that can be embedded and are stable in bilayer membranes and transport selectively water against ions. The AWCs immediately inspired many groups to

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imagine new strategies for their incorporation into future performant membrane materials for desalination and water-purification applications.[12,13] They may overcome the large-scale alternative of using AQPs for desalination.

We first considered the Imidazole-quartet (I-quartet) systems, i.e., stacks of four imidazoles and two water molecules, that can mutually stabilize oriented dipolar water-wires within in a bilayer membrane (Fig. 3).[10] Their hydrophilic pores of 2.6 Å diameter are dimensionally very close to the narrowest constriction (2.8 Å) observed in very efficient biological AQP water-transport channels.[3] The confined water molecules, like in AQPs, form one H-bond with the inner wall of the I-quartet channel and one H-bond with an neighbouring water molecule. Interestingly, the water molecules form a continuous water-wire that adopt a unique dipolar orientation and preserve the overall electrochemical dipolar potential along the channel (Fig. 4).[10]

The I-quartet water channels are able to transport ~1.5 x 10^6 water molecules/second/channel, which is within two orders of magnitude of AQPs' rates and reject all ions except protons. They present total ion-exclusion selectivity, based on dimensional steric reasons, whereas hydrophobic and hydrodynamic effects appear to be less important. The proton conductance through I-quartet channels is high ~ 5 H+/second/ channel and approximately half that of the natural M2 proton influenza protein channel at neutral pH.[6]

Interestingly, a proton *antiport* transport can be determined in the presence of an osmotic gradient and in the absence of any pH gradient. The I-quartets are found to effectively transport protons only when an osmotic pressure is applied, creating water transport gradients. This highlights the importance of the dynamic behaviours of water-wires inside the channels, allowing synergetic *antiport* proton translocation through the bilayer membrane.

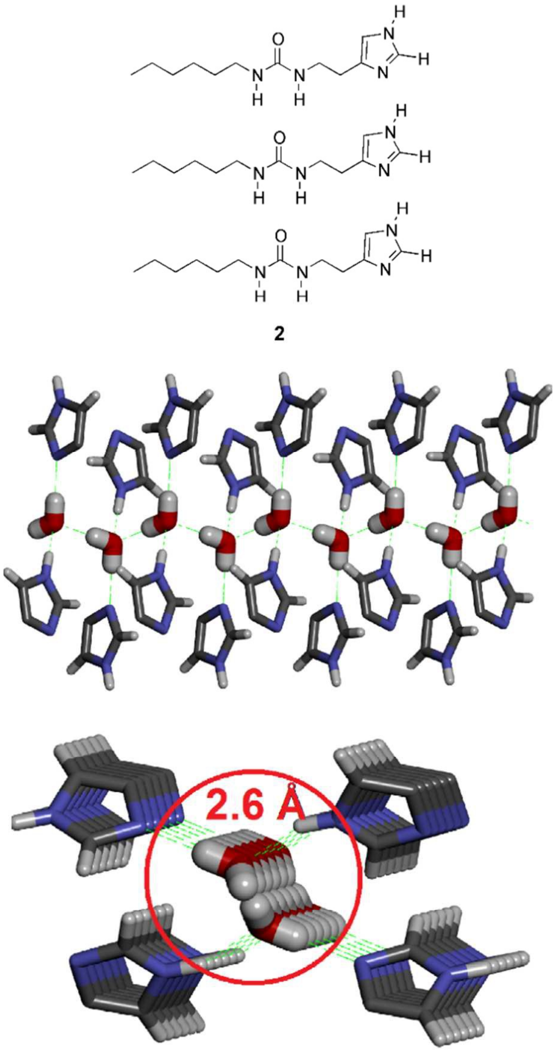

Figure 3. Artificial I-quartet water channels resulted from H-bonding tetrameric self-assembly of alkylureidoimidazole compounds **2**. Side and top views of I-quartet architectures confining dipolar oriented water-wires. Adapted from reference 10.

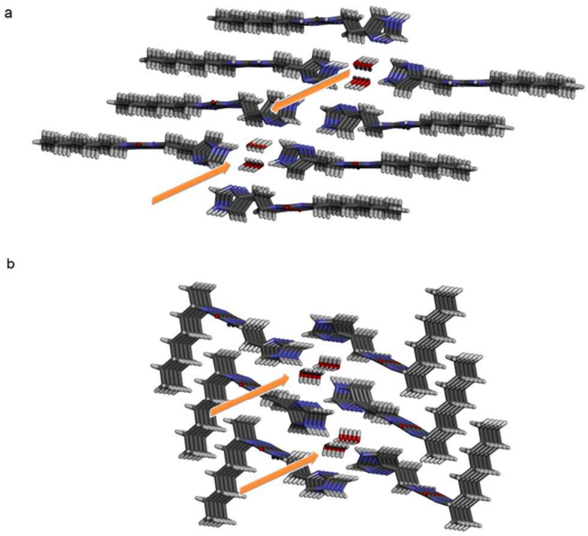

Figure 4. Water-wires dipolar orientations in successive channels showing: a) opposite water dipolar orientations in successive channels of *achiral* and b) a unique dipolar orientation for all the water-channels of *chiral* I-quartets.

Another related example by Zeng and co-workers describes foldameric channel for synergetic proton and water transport. After several explorations, they identify pentamer **3** (Fig. 5a) made from 6-aminopyridine-2-carboxylic building blocks, which self-assembly in chiral helical structures. With an inner pore of ~2.8 Å, comparable to the narrowest opening in natural AQPs and dimensionally adapted for water recognition.[16a,b] Very interestingly, oriented water wires are reading the supramolecular chiral information stored in the helical stacks (Fig. 5b). After unsuccessful tests on water transport under salt-induced osmotic pressure gradient, the helical stacks are found to effectively transport water under a proton gradient. Pentamer **3** facilitates transmembrane proton translocation and its efficiency is comparable to that of gramicidin A - gA.[2] These data are pointing to the important and indispensable role played by the proton gradients across the membranes inducing dynamic osmotic behaviors of

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confined wires, acting synergistically to facilitate the transport of water through the membrane. The “water osmotic gradient-induced proton transport” observed for I-quartets[10] and “proton gradient-induced water transport”[16a] observed for foldameric channels **3** are quite similar. They are directly related to dynamic behaviors water osmotic or proton gradients inside the channel producing synergetic proton or water co-transport, respectively. The dynamic structural changes of the water-wires in response to varying external stimuli, undergo significant rearrangement of the aqufoldamer backbones in order to accommodate water rather than methanol molecules. A series of crystallographic data of water-containing aquafoldamers demonstrated a preferential recognition of the water over methanol molecules with a selectivity factor of at least 17.7.[16c]

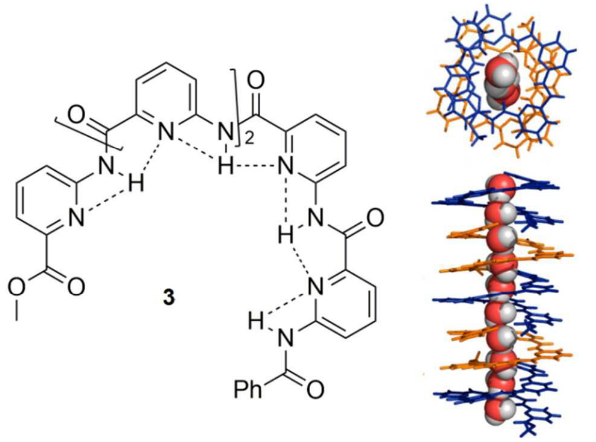

Figure 5. Single crystal structure of aromatic foldameric polyamide **3** and incorporating single water wires. Adapted from reference 16a.

Li, Hou *et al.* have extended this work on hydrazide macrocyclic[17a] and foldameric[17b] unimolecular channels appended with the phenylalanine tripeptides. Their structural stabilization in the lipid bilayers results from the multiple intramolecular H-bonding, resulting in the formation of dimensionally bigger pores showing higher NH_4^+/K^+ selectivity than gA presents, under the identical conditions. In addition, these channels display interesting activities towards transport of Tl^+ cations, almost as effectively as gA does. Importantly, the increase of the pore diameter above 2.8 Å results in formation of ionic-channels in which hydrated ions may be transported selectively.

On the same line, Gong *et al.* have developed a series of hydrophobic macrocyclic nanotubes - MTNs generated *via* manifold H-bonding and aromatic stacking of cyclic arylene-ethynylene macrocycle **4** (Fig. 6).[18a] Computational calculations, X-ray diffraction and microscopic analyses confirm the construction of well-defined shaped-persistent long nanotubes, that form stable pores of 6.4 Å diameter. MTNs show significant water permeability ($2.6 \pm 0.4 \times 10^{-14}$ $cm^3\ s^{-1}$, ~ 22% that of Aquaporin-AQP1 or 4.9×10^7 water molecules/s/channel) and ion channel transport activities: the conductance reaches ~ 5.8 pS for K^+, while no conductance is measured for Li^+ or Na^+ cations. These results have been confirmed by theoretical studies, confirming the selective of hydrated K^+ cations through MTNs.[18b] These studies demonstrate that the spatial distribution of water density profiles in the MNT interior, exhibit more remarkable wave patterns compared to the CNTs. The water transport mechanism would thus involve water molecules hopping between voids until a thermodynamically favorable location is found. Water molecules inside the MNT are subject to not only shape shifting but also rotation to satisfy the steric environment, which results in an inertial loss and slows down the water flow. These results indicate that the channel structure and channel–water or channel-ion interactions have a distinct impact on the transport properties of K^+ ions[18b] and water molecules.[18c]

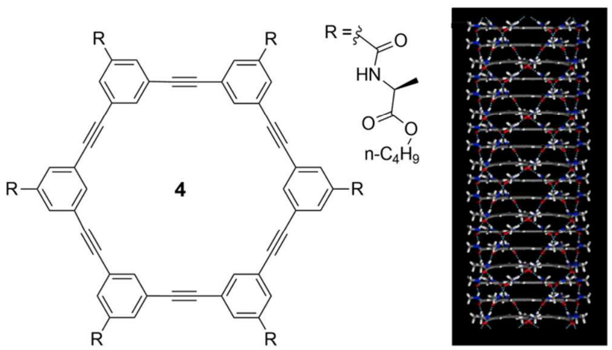

Figure 6. Simulated hydrophobic tubular pores formed via self-assembly of arylene-ethynylene macrocycle **4**. Adapted from reference 18a

Within this context, a model of crystalline water pore with a variable inner diameter between 5.9-9.4 Å, created by self-assembly of a sugar-based organic monomer, may encapsulate two types of water molecules in slow equilibrium that can be distinguished by static ^2H-NMR. Their dynamics are different: the water covering the surface of the pore remains most of the time H-bonded, preventing pore collapse, while the water clusters distributed along the inner pore produces a water-wetting path, that renders the observed permeability and causes the water to reversibly fill the pore, depending on the exterior water vapor pressure.[19]

Unimolecular Artificial water channels

Hou and co-workers introduced for the first time unimolecular artificial water channel systems. Polydrazide-pillar[5]arenes, **PAHs** are used to form tubular H-bonded superstructures of ~6.5 Å diameter, which are robust when embedded in bilayer membranes, present low water permeability (40 water molecules/s/channel) and are non-selective against cations (Fig. 7).[20] The water transport rates are strongly dependent on the length of the tubular assemblies: the former pillar[5]arene-tetraester, **5** which is the shortest on in the series, induce the formation of water-wires in stacked polymeric cylinders, which can successfully be used to translocate protons via bilayer membranes.[20a] The introduction of poly-hydrazide appended

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arms on pillar[5]arene core platform, results in the formation of alternative hydrophobic/hydrophilic regions in compounds **6a,b**, which disrupt the formation of water wires and thus block the proton flux. In crystal structures the water is H-bonded and forms dimers near to the hydrophilic regions of the channel, while other disordered water molecules can be observed in the hydrophobic region in the crystal structure.[9] The medium-length hydrazide pillar[5]arenes **6** transport water only if two molecules are pillared in the bilayer and its activity is depending on concentration.[20b] The longest hydrazide-pillar[5]arene, **7** of 3.5 nm length, perfectly fits the thickness of the bilayer and shows an low activity for water (8.6×10^{-6} µm/s or 40 water molecules/s/channel) and hydroxyl anion transport. Very interestingly, the unimolecular hydrazide-pillar [5]arene, **7** as well as the AQPs, did not transport protons. Oppositely to AQPs, which control the water/proton selectivity based on the opposite dipolar orientation of the half-channel confined water wires, the unimolecular channels of **7** control the proton/water selectivity *via* the water wires' disruption within the channels.

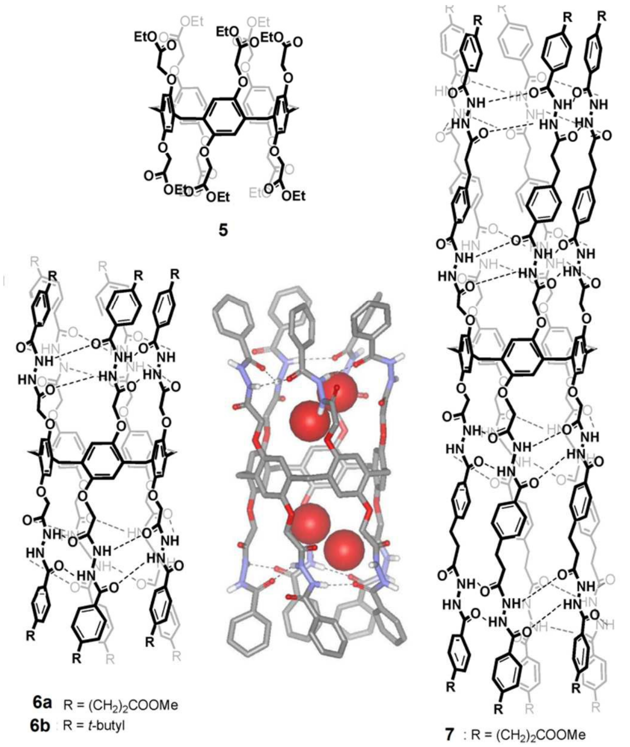

Figure 7 Structures of pillar[5]arene derivatives **5**-**7** used unimolecular artificial water channels. Adapted from reference 20a

Extending the concept of single-molecule AWCs, Kumar and Hou *et al.* described a second generation of peptide-appended pillar[5]arenes, **PAPs** (Fig. 8).[22] The average single-channel osmotic water permeability in swelling mode for PAPs is 3.5×10^{8} water molecules/s, which is in the range of AQPs (10^{8}-10^{9} water molecules/s)[3c] and CNTs (9.0×10^{8} water molecules/s).[15] The water conduction inside the PAP channels is featured by wetting–dewetting transitions, that renders the observed permeability corresponding to the dry and wet states of the channels. A drawback of the **PAHs** and **PAPs** channel is its substrate selectivity. The **PAPs** channels having a diameter of the inner pore of ~ 5 Å, are not suitable to selectively transport water and to remove salts and other small solutes. They are allowing the transport of cations for which the transport selectivity is controlled by their hydration energy: $NH_4^+ > Cs^+ > Rb^+ > K^+ > Na^+ > Li^+ > Cl^-$. Importantly, the **PAPs** channels can self-assemble into 2D arrays that may inspire their incorporation into future membrane materials for water-purification applications.[22]

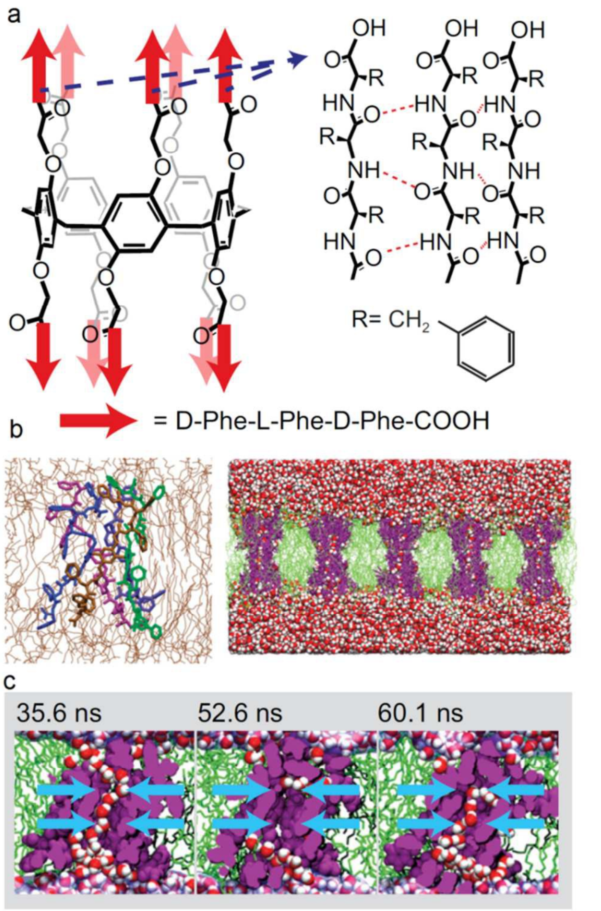

Figure 8. a) Structure of the peptide-appended pillar[5]arene (PAP) channel and b) MD simulation of the PAP channel in a POPC bilayer revealing its interactions with the surrounding lipids. C) Wetting/dewetting of a PAP channel. The channel is shown as purple van der Waals spheres, POPC lipids are shown in green stick representation, and water molecules are shown by red and white van der Waals spheres. Adapted from reference 22.

Chirality and dipolar water orientation

Chirality is a key structural feature of biological matter. Specific interactions of water molecule (which differently to ions, present a dipole) with the chiral synthetic pores or surfaces may align the water molecules, therefore presenting unique directional orientation/order. In fact, the dissymmetric

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net-dipolar orientation of water molecules is in fact, reading the chiral dissymmetry of the chiral pore space.

Experimental and theoretical studies by Fenneri *et al*. established that the H-bonded thermodynamically stable supramolecular nucleobase *chiromers* may form in the presence of well oriented water-clusters.[23] The solvation models revealed unique oriented arrangements of water clusters around the *chiromer* molecules and they are involved in an extensive network of H-bonds with the exocyclic amino group and/or the pyrimidinic G^C bases. These *chiromers* memorize and amplify their chirality in an achiral environment, they change their chirality in response to solvent (i.e. water) or temperature and catalytically transfer their chirality. On the same line, Jeong *et al.* recently shown that a series of indolocarbazole–pyridine oligomers may fold into helical structures with cylindrical internal cavities wherein oriented water-wires are confined.[24]

Several examples indicated that the supramolecular chirality and dipolar alignment of water-wires inside the AWCs may in principle, strongly be associated.[10,25] We have shown that, chirality is a key feature influencing the I-quartet water channels permeability. Within this context, it was observed that the activity of the chiral I-quartets is superior to that of the isostructural non-chiral isomers (Fig. 9). This would firstly suggest that the chiral lipids may exert a conformational preference, stabilizing the chiral superstructures. Secondly, the net-dipolar orientation of the water-wires would impose an internal dielectric polarization within the chiral channels, acting as a supplementary driving force for water/proton translocation.

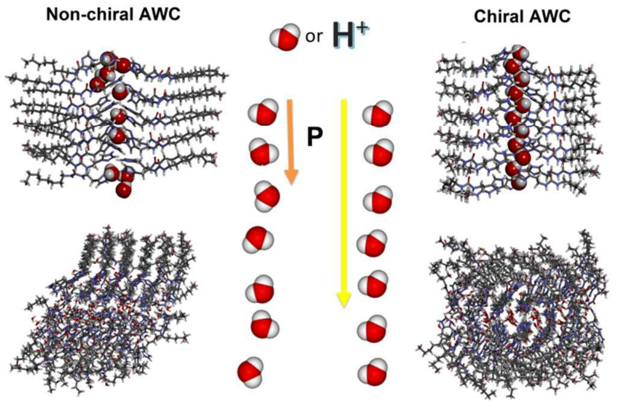

Figure 9. The water and proton permeabilities (*P*) are higher in chiral AWCs (preserving a net-dipolar orientation of water-wires) than the non-chiral isostructural AWCs (presenting non-oriented water-wires). Non-chiral (left) and chiral (right) molecular packing of I-quartet AWCs in stick representation embedded in the bilayer membrane environment (not shown for clarity).

From the conceptual point of view, the chiral oriented water-wires express a synergistic adaptive behaviour: the chiral structure of the channel drives the constitutional self-assembly toward the selection and amplification of the oriented water wires which enhance its own translocation. This is a nice example of dynamic self-instructed system where a solute self-assembly induces the upregulation of its own translocation through the channel!

Similar conclusions emerged from the investigation of the T-channels resulted *via* multiple H-bonding self-assembly of the bola-amphiphilic bis-triazole compound (TCT), **8** (Fig. 10).[25a] The TCT forms stable helical pores in lipid bilayers. Experimental assays revealed that the T-channel with the hydrated carbonyl and amine moieties pointing toward the T-channel centre and surrounding the transport direction, presents moderated water permeability and large open ion-conductance states with high cation/anion selectivity in bilayer membranes.[25a]

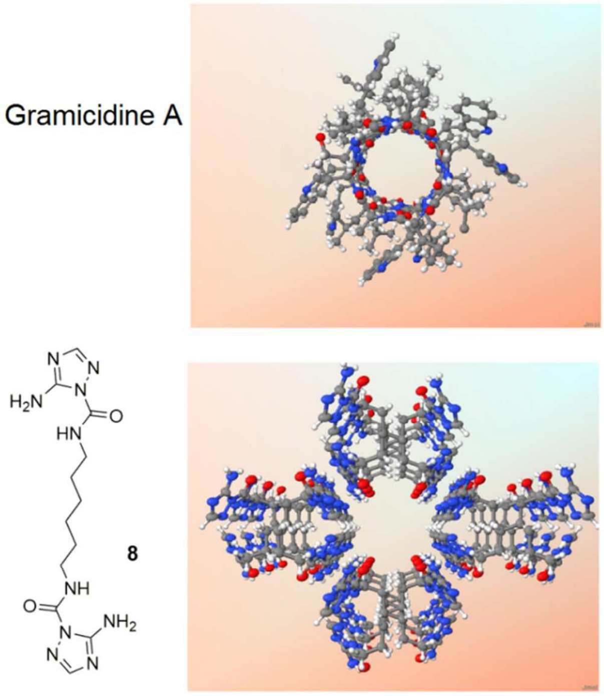

Figure 10. Single crystal structures of Gramicidine A (top) and the helical T-channel pore resulting from the self-assembly of the bola-amphiphile compound triazole **8** (bottom) represented at the same dimensional scale. Adapted from reference 25a.

The T-channel present diastereoisotopic inner hypersurfaces on which double helical water arrays can form (Fig. 11). Theoretical Monte Carlo simulations shed light on important behaviors of the dynamic superstructures of water and electrolyte solutions (alkali chlorides) confined in T-channels.[25b] The strong interaction between water and the surface T-channel groups imposes surface-induced polarization of confined water, having dielectric properties that differ significantly from their bulk counterparts. The result shows that, even in the presence of ions, the average dipole orientation of water in the plane perpendicular to the T-channel axis is driven by the interaction with the functional groups of the surface. In other words, despite the strong coulombic water/ion interaction, water remains significantly ordered in the T-channel.

Consequently, the cation and water permeation through the T-channel is performed in double-file: parallel water and cation-wires translocate along the T- channel via successive

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hydration-dehydration processes. The helical water-wires, acting as lubricant between the internal chiral surfaces of T-channel and diffusing ions, impose an oriented total alignment of water dipoles that influence ion conduction, envisioned to be pumped along the dipolar hydrophilic water-wires.

Table 1. Overview of design principles and the molecular building blocks used to create artificial water channels and pores

Compound	Nature of the channel	Net Permeability/ Selectivity/ Single channel permeability	Reference
Aquaporins - **AQPs**	Natural highly selective protein channels. hourglass structure of the pore, with a narrowest constriction of 2.8 Å	High selectivity for water and perfect rejection of ions and protons/ **4x10^9 water molecules/s/channel**	3c
Carbon Nanotubes- **CTNs**	The estimated diameter of CTNs (12,12) is 16 Å	No ions rejection: stable and high permeability of water/ 9x10^8 water molecules/s/channel	15
Dendritic dipeptide, (4-3,4-3,5)-12G2-CH2-Boc-L-Tyr-L-Ala-OMe, **1**	Hydrophobic H-bonded peptidic central pore (14.5 Å) and stacked dendritic periphery	No permeability reported/ Water against ions except protons	14
I-quartet Channels, **2** Alkylureidoimidazoles	Hydrophilic H-bonded imidazole channel (2.6 Å) and hydrophobic peripheral alkyl chains	1.0- 4.0 μm/s (shrinking mode) / high selectivity for water reject all ions except protons/ **1.5 x 10^6 water molecules/s/channel (shrinking mode)**	11
Aquafoldamers **3**	Hydrophilic helical channel (2.8 Å) via π-π stacking of aromatic units	No permeability reported/ high selectivity for water, reject all ions except protons/	15
Tubular pores formed via self-assembly of arylene-ethynylene macrocycle **4**	Hydropobic tubular channel (6.4 Å) via π-π stacking of aromatic units and H-bonding of peptide appended arms	51 μm/s/ no selectivity for water, high conduction for K$^+$ and protons/ **4.9x10^7 water molecules/s/channel**	18a, 22
Hydrazide appended Pillar[5]arenes, **PAHs 5-7**	Hybrid hydrophobic/hydrophilic cylindrical (6.5 Å) unimolecular systems.	8.6 × 10^{-6} μm/s / no selectivity for water, good conduction for alkali cations but no conduction for protons/ **40 water molecules/s/channel**	19
Peptide appended Pillar[5]arenes, **PAPs**	Hybrid hydrophobic/hydrophilic cylindrical (~5 Å) unimolecular systems.	30 μm/s (swelling mode) / no selectivity for water, good conduction for alkali cations **3.5 10^8 (swelling mode)** and **3.7x10^6 water molecules/s/channel (shrinking mode)**	22
Bola-amphiphile bis-triazole (TCT), **8** T-channels	Self-assembled helical pores (~2.5-4 Å); Double helical water channels with double net-dipolar orientation	No permeability reported for water/ enhanced conduction states for alkali cations and for protons	25a,b

The net-dipolar orientation of water wires is of tremendous importance in the electrostatic enhancement of the pumping of cations across the T-channel. Cation rate transport enhancement is related on the basis that the dipolar alignment of water molecules acts as a driving force for ion permeation. This translocation mechanism may also give rise to novel strategies to mimic protein-channels and describe new scenarios of the polarization on chiral biological surfaces, lubricated with electrostatically active dipolar water clusters.[25b]

The T-channel - associating supramolecular chirality with water alignment inside the channels - represents an amazing alternative for novel scenarios of activated ion-pumping along dipolar water-wires, involving a supplementary dielectric contribution of the net-dipole of the water-wires for the complete description of ion conduction through the T-channel.

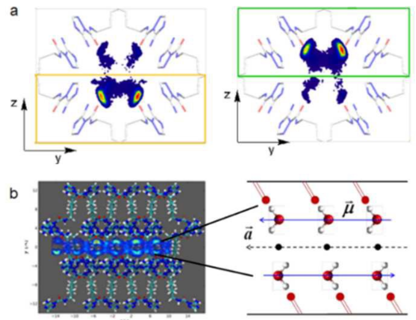

Figure 11. a) Density contour plot of water molecules with the dipole pointing (*left*) downward and (*right*) upward with respect to the vector $\vec{a}$) b) Schematic representation of the T-channel ; the blue vectors illustrate the average dipolar orientation of the water in the lower and upper parts of the T-channel. Adapted from reference 25b.

Conclusions

“Compartmentalization” is a basic feature of biological systems, as most of the physiological processes in biomolecules occur under confined conditions like the ionic/water transport through narrow pores, enzymatic

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reactions in active pockets, etc. Dynamically organized water-clusters would considered having an amazing contribution for understanding complex biological scenarios.[7] Moving from conventional liquid water to biological water is not simply just a matter of size, as the behaviours of confined water are quite different from its behaviours under bulk conditions.[8]

Despite the imagination of chemists to develop artificial architectures confining water clusters, the most employed strategies for water transport through bilayer or polymeric membrane systems use the natural AQPs. These studies have demonstrated that natural AQPs can be used for the construction of highly selective artificial membranes for water transport. Moreover, artificial channels have been explored mostly with the hope to mimic the natural ionic conduction, producing an impressive number of artificial ion-channels, facing the world of natural proteins.

Amazingly, there has been less progress in the area of synthetic water channels and materials presenting highly selective water conductance states, excluding ions within natural conditions. The first developments in this field presented in these paper (Table 1), let us imagine that high conduction activity obtained with natural AQPs can be obtained by using simpler artificial compounds, self-assembling in functional water channels displaying selectivity functions *like the natural ones* (Fig. 12). The future may involve all-made *artificial biomimetic channels* by using synthetic approaches.

All examples presented here would also do much to restore some balance to our understanding of the biomimicking of functions of natural AQPs and remains an important exploring challenge. We are confident that in the short term a compromise is going to be reached and Artificial Water Channels will build up around/together with the abundant Artificial Ionic Channels field. In this way, the requirement of size, high water *vs.* ions selectivity and chirality amplified/ oriented transport can met with welcome efficiency, albeit restricted variety.

These findings show that natural channels can be bio-mimicked using simpler artificial compounds displaying constitutional functions like the natural ones. The water channel systems provides remarkable combinations of functions very close to those encountered in natural systems, and the dynamic orientational behaviors of confined water can be elucidated using such simplified systems**.**

From the examples presented here, we know that a pore with a diameter of ~ 3 Å is a critical prerequisite for ion-exclusion behaviours. The total ionic-exclusion properties of I-quartet, **2** and aquafoldamer, **3** suggests that they hold significant promise for the incipient development of the first effective artificial synthetic systems mimicking the functions of natural AQPs: high water permeability (10^6 water molecules/s/channel - shrinking mode) and total ionic rejection.

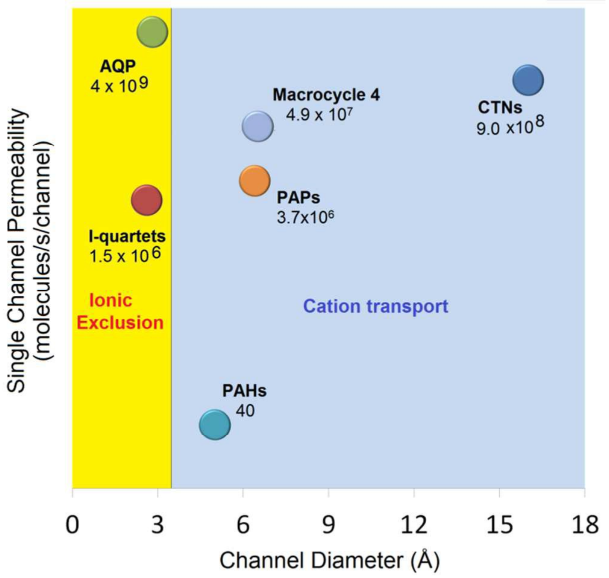

Figure 12. Comparison Single channel Permeabilities versus diameter of the Channel of **AQPs**, **CTNs** and Artificial Water Channels (**I-quartet**, **PAHs**, **PAPs**, Macrocycle 4) discussed in this paper- see also Table 1.

Bigger pore diameters (> 3 Å) of **4**-**7** and **PAPs**, are at long last beginning to meet encouraging signs for high water permeability (10^6-10^8 water molecules/second/), while most of these channels present ionic transport activity.

These assumptions are in line with recent statements on interlayer spacing of less than 7 Å a size identical to the thickness of two confined layers of water (~2x3 Å) between Graphene-Oxide-GO sheets), that can be optimally used as possible GO membranes in water desalination. In contrast, an enlarged GO spacing allow ionic permeation and precise separation of larger biomolecules or waste molecules.[29]

It is also very well known that the water molecules permeate through natural potassium *KcsA* K^+ channel, together with the K^+ ions in a concerted way.[26] Interestingly, potassium depleted *KcsA* K^+ channel is adaptively changing its conformation to allow water transport ~20 time faster than one dimensional bulk diffusion of water.[27,28] The studies of the combined artificial water/ionic channels should relate on synergetic water-ionic translocation through confined in *aqua(iono)pores* and might improve our understanding on complementary ion-water interactions under confined conditions, arousing a great deal of interest as challenges in both water and ion-channels developments.

Chirality is another basic feature of biomolecules. The directional net-dipolar ordering of confined water-wires, as observed inside chiral aquapores[10,25] or CTNs[30] would be more generally assimilated with the water-cluster self-assembly on the surfaces of biological compartments/pockets, which are most of them chiral. The net-dipolar orientation of water may induce specific dielectric properties, which most probably should dielectrically contribute to the molecular interactions inside biocavities and to the metabolite diffusion along the polarized biointerfaces. Correlations between the above mentioned artificial channel superstructures and the wellstudied functional protein, might allow designing novel mechanisms that parallel to natural ion-pumping processes. Conversely, the dynamical yet slow molecular-scale hydrodynamics of confined water is of crucial relevance for understanding complex functions at the heart of interesting biological scenarios.

Oriented self-organization of water dipoles may be directed *via* the molecular information stored in the structural framework of biological matter and read out through collective water-dipole waves/ patterns that define processing algorithms. The overall process is thus target-driven, adaptive and dynamic.

Along another line of thought, one might also consider that the collective ability of such dipolar water molecules to potentially generate *water-waves (waves of water dipoles)*, representing a sort of virtual superposition of all their oriented states operating collectively. They are physically reminiscent with the waves of electrons for which their spins behave collective and stimuli adaptive behaviors. The condition to determine when *water-waves* function becomes observable it rests an unconventional practice and challenge. For some systems presented in this paper (i.e. I quartets[10] or T-channels[25b]) the transport rates of oriented water-wires are determined to be superior to the non-oriented ones.

Finally, this Feature Article is not a comprehensive treatise, but is a timely objective snapshot of the Artificial Water Channels field from which the reader can get a broader insight into this and hopefully a future source of inspiration, precluding to further sustained effort in this area. Farewell.

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References

1 S. Cukiermann, *Biophys. J.* 2000, **78**, 1825-1834.
2 B. Roux, *Acc. Chem. Res.* 2002, **35**, 366-375.
3 a) P. Agre, *Angew. Chem. Int. Ed.* 2004, **43**, 4278-4290; b) E. Tajkhoorshid, P. Nollert, M. O. M. Jensen, L. J. W. Miercke, J. O'Connell, R. M. Stroud, K. Schulten, *Science* 2002, **296**, 525-530; c) M. L. Zeidel, S. V. Ambudkar, B. L. Smith, P. Agre, *Biochemistry*, 1992, **31**, 7436-7440.
4 R. Mackinnon, *Angew. Chem. Int. Ed.* 2004, **43**, 4265-4277.
5 L. H. Pinto, G. R. Dieckmann, C. S. Gandhi, C. R. Papworth, J. Braman, M. A. Saughnessy, J. D. Lear, R. A. Lamb, W. F. De Grado, *Proc. Natl. Acad. Sci. U.S.A.* 1997, **94**, 11301-11306.
6 a) F. Hu, W. Luo, M. Hong, *Science* 2010, **330**, 505-508; b) M. Sharma, M. Yi, H. Dong, H. Qin, E. Paterson, D. D. Busath, H. X. Zhou, T. A. Cross, *Science* 2010, **330**, 509-511.
7 P. Ball, *Chem. Rev.* 2008, **108**, 74-108.
8 a) D. Zhong, S. K. Pal, A. H. Zewail, *Chem Phys. Lett.* 2011, **503**, 1-11; b) S. K. Pal, A. H. Zewail, *Chem. Rev.* 2004, **104**, 2099-2123.
9 a) Y.-X. Shen, P. O. Saboe, I. T. Sines, M. Erbakan, M. Kumar *J. Membr. Sci.* 2014, **454**, 359-381 ; b) M. Kumar, M. Grzelakowski, J. Zilles, M. Clark, W. Meier, *Proc. Natl. Acad. Sci. U.S.A.* 2007, **104**, 20719-20724; c) C. Y. Tang, Y. Zhao, R. Wang, C. Hélix-Nielsen, A. G. Fane, *Desalination,* 2013, **308**, 34–40.
10 Y. Le Duc, M. Michau, A. Gilles, V. Gence, Y.-M. Legrand, A. van der Lee, S. Tingry, M. Barboiu, *Angew. Chem. Int. Ed.* 2011, **50**, 11366-11372.
11 M. Barboiu, *Angew. Chem. Int. Ed.* 2012, **51**, 11674-11676.
12 a) M. Barboiu, A. Gilles, *Acc. Chem. Res.* 2013, **46**, 2814–2823 ; b) Y.-X. Shen, P. O. Saboe, I. T. Sines, M. Erbakan, M. Kumar *J. Membr. Sci.* **2014**, 454, 359-381.
13 a) L. J. Barbour, G. W. Orr, J. L. Atwood, *Nature* 1998, **393**, 671-673; b) M. Yoshizawa, T. Kusukawa, M. Kawano, T. Ohhara, I. Tanaka, K. Kurihara, N. Niimura, M. Fujita, *J. Am. Chem. Soc.* 2005, **127**, 2798-2799; c) Y.-M. Legrand, A. van der Lee, N. Masquelez, P. Rabu, M. Barboiu, *Inorg. Chem.* 2007, **46***,* 9083-9089*;* d) L. E. Cheruzel, M. S. Pometum, M. R. Cecil, M. S. Mashuta, R. J. Wittebort, R. M. Buchanan, *Angew. Chem. Int. Ed.* 2003, **42**, 5452-5455; e) Z. Fei, D. Zhao, T. J. Geldbach, R. Scopelliti, P. J. Dyson, S. Antonijevic, G. Bodenhausen, *Angew. Chem. Int. Engl*. 2005, **44**, 5720-5725; f) Y.-M. Legrand, M. Michau, A. van der Lee, M. Barboiu, *CrystEngComm*. 2008, **10**, 490-492; *g)* C. H. Gorbitz, *Chem. Eur. J.* 2007, **137**, 1022-1031; h) A. Muller, H. Bogge, E. Diemann, *Inorg. Chem. Commun*. 2003, **6**, 52-53; i) T. Mitra, P Miro, A.-R Tomsa, A. Merca, H. Bogge, J. Bonet Avalos, J. M. Poblet, C. Bo, A. Müller, *Chem. Eur. J.* 2009, **15**, 1844 – 1852.
14 a) V. Percec, A. E. Dulcey, V. S. K. Balagurusamy, Y. Miura, J. Smirdrkal, M. Peterca, S. Numellin, U. Edlund, S. D. Hudson, P. A. Heiney, H. Duan, S. N. Magonov, S. A. Vinogradov, *Nature* 2004, **430**, 764-768; b) M. S. Kaucher, M. Peterca, A. E. Dulcey, A. J. Kim, S. A. Vinogradov, D. A. Hammer, P. A. Heiney, V. Percec, *J. Am. Chem. Soc.* 2007, **129***,* 11698-11699; c) see other examples of aquapores in: E. Krieg, M. M. C. Bastings, P. Besenius, B. Rybtchinski, *Chem. Rev.* 2016, **116**, 2414−2477.
15 J. K. Holt, H. G. Park, Y. Wang, M. Stadermann, A. B. Artyukhin, C. P. Grigoropoulos, A. Noy, O. Bakajin, *Science* 2006, **312**, 1034-1037.
16 (a) H. Zhao, S. Sheng, Y. Hong, H. Zeng, *J. Am. Chem. Soc.* 2014, **136**, 14270-14276; (b) H. Fu, Y. Liu, H. Zeng, *Chem. Commun.* 2013, **49**, 4127-4144; c) W. Ma, C. Wang, J. Li, K. Zhang, Y-J. Lu, Y. Huo, H. Zeng, *Org.* Biomol. Chem., 2015, **13**, 10613–10619.
17 a) P. Xin, L. Zhang, P. Su, J.-L. Hou, Z.T. Li, *Chem. Commun.*, 2015, **51**, 4819—4822; b) D. W. Zhang, X. Zhao, Z. T. Li, *Acc. Chem. Res.* 2014, **47**, 1961-1970.
18 a) X. Zhou, G. Liu, K. Yamato, Y. Shen, R. Cheng, X. Wei, W. Bai, Y. Gao, H. Li, Y. Liu, F. Liu, D. M. Czajkowsky, J. Wang, M. J. Dabney, Z. Cai, J. Hu, F. V. Bright, L. He, X. C. Zeng, Z. Shao, B. Gong, *Nat. Commun*. 2012, **3**, 949; b) H. Li, J. S. Francisco, X.C. Zeng, *Proc. Natl. Acad. Sci. U.S.A.* 2015, **112**, 10851-10856; c) X. Li, K. Yang, J. Su, H. Guo, *RSC Adv.*, 2014, **4**, 3245−3252.
19 M. Febles, N. Perez-Hernandez, C. Perez, M. L. Rodrıguez, C. Foces-Foces, M. V. Roux, E. Q. Morales, G. Buntkowsky, H.-H. Limbach, J. D. Martın, *J. Am. Chem. Soc.*, 2006, **128**, 10008–10009.
20 a) W. Si, L. Chen, X.-B. Hu, G. Tang, Z. Chen, J.-L. Hou, Li, Z.-T. Angew. Chem., Int. Ed. 2011, 50, 12564; b) P. Xin, P. Zhu, P. Su, J. L. Hou, Z. T. Li, *J. Am. Chem. Soc.*, 2014, **136**, 13078–13081; c) W. Si, P. Xin, Z.-T. Li, J.-L. Hou, *Acc. Chem. Res.* 2015, **48**, 1612−1619.
21 W. Si, Z.-T. Li J.-L. Hou, *Angew. Chem. Int. Ed.* 2014, **53**, 4578 –4581

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DOI: 10.1039/C6CC01724J

22 Y. X. Shen, W. Si, M. Erbakan, K. Decker, R. De Zorzi, P.O. Saboe, Y.J. Kang, S. Majd, P.J. Butler, T. Walz, A. Aksimentiev, J. L. Hou, M. Kumar, *Proc. Natl. Acad. Sci. U.S.A.* 2015, **112**, 9810-9815.

23 R. S. Johnson, T. Yamazaki, A. Kovalenko, H. Fenniri, *J. Am. Chem. Soc.* 2007, **129**, 5735-5743

24 H.-G. Jeon, J. Y. Jung, P. Kang, M.-G. Choi, K.-S. Jeong, J. Am. Chem. Soc. 2016, 138, 92−95

25 a) M. Barboiu, Y. Le Duc, A. Gilles, P.-A. Cazade, M. Michau, Y.-M. Legrand, A. van der Lee, B. Coasne, P. Parvizi, J. Post, T. Fyles, *Nature Commun.* 2014, **5**, 4142 ; b) M. Barboiu, P. A. Cazade, Y. Le Duc, Y. M. Legrand, A. van der Lee, B. Coasne, *J. Phys. Chem. B,* 2015, **119**, 8707-8717.

26 S. Bernèche B. Roux, *Nature* 2001, **414**, 73-77.

27 S. M. Saparov, P. Pohl, *Proc. Natl. Acad. Sci. USA* 2004, **101**, 4805–4809.

28 S. Furini, O. Beckstein, C. Domene, *Proteins* 2009, **74**, 437–448.

29 B. Mi, *Science* 2014, **343**, 740-742.

30 a) S. Joseph, N. R. Aluru, *Nano Lett.* 2008, **8**, 452-458; b) C. Dellago, M M. Naor, G. Hummer *Physical Rev. Lett.* 2003, **90**, 105902.