Controlling Water Flow through a Synthetic Nanopore with Permeable Cations

Yi Shen, Fan Fei, Yulong Zhong, Chunhai Fan, Jielin Sun, Jun Hu, Bing Gong, Daniel M. Czajkowsky, and Zhifeng Shao*

ABSTRACT: There is presently intense interest in the development of synthetic nanopores that recapitulate the functional properties of biological water channels for a wide range of applications. To date, all known synthetic water channels have a hydrophobic lumen, and while many exhibit a comparable rate of water transport as biological water channels, there is presently no rationally designed system with the ability to regulate water transport, a critical property of many natural water channels. Here, we describe a self-assembling nanopore consisting of stacked macrocyclic molecules with a hybrid hydrophilic/hydrophobic lumen exhibiting water transport that can be regulated by alkali metal ions. Stopped-flow kinetic assays reveal a non-monotonic-dependence of transport on cation size as well as a strikingly broad range of water flow, from essentially none in the presence of the sodium ion to as high a flow as that of the biological water channel, aquaporin 1, in the absence of the cations. All-atom molecular dynamics simulations show that the mechanism underlying the observed sensitivity is the binding of cations to defined sites within this hybrid pore, which perturbs water flow through the channel. Thus, beyond revealing insights into factors that can modulate a high-flux water transport through sub-nm pores, the obtained results provide a proof-of-concept for the rational design of next-generation, controllable synthetic water channels.

INTRODUCTION

Artificial structures with sub-nanometer-sized pores or gaps are presently being actively investigated for a wide range of technological applications such as the development of membrane-bound molecular devices, biomimetic molecular and ion channels, and high-performance membranes for separation and purification. A prime goal in this field is the development of structures that permit the transport of specific atomic or molecular species at a high rate. Indeed, this attribute has been well-demonstrated with many synthetic one-dimensional or two-dimensional architectures. With this success, however, it is becoming clear that a high transport rate is only one of the major parameters required for many applications: equally important is the ability to rationally control the transport rate, thereby affording a means to permit the flow to occur only under specifically defined conditions. Yet, the incorporation of a gating mechanism that enables such regulated flow has presented a daunting challenge for most artificial nanopores known to date.

Among these structures, those designed to specifically transport water have attracted significant attention owing to potential practical applications such as molecular sensing, water purification, and molecular separations, as well as for what they can reveal about fundamental mechanisms of matter flow through confined geometries. The inspiration for many of these synthetic water channels is the family of biological water channels, the aquaporins, which have evolved the ability to exhibit a very high rate of water permeability (up to $3 \times 10^9$ water molecules per second) as well as a means of gating this transport either by divalent cations or phosphorylation. Structural studies of the aquaporins have revealed a narrow hydrophobic lumen, and perhaps as a result, all currently known synthetic water channels also have a sub-nanometer hydrophobic lumen, which is generally believed to be a basic requirement for a high flow rate of water. Indeed, consistent with this expectation, an exceptionally high rate of water flow has been demonstrated with many of these synthetic constructs. Still, it is challenging, if not impossible, to effect controllability to water transport with only hydrophobic moieties. As a result, there is presently no
rationally designed system showing the ability to control water transport in artificial channels.

We recently developed a shape-persistent macrocycle that, in lipid bilayers, spontaneously stacks on top of each other to form a transmembrane nanopore. In particular, we examined four different macrocycles and showed columnar stacking of these macrocycles as well as single-channel electrophysiological data showing ion conductance. The parent macrocycle (1) (Figure 1a) was designed to have a novel hybrid, hydrophobic−hydrophilic lumen: the hydrophobic segment was expected to afford efficient water transport, while the hydrophilic (anionic) segment was included to potentially enable control of water transport. Yet, whether such a hybrid lumen architecture would in fact enable effective water transport, as it permits highly selective cation transport, was not clear.

Here, we show that indeed this hybrid nanochannel exhibits exceptionally high water flow and a means by which this flow can be regulated, namely, by the presence or absence of alkali metal ions. Further, molecular dynamics simulations reveal the importance for this control on both the strength of the interaction of these cations with the luminal anionic moieties and also of the first-shell waters with the cations in the pore. Overall, beyond providing a means by which water flow within synthetic nanochannels can now be controlled, we envision that this mechanism may prove generally useful for the control of molecular or ionic transport with other nanochannels more broadly.

RESULTS AND DISCUSSION

Our previous work demonstrated the spontaneous self-assembly of a macrocycle (1) (Figure 1a) into nanochannels in lipid bilayers that exhibit selective cation transport. To examine the water transport ability of these hybrid nanochannels, we used a lipid-vesicle-based stopped-flow kinetic assay, which takes advantage of the concentration-dependent self-quenching properties of the fluorescent dye, carboxyfluorescein (CF) (Figure 1b). Analyzing the temporal changes in CF fluorescence enables a direct measurement of the transmembrane water permeability (see Methods in the Supporting Information). The water permeability specifically elicited by the nanopores (ΔP\text{nano}) is determined by subtracting the total water permeability measured of vesicles without nanopores from that of vesicles with nanopores.
In most studies of transmembrane water transport, the osmotic driving force for water movement is generated by a difference in the concentration of a monovalent salt across the membrane. However, owing to the presence of the anionic moieties within the lumen of our nanopore, it was necessary to establish a method that excluded all possible permeable cations, since such cations might affect water transport (see below). Thus, we developed a novel strategy based on the creation of a transmembrane concentration gradient of polyethylene glycol (PEG) to generate the osmotic pressure (Figures 1c and S1). Further, to maintain CF solubility, we also used L-arginine, a cationic amino acid incapable of passing through our nanopore (Figure S2), to control the pH. With this strategy, efficient water transport through these nanopores was indeed readily detected (Figure 1d), yielding a measurement of $\Delta P_{\text{nano}}$ of $1.5 \pm 0.2 \times 10^{-3}$ cm s$^{-1}$. To convert the measured $\Delta P_{\text{nano}}$ into the water permeability per channel, $p_{\text{nano}}$, we first directly measured the amount of macrocycles in the vesicle preparation. This was aided by the observation that, when redissolved in CCl$_4$/CHCl$_3$, excitation at 310 nm yielded an emission spectrum in which the integrated intensity from 460 to 490 nm is directly proportional to the macrocycle concentration (Figure S3). Using this, we calculated the mole ratio of lipids to macrocycles in our preparation to be $\sim 2.7 \times 10^3$. With a mean vesicle diameter of $\sim 130$ nm (Figure S4) and assuming that 10 macrocycles form a membrane-spanning nanochannel, we thus estimate that there are $\sim 10$ nanopores per vesicle, and hence, a value of $p_{\text{nano}}$ of $9.7 \pm 1.1 \times 10^{-14}$ cm$^3$ s$^{-1}$ per pore. Thus, water transport through this hybrid nanopore is indeed highly efficient, comparable to aquaporin 1 ($11.7 \times 10^{-14}$ cm$^3$ s$^{-1}$) as well as many existing synthetic nanopores (with purely hydrophobic lumens).43–45

Having established efficient water transport through these nanopores in salt-free water, we next examined for an ability to control this transport. In particular, with an anionic lumen and a pore size ($\sim 0.6$ nm in diameter) that is capable of accommodating only partially hydrated monovalent cations, we expected that the magnitude of water transport would be influenced by the presence of monovalent cations in the pore.

To provide insight into this process, we first performed all-atom molecular dynamics simulations (Figure 2a). Ab initio calculations of the bare macrocycle (that is, without the amide/acyl side-chain) showed that the energy-minimized structure is largely planar: the luminal inwardly pointing carbonyl atoms twist slightly away from directly facing their symmetric counterparts and, consequently, produce a slight warping of the whole macrocycle (Figure 2a). The lumen itself is teardrop-shaped, with a pair of carbonyls at one apex of the central void (the “peripheral” carbonyls) and a pair of central carbonyls (the “central” carbonyls) delimiting the anionic portion of the pore and three aromatic moieties, along with two carbon–carbon triple bonds, lining the hydrophobic side of the pore (Figure 2a). A model for the nanopore was then constructed by attaching the secondary amide/acyl side chains to the energy-minimized macrocycle and by stacking together 10 macrocyclic molecules with the stacking distance of 3.5 Å, the typical aromatic stacking distance (Figure 2b).45 The resultant nanopore was then placed within a lipid bilayer in water (Figure S5).

As shown in Figure 2c, upon reaching equilibrium, the inner pore of the nanochannel was found to be completely filled with water. There were generally water molecules in close proximity to the peripheral carbonyls in the inner pore, oriented with the hydrogen atoms facing the carbonyl oxygens (Figure 2c). However, other than this tendency, water molecules within the
lumen exhibited a broad range of organizations. To examine the transport of water through this nanopore in pure water, we generated a water pressure across the membrane by applying a force to the water oxygen atoms located within a thin slab far from the membrane surface, as previously described (Figures S5 and S6).50 We found that, with this pressure, these nanopores permitted rapid water transport (Figures 2d and S7), corresponding to a transport rate of $28 \times 10^{-14} \text{cm}^3 \text{s}^{-1}$, which is comparable to that measured experimentally ($9.7 \times 10^{-14} \text{cm}^3 \text{s}^{-1}$), with the slight difference possibly owing to the use of a much greater applied pressure in the simulations (see Methods in the Supporting Information).

A closer inspection of this transport revealed two different regimes: short bursts of high flux (examples shown with red bars in Figure 2d) associated with most (≈77%) of the transported water molecules and longer regimes of a slower rate of transport (shown with black bars in Figure 2d). As shown in Figure 2e (left), the short bursts of higher flux occur via the simultaneous, collective movement of nearly all water molecules in the pore in a common (upward) direction by a short distance (∼6–8 Å within 0.2 ns). By contrast, the slower rate of transport is not associated with any obvious collective movement but is instead a much more diffusive process (Figure 2e, right). This collective movement of pore waters is reminiscent of the transport through entirely hydrophobic nanochannels.45 Although, unlike the single-file transport of hydrophobic channels, there are only transient, short-lived organizations of the pore waters for which such collective movement is possible with these hybrid nanopores.

To examine the consequences of the presence of permeable cations on this water transport, we included 100 mM NaCl to the solution subtending the bilayer. During the initial equilibration simulations (that is, without water pressure), up to four Na$^+$ atoms spontaneously entered the pore, consistent with the overall electronegative interior (∼2.5 e$^-$ per macrocycle).46 (Figure 3a).

Interestingly, these cations were located at essentially only one of two radial positions: directly along the central axis (“axial”) or in close proximity to the nanochannel wall (“distal”) (Figure 3a,b). The ions in the distal binding sites were located in very close proximity to the oxygen atoms of two peripheral carbonyl groups, while those ions in the axial sites were positioned approximately in the middle between the central carbonyls of the macrocycle (Figure 3b). The cations located at the distal sites exhibited significantly smaller fluctuations than those at the axial binding sites (Figure S8), consistent with a stronger interaction at the former sites.

In the presence of water pressure, unexpectedly, we found only a very small amount of water transported through the channel (Figure 2d). Inspection of the Na$^+$ ions within the channel during this simulation revealed a remarkably relatively static organization (Figure 3c): a large fraction of the luminal Na$^+$ ions remained localized to the distal site and were thus largely immobile. We suspected that the prolonged binding of the cation to these sites leads to a likewise greater immobility of its associated water molecules, which ultimately results in the low rate of water transport. That is, the cations are effectively “trapped” in the pore, and the waters are delayed by these slowly moving cations, leading to the overall reduction in water transport rate.

As such, we expected that there would be a dependence of water transport on the cation type, since cations with a different size would be expected to bind to the distal location with different frequencies than Na$^+$. We therefore examined the water transport in the presence of Li$^+$, K$^+$, or Cs$^+$ by similar simulations. As shown in Figure 3d, during the initial equilibration simulations, a similar number (three to four) of each of these cations was found to spontaneously enter within the pore as Na$^+$. During the simulations with applied water pressure, we indeed found that water transport through the pore was significantly higher in the presence of each of these other cations compared to Na$^+$ (Figure 3e). Interestingly, while

Figure 3. Molecular dynamics simulations of water transport through the hybrid nanopores in the presence of cations. (A) Snapshot of the Na$^+$ and water organization within the pore during the equilibration simulations. The ions are found to localize either at the distal sites (left) or within the axial sites. (B) Two views showing the binding sites in more detail. The top panel shows the ion in the distal site (right) between two macrocycles, whereas the ion in the central site is not as precisely positioned along the central axis and can be found within a single macrocycle as shown. The lower panel is a top-down view showing the location of the ions with respect to the central axis of the pore. (C) The axial and radial positions of the Na$^+$ ions that were in the pore during the simulation, including one (Sodium #4) that entered the pore after about 40 ns. The ions in the distal binding site are at approximately 2 Å in the radial direction, while those in the axial binding site are near 0 Å. (D) Snapshot during the equilibration simulations showing the number and locations of Li$^+$, K$^+$, or Cs$^+$, together with the water molecules in the pore. (E) Number of water molecules transported through the nanopore after 70 ns of simulations in the presence of 100 mM LiCl, NaCl, KCl, or CsCl or in the absence of any salt in the solution. (F) Axial and radial positions of all Li$^+$, K$^+$, or Cs$^+$ in the pore during the simulations.
both K⁺ and Cs⁺ were found to be located at either a distal or axial binding site (like Na⁺), Li⁺ was only associated with the central site (Figure 3f).

To probe in greater detail the underlying mechanism for these differences in water transport rate, we examined the lifetime of the water molecules within the first shell of the pore cations. In general, we found that the lifetime of the first-shell waters is significantly different for cations in the distal binding site compared to the central site: it is ~5× longer for the cations in the distal binding site. Thus, since, among the different cations, the Na⁺ is most often located in the distal binding sites, the lifetime of its first-shell waters is the longest among the different cations, and thus, the water transport rate is lowest in the presence of Na⁺. For Li⁺, K⁺, and Cs⁺, we found that their first-shell lifetimes are 1.8×, 1.7×, and 3.4× shorter than the lifetime for Na⁺, respectively. These differences in lifetimes (inversely) recapitulate the extent by which the water transport rates in the presence of each of these cations are greater than in the presence of Na⁺ (Figure 3f). That is, (i) each of the permeable cations “delays” the movement of their first-shell water molecules (and so the water transport is lower than in the cation-free case); (ii) Li⁺, K⁺, and Cs⁺ delay their first-shell waters less than Na⁺ delays its first-shell waters (and so their water transport rates are higher); and (iii) the extent by which they are “less delayed” matches the extent by which the water transport rate is higher than that in the presence of Na⁺. Thus, the rate at which the water molecules translocate through the pore is essentially dependent on the average lengths of time that the water molecules remain within the first-shell of the pore cations.

To examine the possibilities revealed by these MD simulations, we measured water transport through these nanopores using the aforementioned stopped-flow kinetic assay in the presence of monovalent cations. The use of PEG, rather than any salt, to produce the osmotic pressure enables the effects of the permeant cations on water transport to be ascribed solely to their effects within the nanopore. We found that the water transport through this nanopore is indeed highly dependent on cation type (Figure 4). In particular, the presence of Li⁺, Na⁺, K⁺, or Cs⁺ was found to suppress the transport of water relative to that in the absence of these ions, consistent with what was revealed by the MD simulations. The presence of Na⁺ results in the largest reduction in transport rate, with a \( P_{\text{nano}} = 0.3 \pm 0.3 \times 10^{-14} \text{ cm}^3 \text{ s}^{-1} \); followed by K⁺ (\( P_{\text{nano}} = 3.7 \pm 0.8 \times 10^{-14} \text{ cm}^3 \text{ s}^{-1} \)), Li⁺ (\( P_{\text{nano}} = 4.0 \pm 0.6 \times 10^{-14} \text{ cm}^3 \text{ s}^{-1} \)), and Cs⁺ (\( P_{\text{nano}} = 6.4 \pm 0.9 \times 10^{-14} \text{ cm}^3 \text{ s}^{-1} \)), which gives the smallest decrease of water transport rate among the four metal ions. Therefore, the same trend observed in the MD simulations in the water transport in the presence of different cations was experimentally observed with this assay, including the virtual absence of water transport in the presence of Na⁺ (Figure 4b).

### CONCLUSIONS

In conclusion, the results presented here demonstrate that it is highly feasible to design hydrophobic–hydrophilic hybrid sub-nanopores with which the rate of water transport can be readily controlled. The hybrid nanopore described here with multiple luminal carbonyl oxygens exhibits a comparable water conductance as fully hydrophobic nanopores, demonstrating that a purely hydrophobic lumen is not, in fact, an absolute requirement for highly efficient water transport through nanochannels. Further, and perhaps more importantly, such a hybrid architecture offers the significant advantage of having binding sites for metal ions, which provides the possibility to effect control of water flow. As shown by this work, both the
size and hydration energy of metal ions can be exploited to manipulate the efficiencies of water transport. With its synthetic and self-assembling nature, our approach offers ready tunability by allowing the incorporation of different binding sites for other metal ions and thus provides a flexible platform with which various factors influencing water transport through sub-nanopores can be systematically probed. More generally, we anticipate that it will be possible to exploit the mechanism described here for technological applications involving water transport, whereby a high rate of transport could be easily turned on and off, or more subtly modulated, simply by adding or removing particular ions that bind within rationally designed sub-nanopores.

**ASSOCIATED CONTENT**

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsscience.1c01218.

Methods for the preparation of vesicles, the stopped-flow assay, the measurement of macromolecules in the vesicles, the calculation of water permeability per nanopore, the ab initio calculations, and the molecular dynamics simulations; Supporting Figures S1 to S9 showing osmotic pressure data, size-dependence of cation permeability through the nanopores, macrocycle emission spectra, vesicle size, simulations initial conditions, convergence of simulations, sodium ion location within the pore, lifetime of first-shell waters of cations within the pore (PDF)

**AUTHOR INFORMATION**

Corresponding Authors
Bing Gong – Department of Chemistry, The State University of New York at Buffalo, Buffalo, New York 14260, United States; Email: bgong@buffalo.edu
Daniel M. Czajkowsky – School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China; orcid.org/0000-0002-2745-9546; Email: dczaj@sjtu.edu.cn
Zhifeng Shao – School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China; Email: zfshao@sjtu.edu.cn

Authors
Yi Shen – School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China
Fan Fei – School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China
Yulong Zhong – Department of Chemistry, The State University of New York at Buffalo, Buffalo, New York 14260, United States
Chunhai Fan – School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China; orcid.org/0000-0002-7782-2316
Jiclin Sun – Shanghai Center for Systems Biomedicine, Key Laboratory of Systems Biomedicine (Ministry of Education), Shanghai Jiao Tong University, Shanghai 200240, China
Jun Hu – Key Laboratory of Interfacial Physics and Technology, Shanghai Synchrotron Radiation Facility, Shanghai Advanced Research Institute, Chinese Academy of Sciences, Shanghai 201204, China; orcid.org/0000-0002-7282-2316

Complete contact information is available at: https://pubs.acs.org/10.1021/acscentsci.1c01218

**Author Contributions**
Y.S. and F.F. contributed equally.

**Notes**
The authors declare no competing financial interest.

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