Host-Guest Sensing by Nanopores and Nanochannels

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51.1 Introduction

Nanopore sensing is an emerging and useful tool of single-molecule analysis especially for biomolecules [1]. In contrast with macroscopic sensors like electrophoresis, the realization of single-molecule analysis by nanopore sensors does favor to multifarious biological sample, because every biomolecule exports exclusive signal. The principle of sensing is that individual molecules generate detectable changes in ionic current as they pass through a nanoscale pore. Therefore, many nanopore sensing were size-regulated and stochastic at the beginning of the study, where were some unresolved issues such as the discrimination of micromolecules with similar molecular weights and geometric, the signal-to-noise ratio, and the inherent flaw of quantification [2]. To develop the selectivity of label-free synthetic nanopore sensors, investigators applied biological nanochannels or labeled analytes to achieve exclusive recognition of specific chemical structure or geometric structure [3]. Although above strategies didn't satisfy the need of material stability or

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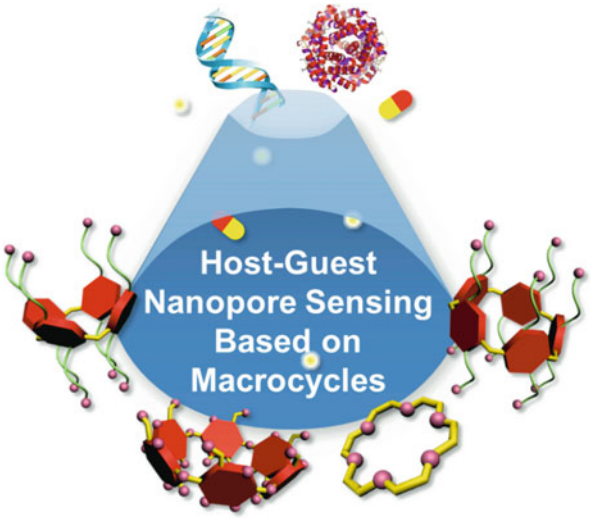
detection in situ, they inspired that the host-guest system is a breakthrough of high-selective single-molecule analysis of biomolecules by nanopore sensors.

Host-guest sensing bases on the selective recognition between host and guest molecules deriving from specific intermolecular interaction, just as receptors and ligands. The most important host-guest interactions consist of solvophobic forces, electrostatic interactions, Van der Waals interactions, and hydrogen bonds. And because of the additivity of noncovalent bonding increments, the hosts with multisite of recognition and bonding show better sensitivity and selectivity [4]. Macrocycle is one kind of excellent multisite hosts, consisting of crown ethers, cucurbituril, cyclodextrins, pillararenes, calixarenes, etc. [5]. Due to the change of fluorescence characteristics and prototropic behavior after the formation of host-guest inclusion complex, macrocyclic hosts are applied as photochemical sensors in aqueous solution or on solid surface [6]. Moreover, another kind of useful macrocycle-based sensors is electrochemical biosensor, which transforms the recognition event on account of selective electrostatic interactions occurring at the solid-liquid interface into a readable electrical signal [7]. Numerous studies have indicated that the host-guest sensing based on functionalized macrocycles shows good selectivity to ions, proteins, and chiral enantiomer including amino acids and drugs.

Inspired by biological nanochannels, the host-guest strategy of nanopore biosensors was of interest to investigators and contributed to better selectivity of single-molecular biomolecular analysis [8]. The introduction of host molecule into nanopore sensor enriches the recognition capability from finitely size selection to charge selection, functional group selection, chirality selection, and so on [9]. One prominent example is crown ether modified nanopore sensor of Na^+ and K^+ [12], two cations with tiny difference of hydrated ionic radius as 0.27 Å, which show excellent selectivity in comparison with size-regulated and charge-regulated label-free nanopore sensors. Another delicate example is cyclodextrin modified nanopore sensor of chiral enantiomers, and many other investigation also indicate that macrocycle is one kind of the most excellent host molecules for nanopore sensing. In this account, we provide a comprehensive overview of host-guest sensing by macrocycles functionalized nanopores and nanochannels for biomolecules detection, especially for ions and chiral micromolecules. According to the sorts of macrocycles, here includes four parts such as crown ethers, cyclodextrins, pillararenes and calixarenes. Additionally, compared with label-free nanopore sensing and other macroscopic sensing, we expound the inherent advantage of host-guest sensing by nanopores and nanochannels on single-molecule analysis of biomolecules, especially for ions and chiral micromolecules (Scheme 1).

51.2 Crown Ether Functionalized Nanopores for Bio-sensing

Crown ethers are macrocyclic polyether with oxygen atoms directing toward the center of the cavity and roughly defining a plane. Crown ethers with different cavity sizes can preferentially include different alkali metal ions through formation of unique 1:1 or 2:1 complexes and show different selectivity and sensitivity toward



Scheme 1 Macrocycle-based host-guest nanopores and nanochannels for biosensing and analysis

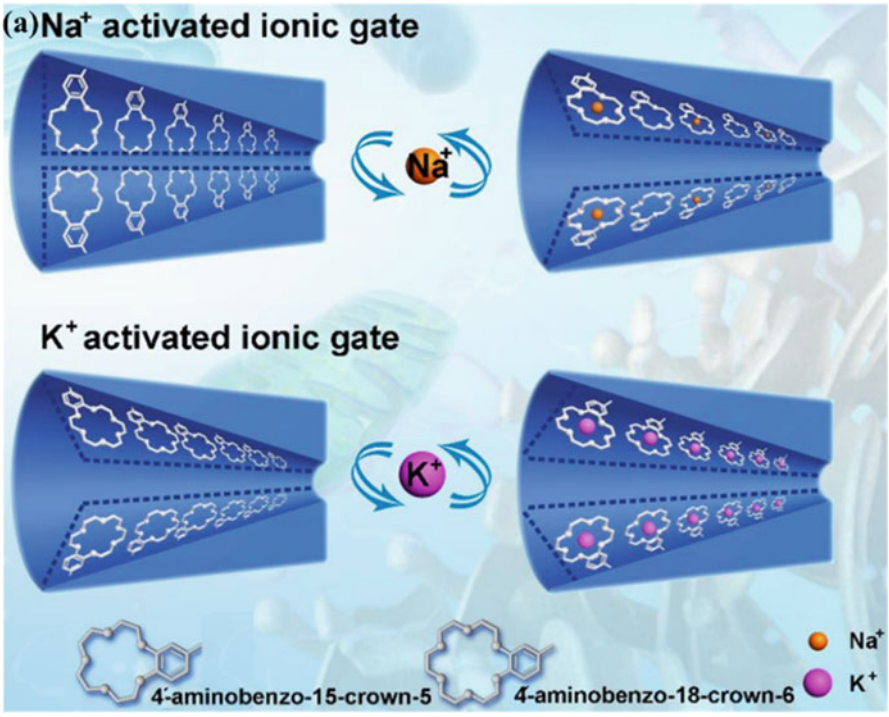
these cations based on the "hole-size" principle. Therefore crown ethers are well-recognized as effective ionophores of alkali and alkaline cation. For instance, 18-crown-6 ether (18C6) is known as a K^+-selective ionophore in aqueous solution. Lisy and coworkers explained the special affinity for K^+ by 18C6 based on the investigation of $M^+(18C6)(H_2O)_{1-4}$ Ar complexes (M^+ include Li^+, Na^+, K^+, Rb^+, and Cs^+). On the condition that micro-hydration is indispensable, the $18C\cdots K^+$ interaction dominates and weakens the ability of the ion to interact with H_2O, resulting into the "best fit" of K^+ with 18C6. Furthermore, a linear relationship between the ion diameter and cavity size is found in stable 2:1 "sandwich" complexes by Chu and coworkers. Crown ethers are also capable of complexing with ammonium and primary amines by three $N–H\cdots O$ hydrogen bonds in a tripod arrangement. Additionally, some derivatives of crown ether, such as (+)-(18-crown-6)-2, 3, 11, 12-tetracarboxylic acid, could selectively recognize amino acids enantiomers and peptides [10].

Metal ions in biological systems take part in a variety of essential processes; some of them even cause adverse effects. Ion channels display selective gating and transmitting to specific ion, due to the suitable size controlled by allosteric effect and the asymmetric recognition sites of amino acid residues [11]. Artificial analogues of biological ion channels were investigated in recent two decades. Although the control over pore dimensions (size and geometry) of various solid materials has been mature, it is not able to compare to the size of biological ion channel below nanoscale or break through the ionic selectivity. Inspired from nature, surface functionalization in nanopores has received great interest. The introduction of host-guest system to nanopore sensing solved the selectivity of metal ions, where crown ethers were classical guest.

Two biomimetic ionic sensors and gates for sodium cation (Na^+) and potassium cation (K^+) based on crown ether functionalized conical nanochannels were

reported by Jiang and coworkers [12]. The ionic nanochannels recognized Na^+ and K^+ by the 4′-aminobenzo-15-crown-5 (4-AB15C5) and 4′-aminobenzo-18-crown-6 (4-AB18C6) and formed specifical complexes, respectively. The selective host-guest sensing of crown ethers and cations is proved over other alkali metal ions due to the matching of cation size and the crown ether cavity and leads to significant changes in the surface charge, wettability, and finally electronic conduction of the nanopores (Fig. 1). The similar results were also proved by Azzaroni [13]. Moreover, the differences in bonding strength between these two complexes, the association constant of 4-AB15C5 ⊃ Na^+ is 13.2 M^{-1} as a half of 4-AB18C6 ⊃ K^+, result to different switch properties of ionic nanochannels. Na^+ regulates the states of ion conduction through the hydrophobic 4-AB15C5-modified nanochannel from close to open, while more bonding of K^+ in 4-AB18C6 reverses the anion conduction to cation.

Furthermore, these two ionic gates are reversibly regulated by the immobilization of Na^+/K^+ and the release using [2.2.2]-cryptand competitively bonding with Na^+/K^+. Then, Wen [14] and coworkers found the voltage-response property of the K^+-activated 4′-aminobenzo-18-crown-6 functionalized nanochannel. The ionic gating could tuned to close by releasing K^+ under the voltage higher than 2 V, which was similar with the biological voltage-gated nanochannels (Fig. 2).



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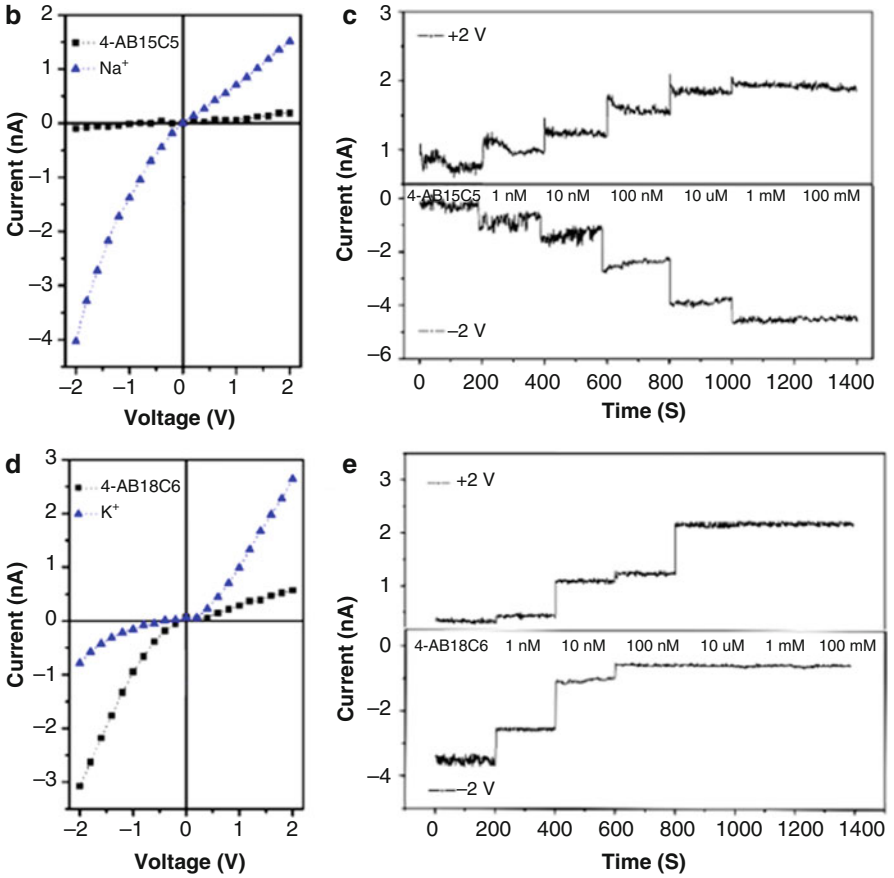


Fig. 1 (**a**) Schematic demonstration of the Na^+- and K^+-regulated ionic nanochannels. (**b**) I–V characteristics of the 4-AB15C5-modified nanochannel before and after activation with 10 μM Na^+. (**c**) The current variation of the 4-AB15C5-modified nanochannels before and after activation with different concentrations of Na^+ at constant voltage +2.0 V and −2.0 V. (**d**) I–V characteristics of the 4-AB15C5-modified nanochannel before and after activation with 10 μM K^+. (**e**) The current variation of the 4-AB18C6-modified nanochannels before and after activation with different concentrations of K^+ at constant voltage +2.0 V and −2.0 V. (Reprinted with the permission from Ref. [12]. Copyright 2015, American Chemical Society)

Ali and Ensinger synthesized two specific crown ether analogues, amine-terminated *p-tert*-butylcalix[4]arene-crown (*t*-BuC[4]C-NH_2) and aminoethyl-benzo-12-crown-4 (BC12C4-NH_2), as selective host molecule of cesium ion (Cs^+) and lithium ion (Li^+), respectively. Then *t*-BuC[4]C-NH_2 was modified into the asymmetric nanopore to fabricate a cesium-response nanofluidic diode [15a]. The inner surface of the nanopore was switched from a hydrophobic and uncharged non-conductive state to a hydrophilic and positive charged conductive state upon complexation of

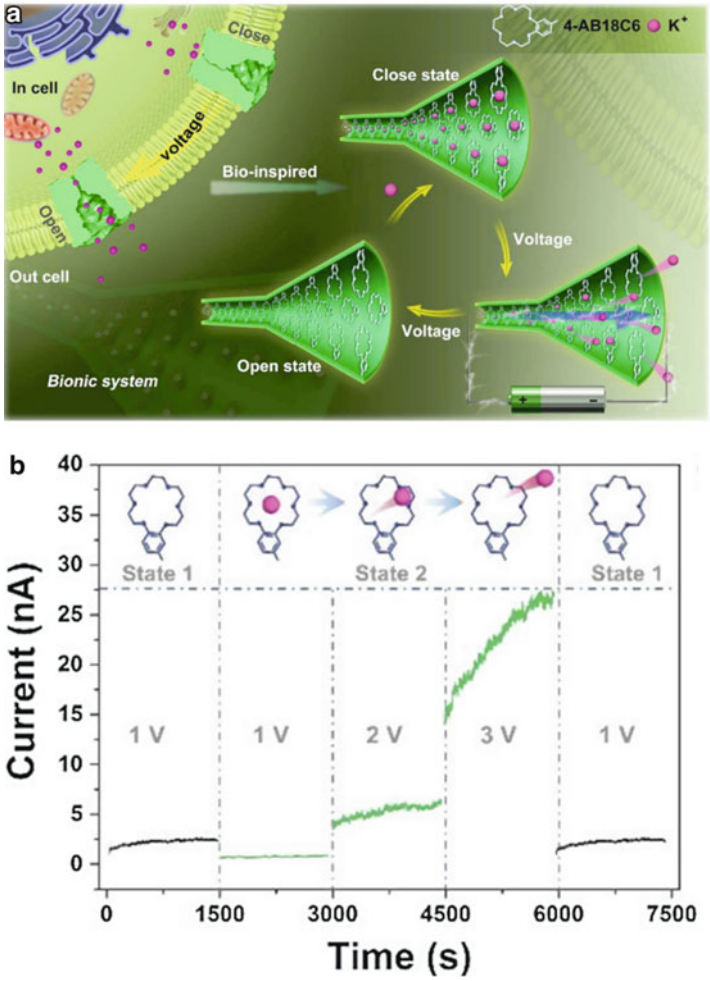


Fig. 2 (**a**) Schematic demonstration of the artificial voltage-responsive potassium-activated ionic gating. (**b**) Ionic currents before (black line) and after (green line) activation with 10^{-5} MK^+ at different constant voltage. (Reprinted with the permission from Ref. [14]. Copyright 2017, American Chemical Society)

Cs^+ ion. And the conductance of nanopore increased directly proportional to the concentration of Cs^+ ion, suggesting the quantitative ability of this nanopore sensing. Similarly, the BC12C4-NH_2 functionalized nanofluidic device exhibited selectivity to Li^+ in the presence of other alkali cations [15b] (Fig. 3).

Based on the complexing of crown ethers with primary amines, the chiral derivative (+)-(18-crown-6)-2, 3, 11, 12-tetracarboxylic acid (18C6H_4) is developed to the chiral sensing and separation of amino acid enantiomers [16]. Two kinds of host-guest interaction synergistically contribute to the chiral recognition: (i) four carboxylic acids of the crown ether act as chiral barriers for the chiral guests

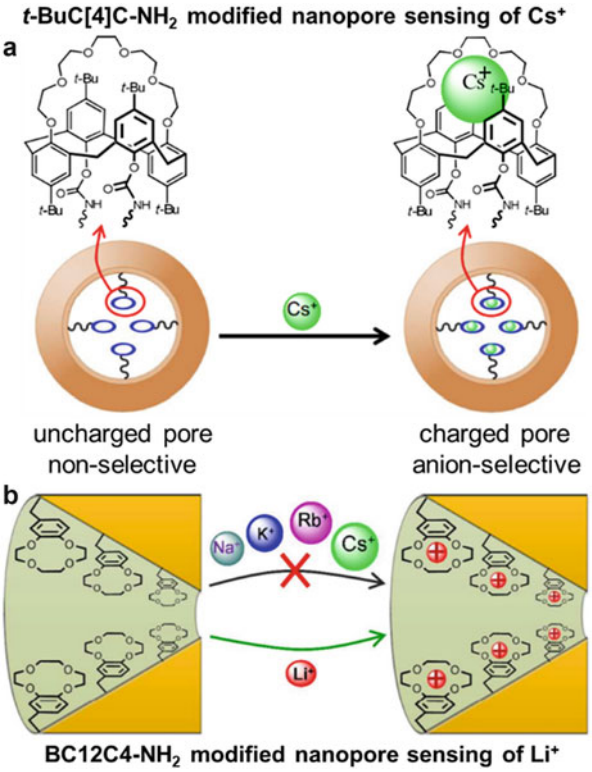


Fig. 3 Schematic demonstration of (**a**) the Cs^+ complexation with *t*-BuC[4]C moieties on the pore surface and (**b**) the Li^+ ion complexation with the B12C4 moieties immobilized on the pore surface. (Reprinted with permission from Ref. [15a]. Copyright 2017, American Chemical Society. Reprinted with permission from Ref. [15b]. Copyright 2018, American Chemical Society)

(according to the size and the spatial orientation, diastereomeric complexes with different formation constants are formed), and (ii) the other is the electrostatic interaction such as hydrogen bonds or coulombic attraction or repulsion forces between $18C6H_4$ and polar guest. Barnhart and coworkers utilized $18C6H_4$ as chiral stationary phase in chiral separations of amino phosphonic acids and amino carboxylic acid enantiomer. Liu and coworkers synthesized the tetrasulfonated 1, 5-dinaphtho-32-crown-8 with high monovalent affinity and non-pre-organized characteristic [17]. This crown ether derivative was able to form complexation with pyridinium and recognize NAD^+ from NADH, which suggested a wider prospect of crown ether for biological detection and separation.

51.3 Cyclodextrin Functionalized Nanopores for Bio-sensing

Cyclodextrins (CDs), as sugar-based macro rings, consist of D-glucopyranose units linked with α-1,4 glycosidic bonds; therefore CDs possess apolar and chiral cavities. CDs have a hydrophilic outer surface and slightly lipophilic inner cavity; therefore CDs are water-soluble. Based on the combination of noncovalent interactions and

steric interactions between the host CDs and guest analytes, CDs are capable of recognizing chiral enantiomers and forming host-guest inclusion complexes. Depending on these features, nontoxic and environmentally friendly CDs have a great utility in analytical chemistry, such as the enhancement of detection sensitivity and the separation of isomeric mixtures [18]. Several typical guest moieties include adamantane, azobenzene, ferrocene, cholesterol, lithocholic acid (LA), acridine orange (AOH^+), pyrene, etc. [19]. The controlled release can also be triggered by external stimuli such as pH, temperature, magnetic field, voltage, as well as molecular competition [20].

The computational study on the interactions of IIA/IIB group metal cations with the host α-CD shed light on the key factors governing the process of metal bonding to α-CD [21]. The α-CD preferentially binds smaller cations with enhanced charge-accepting ability, which is related to the properties such as ion radius, electron configuration, and coordination number. And the flexibility of CDs also influence the energetics of the metal-CD complex formation. Kang and coworkers developed a nanopore sensing as the heptakis-(6-deoxy-6-amino)-b-cyclodextrin embedded α-hemolysin nanopore (am7β-CD α-HL pore) for the detection of Cu^{2+} [22a]. The selectivity was contributed to the high affinity between Cu^{2+} and the amino groups of am7β-CD and showed the low detection limit of 12 nM and linear range of 0.08–20 mM. Furthermore, the Cu^{2+} complexed am7β-CD α-HL pore was able to simultaneously discriminate six enantiomers of aromatic amino acids [22b]. Each enantiomer of aromatic amino acids (AAA) interacting with cyclodextrin-metal binary complex generated obviously different characteristic current block signals (Fig. 4). The highly efficient enantioselectivity was suggested to be contributed by the cooperation between hydrophobic cavities of am_7β-CD with Cu^{2+}.

In fact, the principle of chiral recognition of amino acids by CDs is substantially investigated from the viewpoints of induced-fitting mechanisms, geometric complementary and cooperative bonding processes. Among nature amino acids, the hydrophobic aromatic amino acids are preferentially self-included in the cavity. Furthermore, CDs and their derivatives displayed considerable L-enantioselectivity to the chiral isomers, especially to L-histidine (L-His) in aromatic amino acids, L-leucine (L-Leu) in aliphatic amino acids, and L-arginine (L-Arg) in alkaline amino acids [23]. Based on the chemoselectivity and enantioselectivity of CDs for amino acids, Li and coworkers reported a simple enantioselective nanopore sensor based on the β-CD covalently modified nanochannel for highly chiral-specific sensing of L-His over D-His and the enantiomers of phenylalanine (Phe) and tyrosine (Tyr) [24] (Fig. 5). Furthermore, β-CD and its derivatives were proved as better host molecules of drugs, showing the preference for one of the enantiomers. Therefore, β-CD are utilized in the control release and enantioseparation of chiral drugs. Such as the investigation reported by Bayley and coworkers, a β-CD disulfide lodged α-hemolysin protein pores (S2β-CD α-HL pore) could screen sodium deoxycholate (DOC) from a large number of "guests." Tian and coworkers established a thermoresponsive drug delivery system based on β-CD-functionalized porous amphiphilic block copolymer films (β-CD-PBCPFs) to selectively load and release doxorubicin (DOX) [25].

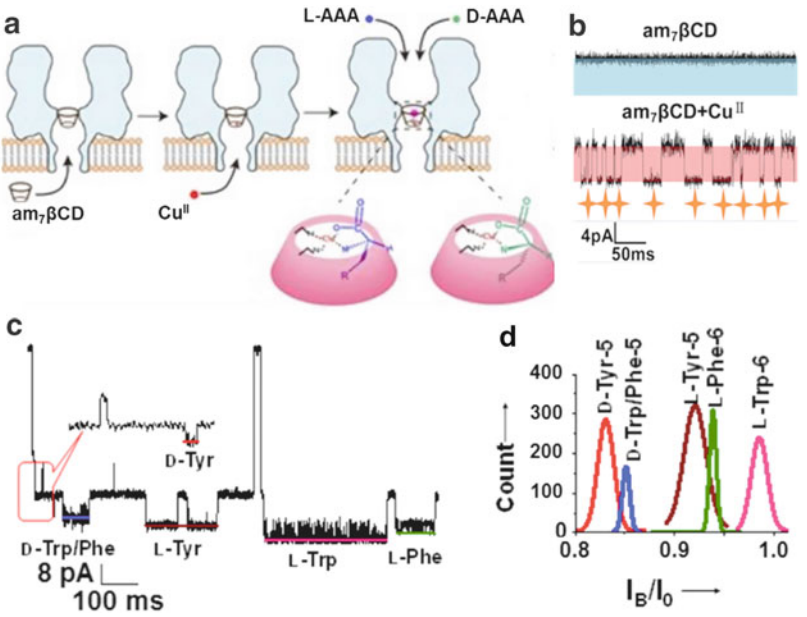


Fig. 4 Schematic demonstration of $am_7\beta CD$ functionalized protein nanopore for recognition of Cu^{2+} and AAA enantiomers, continuously. (Reprinted with the permission from Ref. [22a, 22b]. Copyright 2017, Royal Society of Chemistry)

Another popular guest of CDs is azobenzene, which is usually used as a photosensitive adjuster. The *trans* and *cis* isomers of azobenzene can be reversibly switched by photoirradiation, and *trans*-azobenzene is selectively recognized by α-CD while is released after switched to *cis*-azobenzene. Utilizing this character, the host-guest system of CDs and azobenzene was introduced into nanopore sensors by Jiang and Wen [26]. The azobenzene-derivative-modified polymer nanochannel (*cis*-Azo channel) was fabricated as a hydrophobic nanopore to interdict ion transport and controlled the immobilization and release of β-CD by light and electric field to regulate ion transport at the condition of hydrophilic β-CD nanochannel (Fig. 6).

As Bayley and coworkers' research, CDs as a molecular adapter also discriminate nucleobases and generated specific current blocking signal when different nucleobases move through the cavity. In detail, the difference in the amplitude and the mean dwell time of current blocking signal enabled the identification of the DNA sequence, and the frequency correlates with the quantity. These above results were the basis for the function of DNA/RNA sensing and DNA sequencing. Then they covalently attached a β-CD derivative ($am_7\beta CD$) inside the protein nanopore, permitting the recognition of mononucleotides and continuously reading DNA and RNA sequences [27].

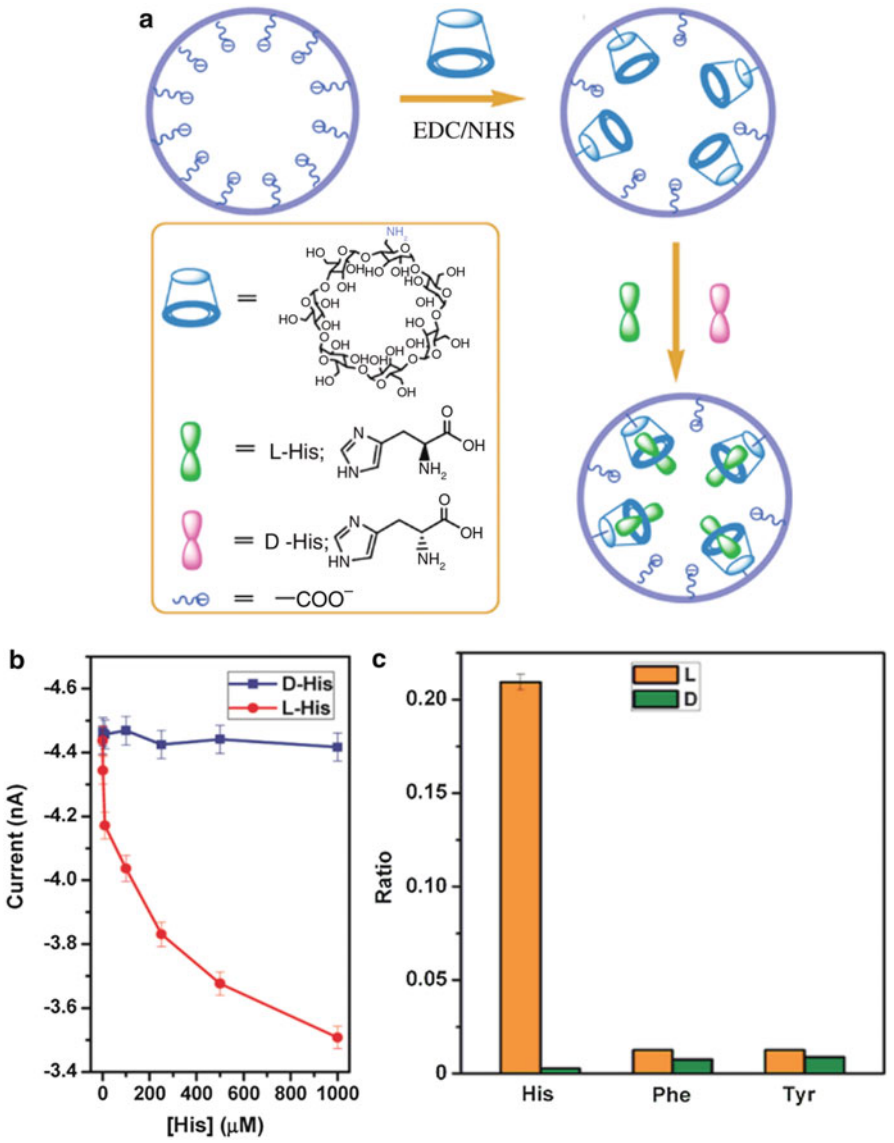


Fig. 5 (**a**) Schematic demonstration of β-CD-modified single nanochannel for enantioselective sensing of L-His. (**b**) Current-concentration properties of the β-CD-modified single nanochannel to L/D-His. (**c**) Current change ratios for the β-CD-modified single nanochannel in 50 mM PBS (pH 7.2) upon addition of 1 mM L- or D-His, L- or D-Phe, and L- or D-Tyr, respectively. (Reprinted with the permission from Ref. [24]. Copyright 2011, American Chemical Society)

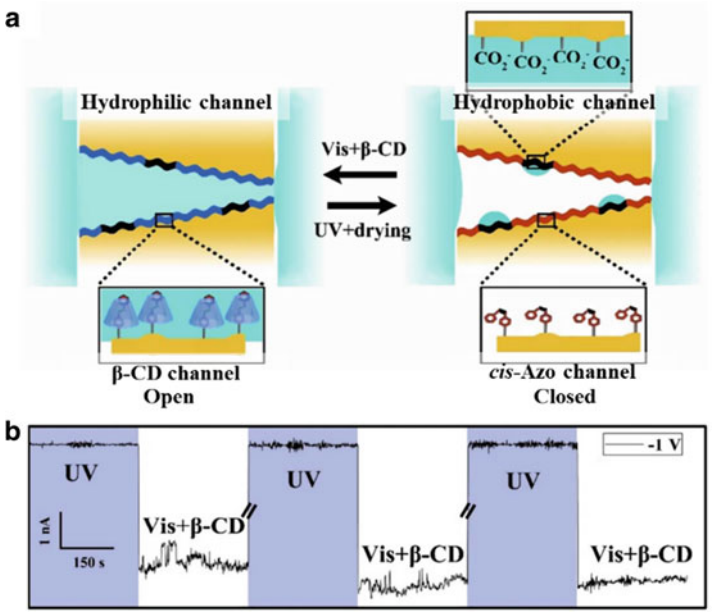


Fig. 6 (**a**) Schematic demonstration of wettability control in nano-confined environments with optical method. (**b**) Optical reversibility of the opening and closing in this system by recording currents at −1 V. (Reprinted with the permission from Ref. [26]. Copyright 2018, American Chemical Society)

51.4 Calixarene Functionalized Nanopores for Bio-sensing

Calixarenes with a relatively robust macrocyclic structure can be easily and selectively functionalized with a variety of chemical groups at either or both rims of the phenolic moieties. Calixarenes act as the sensor of metal ions, amino acids, drugs, and many biomolecules with attractive characteristics such as high sensitivity and selectivity, label-free and real-time detection, cost-efficiency, fast response time, etc. Takahashi and coworkers reported a calix[4]arenecrown selectively recognizing Na^+ from alkali metal ions. An anthracenyl-triazolyl functionalized bimodal calix[4] arene was synthesized by Georghiou and coworkers, which sensitively and reproducibly responded to low concentrations of Hg^{2+} among other divalent metal ions, based on the structure of para-triazole rings with the distance of 6 Å best matching with the size of Hg^{2+}. Furthermore, the phenyl skeleton of calixarene could form compound with NO^+ as sandwich structure, and the structure difference between of cone, partial cone, and 1,3-alternate cone leaded to different bonding strength with

NO^+. Except for cations, the calixarene derivatives with amino group and amide group could respond to anions, such as Cl^-, SO_4^{2-}, and $H_2PO_4^-$ [28].

Functionalized calixarenes are designed to selectively detect natural molecular, such as VX nerve agents, cancer biomarkers, glucose, and especially amino acids [29]. The ability of calixarene carboxylic acid derivatives for selective recognition of aromatic amino acid (Trp, Phe, and Tyr) was studied by Oshima; results showed carboxylic calix[6]arene processes better interaction with aromatic amino acids, especially for Trp, than calix[8]arene and calix[4]arene. Demirtas and coworkers reported the synthesis of chiral calix[4]azacrown ethers for enantiomeric recognition of α-amino acid with exhibited bonding ability and certain chiral recognition to L-Phe. As amino acids are basic structural building blocks of proteins, the chemoselectivity and enantioselectivity of calixarenes for amino acids provide the basis of following peptide and protein sensing. Hamilton and coworkers functionalized the calix[4]arene by a cyclic peptide (with GDGD sequence) and carried out the bonding with the active site of α-chymotrypsin and the slow bonding inhibition. Prata and Barata reported wo isomeric bis-calixarene-carbazole conjugates endowed with carboxylic acid functions at their lower rims, displaying a high sensing ability (K_{SV} up to 6×10^7 M^{-1}) and selectivity toward cytochrome *c* in an aqueous-based medium. Also targeted to cytochrome *c*, Crowley synthesized the *p*-phosphonate methyl-calix[4]arene (pmclx4) and investigated the crystal structure of lysine-rich cytochrome *c* complexed with pmclx4, identifying a bonding site at Lys54 [30].

Based on the selective recognition of calixarenes for ions due to the appropriate cavity of calixarenes matching the size of ions, and the reversible complexation, an interesting imagination that calixarenes could play a role as ionic receptor and transporter was proposed and investigated (Fig. 7). Now calixarenes are frequently used in ionic recognition and separation processes. Davis showed a transmembrane

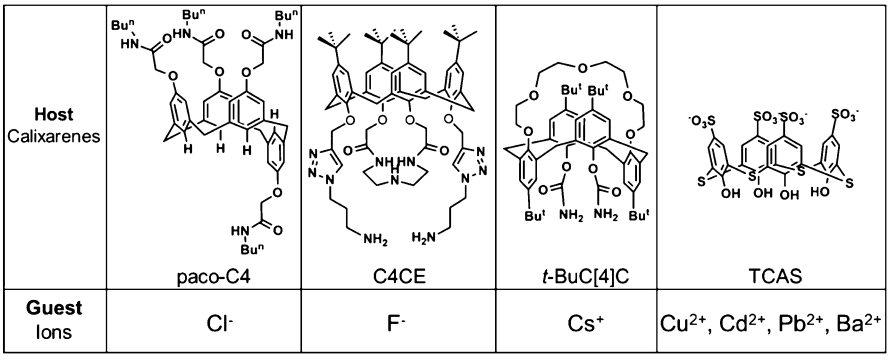


Fig. 7 Host-guest sensing of calix[4]arene derivatives and ions. (Reprinted with permission from Ref. [31]. Copyright 2006, Wiley. Reprinted with permission from Ref. [32]. Copyright 2015, Royal Society of Chemistry. Reprinted with permission from Ref. [15a]. Copyright 2017, American Chemical Society. Reprinted with permission from Ref. [33]. Copyright 2018, American Chemical Society)

transporter of Cl^- as partial-cone calix[4]arene (*paco*-H), and compared with the inactive *para*-substituted analogue (*paco*-*t*Bu), the results suggested that the self-association and Cl^- transport activity were identified to be controlled by the conformation of the side chain on the inverted arene of the partial cone [31]. Similarly to accomplish selective sensing and transport of F^-, an artificial single conical nanochannel modified with 1,3-dipropargylaza-*p*-*tert*-butyl calix[4]crown (C4CE) was designed and established by Li's group, and the selective and sensitive recognition from other anions with the detection limit of 9.7×10^{-7} M was reached due to the N–H···F hydrogen-bonding interactions [32]. Ali and Ensinger demonstrated a Cs^+-induced nanofluidic device by exploiting host-guest interactions of the amine-terminated *p*-*tert*-butylcalix[4]arene-crown (*t*-BuC[4]C-NH_2) and Cs^+ inside confined geometry. Furthermore, theoretical results based on the Nernst-Planck and Poisson equations further proved that the bonding of Cs^+ cations to calixcrown moieties increased the Cs^+ concentration leading to a gradual increasing conductance of the positive charged pore [15a]. Zhang and Liu developed a novel method for the sequential separation of heavy metal ions from wastewater by thiacalix[4]arene-*p*-tetrasulfonate (TCAS) modified porous membrane, with the best separation rate of 94.8%, 95.2%, 92.8%, and 93.6%, for Cu^{2+}, Cd^{2+}, Pb^{2+}, and Ba^{2+}, respectively [33].

Numerous calixarene derivatives functionalized nanopore work as biosensors of amino acids, peptides, and biomolecules, and they are improved as a novel method of ionic/molecular transporters and drug delivery systems. Li's group introduced p-sulfonatocalix[4]-arene (SCX4) to the surface of a single conical nanochannel by layer-by-layer assembly and successfully realized the highly sensitive recognition of acetylcholine (Ach) [34] (Fig. 8). Layer-by-layer (LBL) assembly is a more efficient functionalization method achieved by electrostatic assembly for incorporating than that associated with covalent amidation reactions. The SCX4 was assembled after polyethyleneimine (PEI) assembly, and the coating process had no apparent influence on the diameter of the nanochannel. In this Ach nanochannel biosensing, the sensor sensitivity reached a level of 1 nm contributed to the specific host-guest recognition. Compared with other methods of Ach sensing such as

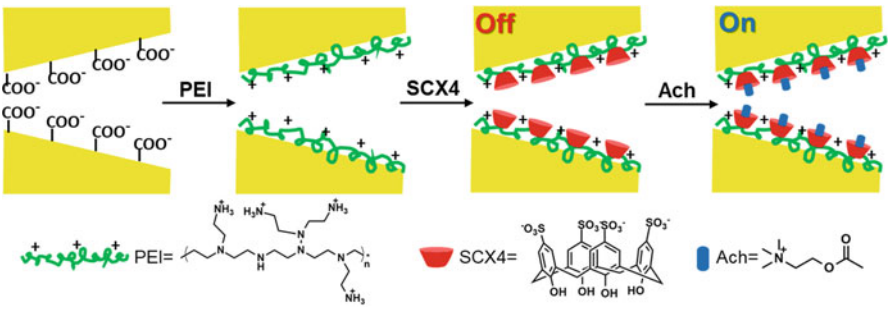


Fig. 8 Schematic demonstration of LBL assembly and Ach sensing of SCX4 nanochannel. (Reprinted with permission from Ref. [34]. Copyright 2013, Wiley)

microdialysis-electrochemical device, smart biochip, and functionalized quantum dots, this SCX4 functionalized nanopore is an efficient biosensor of Ach (Table 1) [35]. Then they designed and prepared a aldehyde calix[4]arene (C4AH) functionalized nanopore sensor, where the C4AH was attached to the interior surface of single nanochannel by click reaction and showed high selective response for arginine (Arg). A significant decrease in the ionic current was observed in the presence of 1 mm Arg, whereas the ionic current did not change in the presence of lysine (Lys), histidine (His), tryptophan (Trp), glutamine (Gln), or methionine (Met) [36].

Guo and Hennig [37] reported a phosphorylation-responsive membrane transport of peptides, which is based on the discriminated bonding of the anionic amphiphilic calixarene (CX4-C5) for dephosphorylated cell-penetrating peptides (CPPs) over phosphorylated CPPs. The CX4-C5 embedded in the phospholipid bilayer can recognize dephosphorylated CPPs and process the transmembrane transport (Fig. 9). As an application of calixarene-peptide sensing system, an L-glutathione (L-GSH) controlled drug delivery system was functionalized with supramolecular switches by Yang and coworkers [38], based on the reversible complexing of

Table 1 Various LODs for typical Ach sensing systems. (Reprinted with permission from Ref. [34]. Copyright 2013, Wiley)

Sensing system	LOD [nm]	Ref.
Microdialysis-electrochemical device	63	[35b]
Au NPs-decorated multiwalled carbon nanotubes	300	[35c]
Biosilicated CdSe/ZnS quantum dots	1000	[35d]
H_2O_2-sensitive quantum dots	10,000	[35e]
Charge-transfer technique on a smart biochip	10,000	[35f]
Layer-by-layer assembled biomimetic nanochannels	1	[34]

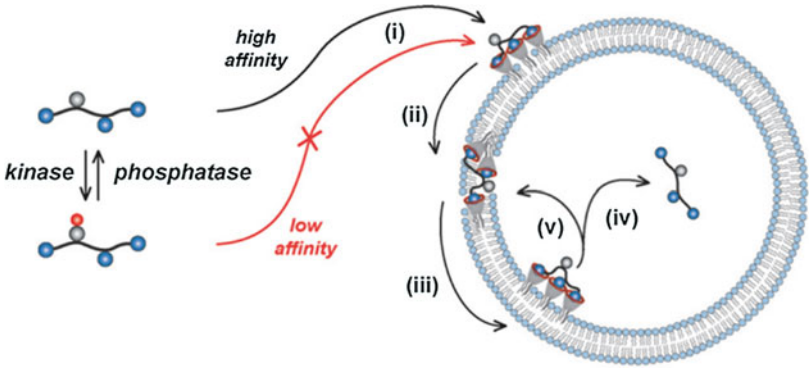


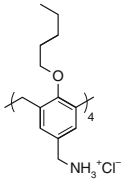
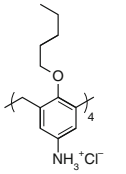
Fig. 9 Schematic demonstration of selective nanoporous transporter of peptide based on calixarene embedded phospholipid membrane. (Reprinted with permission from Ref. [37]. Copyright 2017, Wiley)

biocompatible sulfonatocalixarene-alkylammonium and L-GSH. Zadmard and Schrader [39] investigated a series of nanomolar protein sensing with embedded polar calixarene receptor. The sensitivity of the sensor system toward proteins requires a self-assembly of multiple calixarenes over the protein surface due to their hydrogen bond donor and acceptor capacities. Thereinto, tetrabenzylammonium calixarene (Bzalm. 2) and tetraanilinium calixarene (anil 3) are two of the sensitive receptors and efficient transporters, and Bzalm. 2 embedded phospholipid membrane and anil 3 embedded phospholipid membrane recognize basic, neutral, and acidic proteins with the detection limit of 10 pM (Table 2).

51.5 Pillararenes Functionalized Nanopores for Bio-sensing

Pillararenes as a new class of macrocyclic molecules are made up of hydroquinone units linked by methylene bridges at para positions. Compared with other macrocycles, pillararenes are symmetrical, rigid, and easily modified at all positions or selectively on one or two positions. The electron-donating cavity is a foundational inclusion unit based on C-H···π interaction. As the recognition unit, the structure and position of functional moieties on two rims of pillararenes both influence the selectivity of host-guest interaction. These features afford pillararene selective host-guest bonding to electron-accepting or neutral guests such as viologen

Table 2 Basic, neutral, and acidic proteins recognized by tetrabenzylammonium calixarene (Bzalm. **2**) and tetraanilinium calixarene (anil **3**). Insert: host structures of Bzalm. **2** and anil **3**. (Reprinted with permission from Ref. [39]. Copyright 2005, American Chemical Society)

Host	Subphase (M)	pI	ΔA (A^2)	MV (kDa)
Bzlam. **2** 	Water		0.0 (7.2)	
	Histone H1 (10^{-8})	10.4	0.8 (8.0)	7.7
	Cytochrome *c* (10^{-8})	9.5	1.4 (8.6)	12.3
	Thrombin (10^{-8})	7.5	2.0 (9.2)	32.0
	Albumin (10^{-8})	6.0	2.8 (10.0)	86.3
	ACP (10^{-8})	4.2	4.0 (11.2)	8.4
anil **3** 	ATP (10^{-4})	1.8	−2 (6.0)	0.6
	ATP (10^{-6})	1.8	−2 (6.0)	0.6
	ATP (10^{-8})	1.8	−1.2 (6.8)	0.6
	NADP (10^{-8})	1.8	−2 (6.0)	0.7
	DNA (10^{-7})	1.8	−2.5 (5.5)	23.7
	ACP (10^{-8})	4.2	−1 (7)	8.4
	Ferritin (10^{-8})	5.5	Plateau	455.3
	Dps (10^{-9})	5.9	Plateau	190.0
	Albumin (10^{-8})	6.0	1 (9)	86.3
	Thrombin (10^{-9})	7.5	1 (9)	32.0
	Cytochrome *c* (10^{-8})	9.5	3 (11)	12.3
	Histone H1 (10^{-8})	10.4	5 (13)	7.7

derivatives and alkyl chains. The host-guest interaction, which forms and stabilizes the complexes of pillararenes and guests, is influenced by the combination of different driving forces, such as charge transfer interactions, C–H···π interactions, hydrogen-bonding interactions, solvent effects, as well as hydrophobic and electrostatic interactions, and can be regulated by pH effects and counterion effects [40]. The ions or molecules with higher strength of interaction can selectively and competitively bind to pillararenes. Wei and coworkers synthesized an 2-aminobenzimidazole functionalized pillar[5]arene (PN) and demonstrated the selective coordinated of Fe^{3+} with two nitrogen atoms of primary amine on PN. Furthermore, F^- could competitively coordinate with Fe^{3+} restoring the PN-Fe complex to PN. And the addition of ions proportionately changed the fluorescence intensity of pillararenes; therefore this kind of pillararenes is prepared as fluorescent chemosensor for detection of ions, such as Fe^{3+}, Th^{4+}, and $H_2PO_4^-$. Based on the competitive coordination, ions are able to regulate the host-guest complex, and similar regulation can also be executed by proton H^+ and gas CO_2/ N_2 [41]. Another large category of guests of pillararene-based chemosensor are biomolecules, including amino acids, peptides, ATP, etc. [42]. More interesting is the enantioselective sensing for chiral enantiomers and cis-trans isomers based on the chiral pillararenes, which are functionalized by chiral groups or induced by chiral guests [43].

An artificial mercury (II) (Hg^{2+}) ion gate modulated by mercaptoacetic acid-pillar[5]arene (MAP5) is reported by Li and coworkers [44]. By virtue of the unique design of the host-guest competition, ion transport can actualize the reversible switching between "on" and "off" in the absence and presence of Hg^{2+}. Moreover, the MAP5-immobilized nanochannel is highly effective at distinguishing Hg^{2+} from other metal ions; therefore this nanochannel sensor can be used to detect Hg^{2+} and act as an excellent robust gate valve for developing nanoelectronic logic devices.

In living systems, ion channels respond to many different stimulations, such as temperature, pH, light, and so on, playing a vital role in numerous cellular processes. Facile carboxylic pillar[5]arene-based host-guest interactions are introduced into a nanochannel for constructing a temperature-sensitive artificial channel by Li and coworkers [45]. Ion transport was switched from cations to anions by controlling the extent of the host P5A bound to the guest ionic liquids (IL) with temperature stimuli (Fig. 10). This effect is suggested due to the changing of the inner surface charge and wettability of the nanochannel during the process. This study paves a new way for better understanding the mechanism of temperature-sensitive properties and shows great promise for biomedical research.

Inspired by channel rhodopsins, a facile noncovalent approach toward light-responsive biomimetic nanochannels was established by Li and coworkers, based on host-guest interactions between a negative charged pillar[6]arene host (P6A) and a positive charged azobenzene guest [46]. By switching between threading and rethreading states with alternating visible and UV light irradiation, the host-guest nanochannel can flexibly regulate the inner surface charge to reversibly reverse the ion transport from cation-selective to anion-selective (Fig. 11). Additionally, the pillar[6]arene-azobenzene-based nanochannel system could be used to construct a light-activated valve for molecular transport.

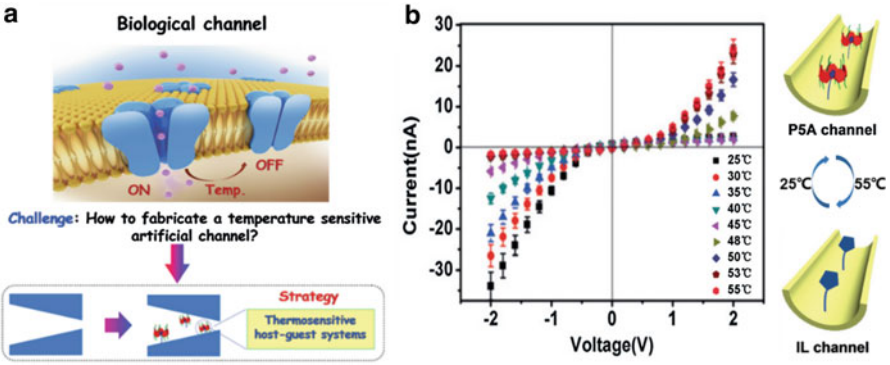


Fig. 10 (**a**) Schematic demonstration of temperature-sensitive artificial P5A-modified nanochannel. (**b**) Sensitive temperature-responsive ionic current of P5A-modified nanochannel. (Reprinted with permission from Ref. [45]. Copyright 2017, Wiley)

After the light-responsive biomimetic nanochannel, Li and coworkers reported a biomimetic chiral-driven ionic gating in L-alanine-decorated pillar[6]arene (L-AP6) modified host-guest nanochannel [47]. The chiral nanochannels show a high chiral-driven ionic gate for glucose enantiomers and can be switched between "off" by D-glucose (D-Glu) and "on" by L-glucose (L-Glu). Remarkably, the chiral nanochannel also exhibited a good reversibility toward glucose enantiomers. Further research indicates that the switching behaviors differed due to the differences in bonding strength between chiral L-AP6 and glucose enantiomers; the selectivity for D-Glu is greater than ca. 10 times that of affinity of L-AP6-AZO complex for L-Glu. And then the more bonding with the L-AP6-AZO complex on the inner surface leads to the decreasing of surface charge within nanochannel; therefore the ion transport is restrained (Fig. 12).

The pillar[5]arene with terminal positively charged peptides, as an unimolecular transmembrane channel, was reported by Hou and coworkers [48]. The peptide functionalized pillar[5]arene displayed high ability of inserting into phosphatidylcholine bilayers (diPhyPC), which was driven by the electrostatic interaction between the positively charged peptides of the pillar[5]arene and the negatively charged phosphate groups of lipid molecules. The insertion of pillar[5]arene would destroy the flux of ions and kill cells. The effective activity concentration against HepG2 cancer cells is measured to be 5.1 μM, although currently the pillar[5]arene is obviously cytotoxicity to normal cells.

Modulating protein selective translocation is a significant process, therefore to construct a nanochannel that can well gating protein transport is a vital challenge. Herein, inspired by nature, Li and coworkers presented a robust strategy to construct a switchable nanochannel by introducing a pH-responsive binary host-guest system into nanochannel [49]. Benefit from the novel design of the *N*-acetyl-L-cysteine-pillar[5]arene (ACP5) as gatekeeper, the functional nanochannel can well facilitate histone transport. Under pH regulation, the host-guest assembled nanochannel is capable of switching "on" and "off" to manipulate histone translocation process,

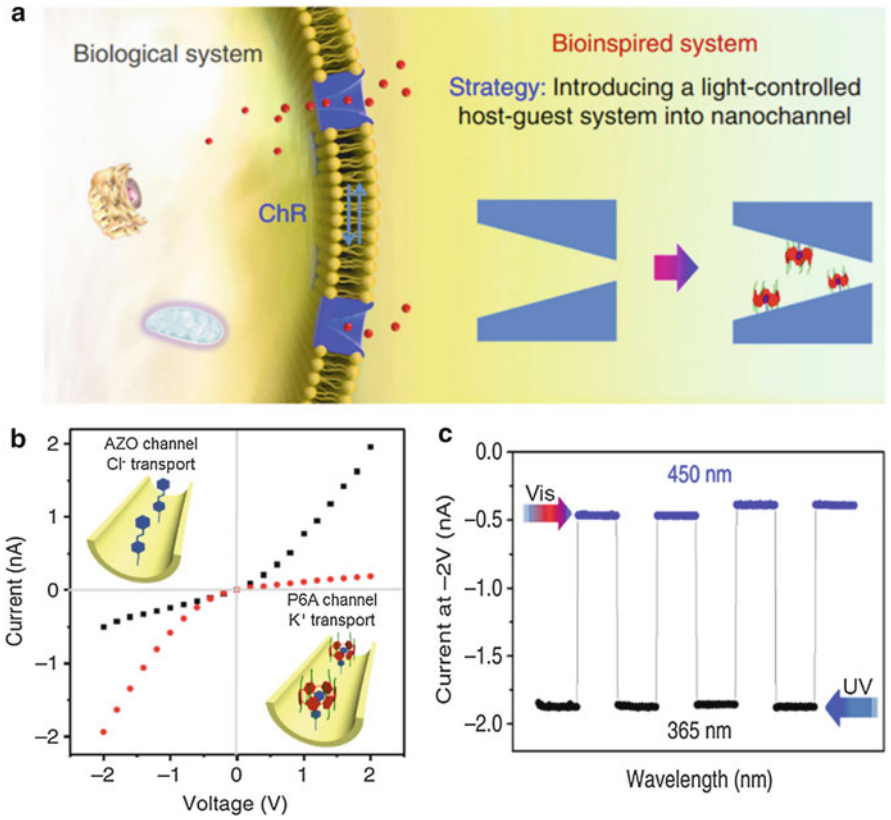


Fig. 11 (**a**) Schematic demonstration of light-regulated P6A-modified nanochannel. (**b**) The ionic current of different states regulated by light-responsive host-guest nanochannel. (**c**) The reversibility of the different states of the P6A-based nanochannels by measuring the current after alternating irradiation with different light. (Reprinted with permission from Ref. [46]. Copyright 2017, Nature)

which was clearly recorded by patch clamp technique as the distinct current blocking events (Fig. 13).

51.6 Conclusions and Perspectives

In conclusion, the host-guest sensing by macrocycles functionalized nanopores process the inherent advantage of single-molecule analysis of biomolecules, especially ions and chiral biomolecules. More and more macrocycles functionalized nanopores are designed and fabricated for single-molecule biosensing, based on the selective recognition of macrocycles for biological

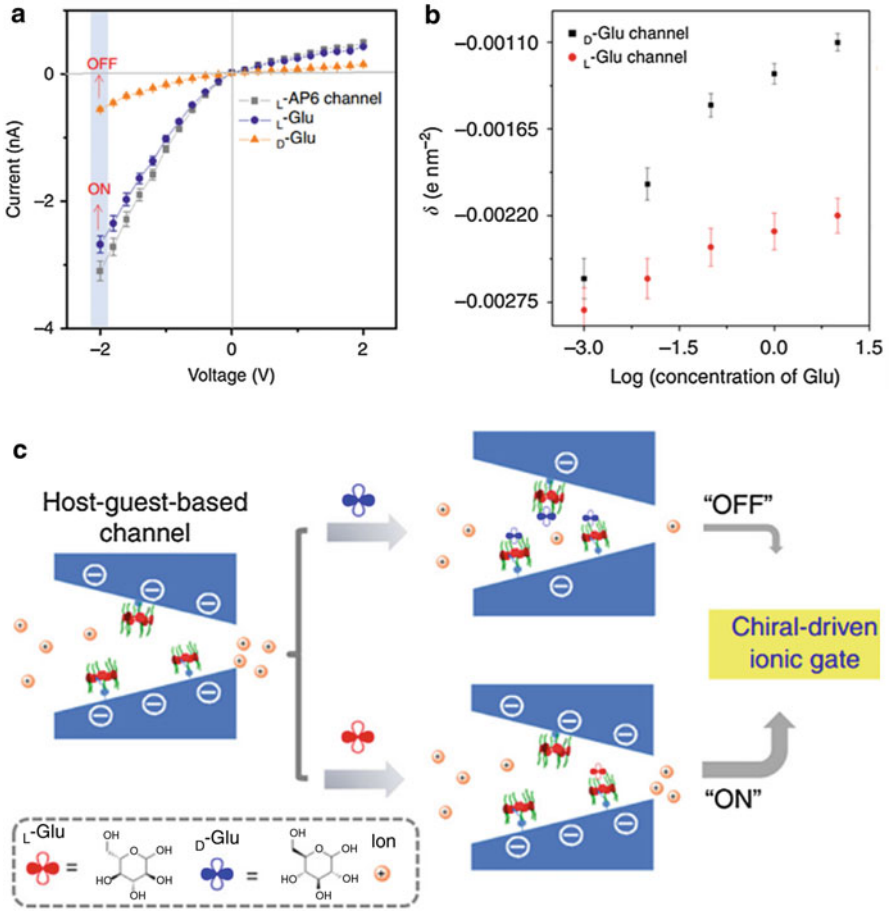


Fig. 12 (**a**) I–V curves of the L-AP6 nanochannel in 0.1 M KCl electrolyte in the presence of 1 mM glucose enantiomers. (**b**) The relationship of surface charge density versus log (concentration of Glu). (**c**) The mechanism of glucose-enantiomer-driven ion gate using host-guest systems. (Reprinted with permission from Ref. [47]. Copyright 2018, Nature)

analytes. We review recent advances in the host-guest sensing by macrocycles modified nanopores and nanochannels, including crown ethers, cyclodextrins, pillararenes, and calixarenes. The macrocycle-based nanopore bio-sensors process excellent selectivity and sensitivity of biomolecules and the advantages of label-free, real-time detection, cost-efficiency, and fast response time over other analytical methods. And macrocycle-based nanopores have potential applications on heavy metal ion purification [33], chiral drug separation [38], cancer cell detection [48], and so on [50].

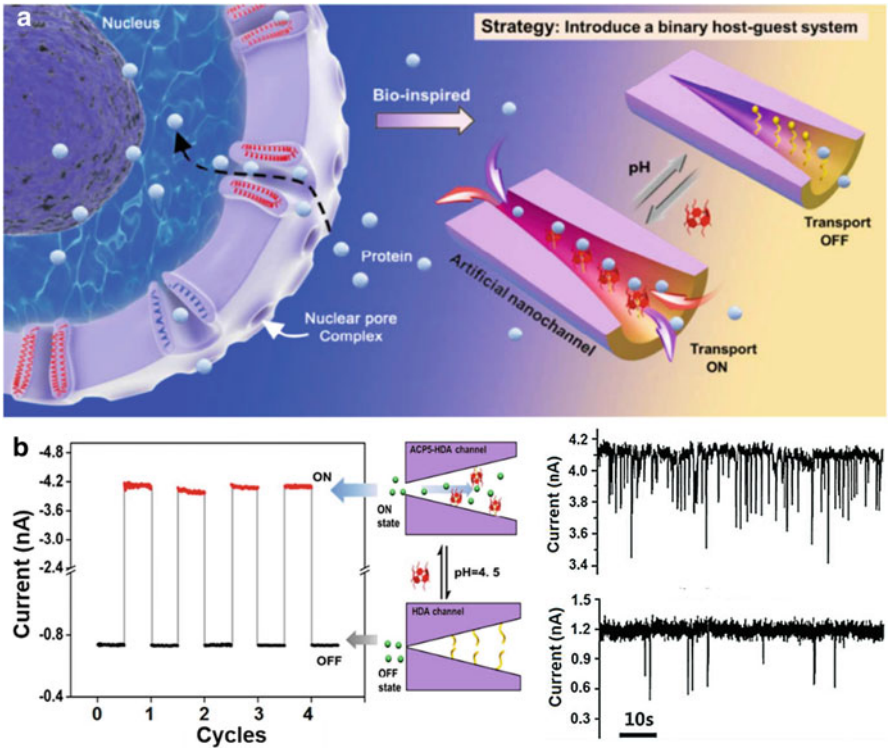


Fig. 13 (**a**) Design of a binary host-guest gated nanochannel for protein transport inspired from biological nucleopore. (**b**) Switching ability of the pH-regulated host-guest nanochannel and the current blocking signals at different states. (Reprinted with permission from Ref. [49]. Copyright 2018, American Chemical Society)

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