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Recent Advances in Synthetic Membrane Transporters

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It is 25 years since the first report of a synthetic ion channel transporter. Today, dozens of molecular and supramolecular designs have been developed to facilitate ion and small molecule transport across a bilayer membrane. Presented here is a concise summary of the advances made over the past four years. The transporters are grouped into three mechanistic classes: mobile carrier, monomeric channel, and self-assembled pore. Common building blocks are crown ethers, steroids, cyclodextrins, peptides, curcubiturils, and calixarenes. The eventual goal is to produce functional supramolecular devices such as sensors, enzyme assays, and lead candidates for pharmaceutical development.

Keywords: Membrane transport; Ionosphere; Ion channel; Mobile carrier; Membrane pore; Self-assembly; Phospholipid bilayer

INTRODUCTION

Biological membranes are the defining boundaries of cells and their internal organelles. A major role of these membranes is to maintain concentration differences between the various intracellular compartments and the cell exterior. Buried in the membranes are transport proteins that control the permeability of small polar molecules and inorganic ions. Controlled ion transport across membranes is a central feature in many cellular processes such as respiration, nerve conduction, and osmotic homeostasis. Indeed, several human diseases are attributed to an anion transport deficiency, including cystic fibrosis and diabetes; whereas, cation transporters often have antibiotic activity because of their ability to destroy transmembrane electrochemical gradients. The importance of membrane transport has generated considerable attention from the supramolecular chemistry community for several decades. Numerous supramolecular structures have been designed to mimic natural transport systems, and produce functional devices such as sensors, enzyme assays, and lead candidates for pharmaceutical development. Presented here is a concise summary of recent efforts and advances in synthetic membrane transporters over the past four years [1]. Because of space constraints, membrane disruptor molecules that are derived from natural products, such as polyether antibiotics and pore-forming peptides, will not be discussed.

BIOLOGICAL TRANSPORT PROTEINS

Since the first crystal structure of a biological ion channel was reported in 1998 [2], the mechanistic understanding of ion channel transport has increased substantially, especially with the aid of sophisticated Molecular Dynamic simulations [3]. The structures of the KcsA and ClC channels, selective for K^+ and Cl^- respectively, give insight into nature's method of rapidly moving charged ions across bilayer membranes. These proteins contain water filled pores for the passage of hydrated ions. The ions must subsequently pass through the protein's selectivity filter (Fig. 1), which comprises only a small section of the entire structure. The selectivity filter controls transport flux by coordinating to the ions via carbonyls for cations (K^+, Na^+), and hydroxyls and amide protons for anions (Cl^-). An additional structure has been reported for the functionally related ATP dependant Ca^{2+} pump (Fig. 1C). In this case, there is evidence that the controlling interaction is also cation coordination by side-chain carboxyls and backbone carbonyls within the protein.

The mechanism of K^+ transport by the KcsA channel is now known in considerable detail.

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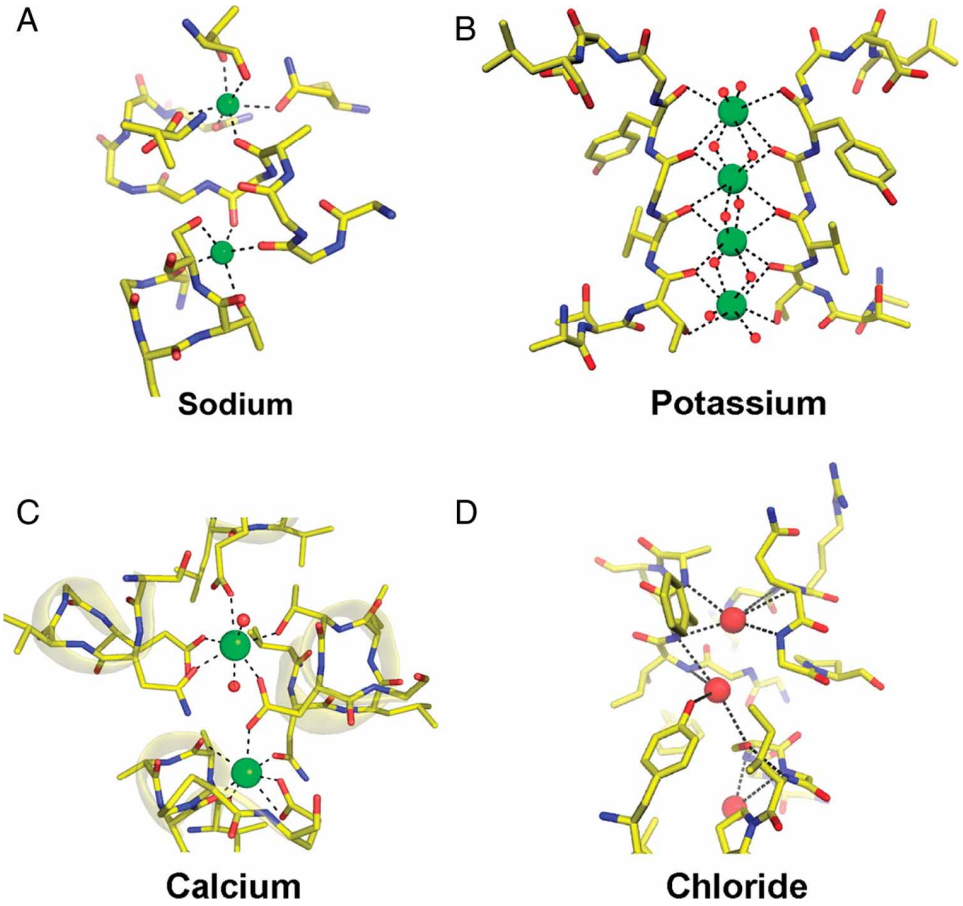

FIGURE 1 Transport protein selectivity filters. Reprinted from reference 3 with permission from AAAS.

It possesses a selectivity filter with 4-fold symmetry (2 fold shown in Fig. 1B) that positions 8 backbone carbonyls above and below each of four K^+ ions. The coordinating carbonyl oxygens decrease the energetic penalty for cation desolvation by acting as surrogates of water coordination (the mean K^+-O distance is 2.84 Å) [4]. The selectivity of the K^+ channel is attributed to the spatial orientation of the carbonyl oxygens which provides an ideal binding cavity to dehydrate a K^+ ion (radius = 1.33 Å) but not its smaller counterpart, Na^+ (radius = 0.95 Å) [5]. In support of this concept is an X-ray structure of the protein LeuT (Fig. 1A), a Na^+-dependent leucine transporter with a Na^+-O distance of 2.28 Å, a much more effective distance for dehydrating this smaller and more charge-dense cation [3]. Overall, it is quite satisfying to see that some of the crucial ion recognition features within biological ion channels are similar to the coordination phenomena reported thirty years ago by the pioneers of crown ether host-guest chemistry.

TYPES OF SYNTHETIC TRANSPORTERS

Progress in the field of synthetic ionophores has lead to a broad range of ion transport designs [6,7]. It is difficult to group all of these designs into rigorous mechanistic classes, however in this short review we will define three types of synthetic transporters: the mobile carrier, the monomeric channel, and the self-assembled pore. Mobile carriers are usually molecular ionophores that are not large enough to span the bilayer membrane. The ionophores associate reversibly with ions and form lipophilic ion-carrier complexes that diffuse across the bilayer. They are often highly selective transporters but fluxes are limited by the rate of transmembrane diffusion. A monomeric channel is able to span a membrane and create a hydrophilic tunnel through which ions may pass. A single ion channel can pass upwards of 1×10^9 ions/sec, about three orders of magnitude faster than a mobile carrier. Finally, a self-assembled pore is similar in function to a monomeric channel, but it requires the self-assembly of two or more subunits to create a viable transport passage for ions or hydrophilic small molecules. Because of the dynamic structure, it is harder to achieve high transport selectivity with a self-assembled pore but the design has an advantage that the subunits are potentially quite small so they may have more favorable pharmacokinetics as compared to a structurally larger monomeric channel.

MOBILE CARRIERS

In recent years, the field of mobile carriers has expanded beyond cationophores to include anion carriers as well as salt co-transporters. A salt-binding macrobicycle, **1**, was developed by Smith and colleagues to co-transport KCl or NaCl across vesicle membranes [8]. The macrocycle is able to bind either of these salts as a contact ion-pair, which minimizes the polarity of the carrier-salt complex, and allows strong partitioning into the membrane interior. Another effective set of mobile carriers are the cholapod receptors, developed by Davis and co-workers (**2**), which transport anions by an exchange mechanism. The cholapods are particularly effective at transporting Cl^- across vesicle membranes as long as there is a suitable anion for exchange in the reverse direction. Structure activity studies of these cholapods have uncovered an interesting trend that Cl^- fluxes increase with anion binding affinity [9]. The chloride binding constants for these compounds spanned four orders of magnitude with a maximum K value of 1.1×10^{11}. Mobile carriers often suffer from transport inhibition if substrate binding is too high, as the complex does not release its cargo. Yet, this effect was not observed for the range of binding constants and transport rates measured for the cholapods. From a practical perspective, a cholapod similar to **2** has been reported to transport Cl^- across the membrane epithelial layers of Madin Darby Canine Kidney (MDCK) cells [10]. This promising result raises the idea of using organic molecules with Cl^- transport ability as tools for cell biology research or perhaps eventually as therapeutic agents that correct Cl^- transport deficiencies.

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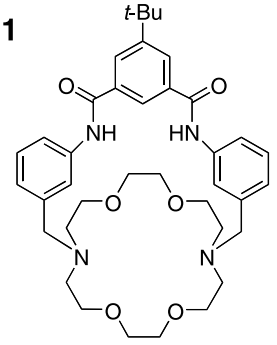

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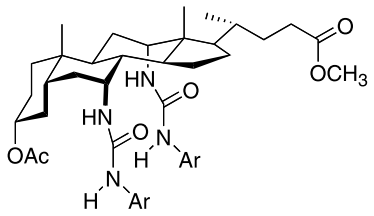
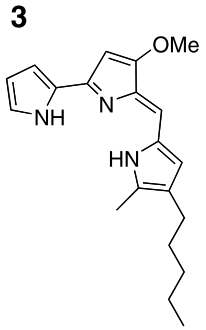


The Cl^- transporter prodigiosin, **3**, is a rare example of a low-molecular-weight, natural product with anion transport ability. Prodigiosin is known to act as a carrier for H^+/Cl^- co-transport, however, J. T. Davis and colleagues recently demonstrated that under certain conditions it can utilize an anion exchange mechanism to transport Cl^- [11]. There is ongoing debate as to whether prodigiosin's various biological activities can be attributed to its transport properties, and this question has stirred efforts to develop analogues and mimics of **3**. Gale and Smith designed the pyrrole based prodigiosin-mimic, **4**, and showed that it can co-transport H^+/Cl^- [12]. The co-transport mechanism was supported by an X-ray crystal structure of the HCl salt and the fact that transport was enhanced by the presence of a pH gradient. The relatively simple prodigiosin analogues, **5**, were synthesized by Sessler and colleagues, who demonstrated that Cl^- transport rates "closely correlated" with anti-cancer activity [13]. The H^+/Cl^- co-transport mechanism was supported by an X-ray structure of the HCl salt of two of the analogues. In addition, isothermal titration calorimetry (ITC) studies confirmed that the protonated complexes of **5** had greater affinities for chloride. The anti-proliferative activity of these derivatives against A549 human lung cancer cells ($EC_{50} = 1–10\,\mu M$) suggests that they may have pharmaceutical potential.

3



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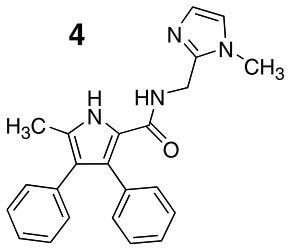

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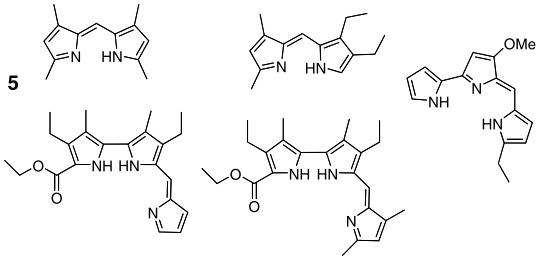
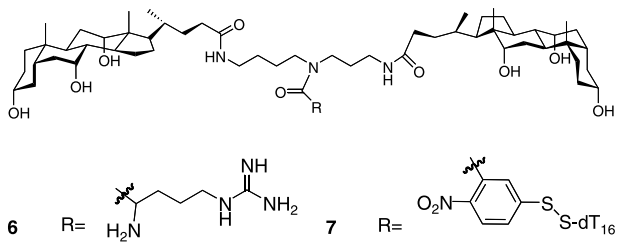
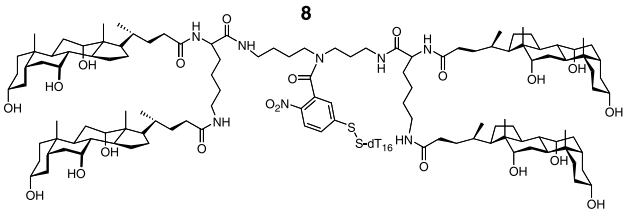


Turning to other anions, Regen and colleagues have employed their "molecular umbrella" architecture to transport anionic biomolecules across

membrane bilayers. Attachment of arginine to a cholic acid-spermidine scaffold gave amphiphilic umbrella **6**, which selectively transported ATP over glutathione (GSH) [14]. The greater affinity of guanidinium cation for phosphate over carboxylate supports this transport selectivity. In a related project, a 16-mer oligonucleotide was covalently attached to the cholic acid-spermidine scaffold through a 5-mercapto (2-nitrobenzoyl) linker to give **7**. A "needle and thread" transport mechanism was invoked to explain how the 16-mer was transported into vesicles and released through a thiolate-disulfide interchange with entrapped GSH. The transport process occurred with an approximate half-life of 30 hours [15]. Transporter **8**, with twice the number of cholate units, was found to have 10-fold better transport ability. This dramatic increase was attributed to increased shielding of the polar oligonucleotide by the facially amphiphilic cholate units [16].

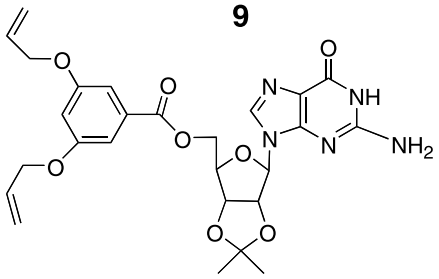


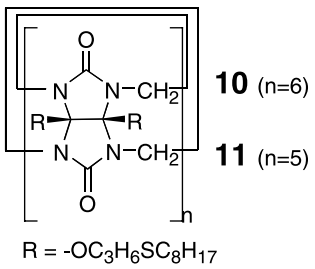


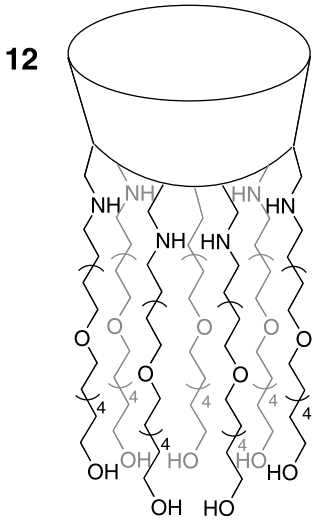
selective order with the smaller CB[5] compound, **11**, was only $Li^+ > Na^+$. Interestingly, these monomeric channels could be blocked by complexation with the neurotransmitter acetylcholine, a known cucurbit[n]uril substrate. The precise mechanism of channel formation is not yet known, however, it appears that cucurbit[n]urils are a promising new macrocyclic scaffold for designing monomeric channels. An example of the changes in transport behavior that can be achieved by functional manipulation of a familiar scaffold is the cyclodextrin-based channel recently reported by the Gin group. They used an amine linkage to attach oligoether chains to β-cyclodextrin to form a monomeric ion channel, **12**, which co-transports cation and anion across the bilayer [19]. Transport flux is unchanged with different cations, however the identity of anion significantly altered transport rates ($I^- > Br^- > Cl^-$). This effect is attributed to the anion forming hydrogen bonds with the secondary amine in the oligoether chains.

MONOMERIC CHANNELS

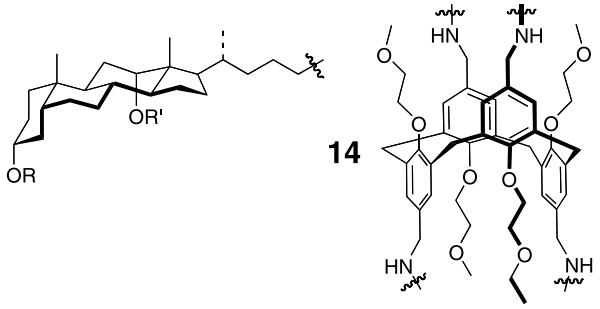
Several clever transporter designs have recently been shown to function as monomeric ion channels. A remarkable ionophore was reported by J. T. Davis and colleagues, who covalently attached sixteen guanosine units together using olefin metathesis (the guanosine monomer is shown as **9**). This compound was synthesized using a templated synthesis in which multiples of four guanosines would self associate around K^+ cations to form "G-quadruplex" units. Under reaction conditions, four of these G-quadruplexes would stack, after which the polymerization would occur to give a templated hexadecamer of guanosine. Upon insertion into a lipid bilayer, the compound formed a G-quadruplex sodium transporter of similar length (26 Å) to gramicidin A (gA) [17]. A more straightforward design was reported by Kim and colleagues, who prepared the lipophilic cucurbit[n]urils **10** and **11** and observed classic open/closed channel behavior during bilayer patch clamp experiments [18]. Further studies in liposomes showed that the CB[6] cavitand, **10**, elicited selectivity in the order $Li^+ > Cs^+ \approx Rb^+ > K^+ > Na^+$. Meanwhile the

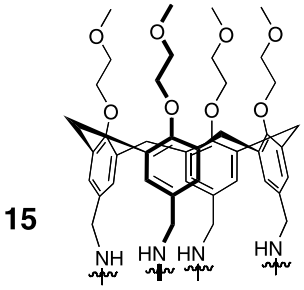


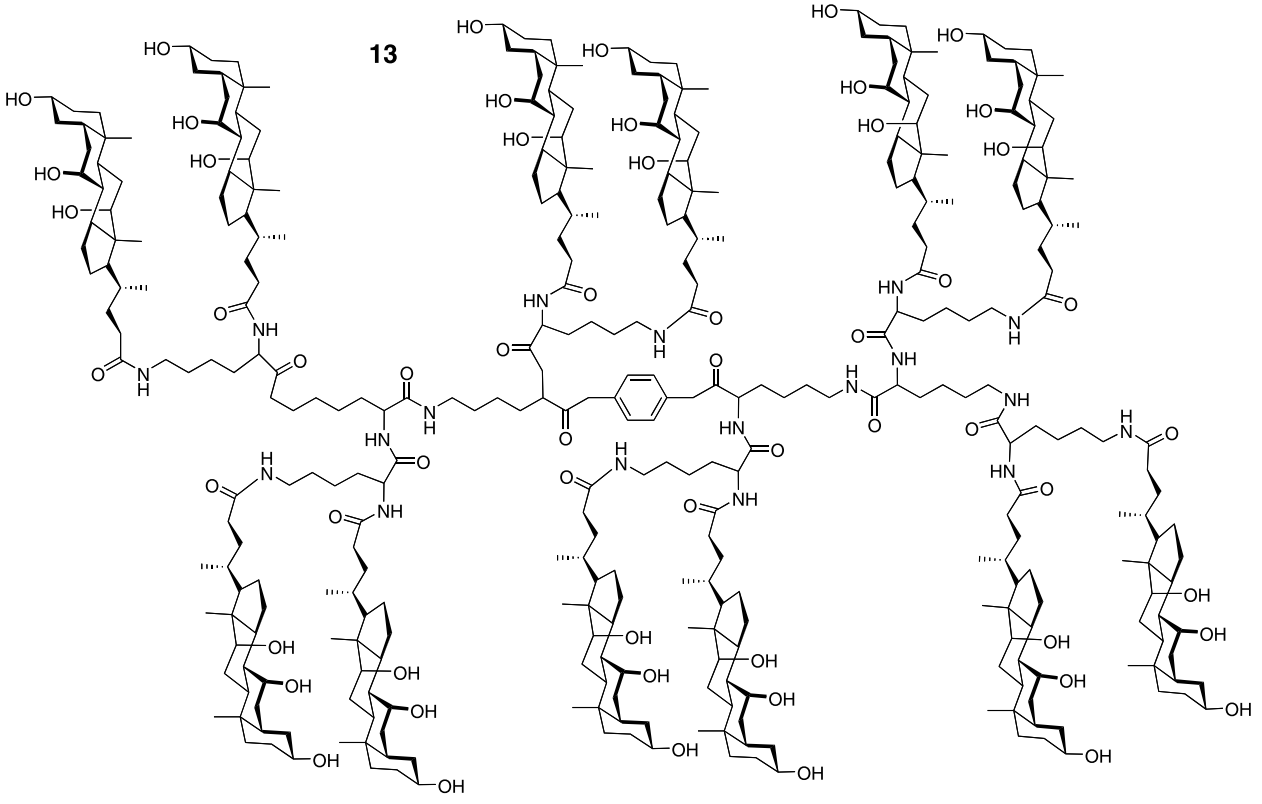




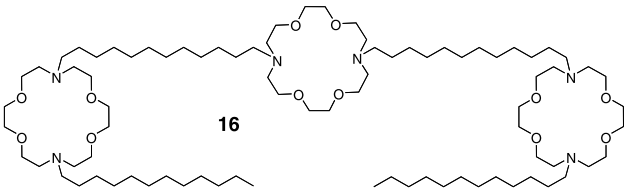
Not surprisingly, steroids continue to be employed as rigid building blocks for momomeric channel structures. Regen has prepared amphiphilic channel compounds using a series of 4 to 12 cholic acids connected by lysine and *p*-phenylenediamine (**13**). The steroids are thought to form the walls of a barrel-stave structure that facilitates Na^+ transport. Interestingly, the ability of these compounds to act as a monomeric or self-assembled pore depended on the flexibility of the steroid linker [20]. An ionophore designed by Izzo, De Riccardis, and colleagues appends cholic acid units to a calix[4]arene scaffold [21]. Various derivatives of two fixed calix conformations, *1,3-alternate*, **14**, and *cone*, **15**, were observed to accelerate the rates of H^+ and Na^+ transport in a dose dependent manner. The *1,3 alternate* was a better transporter than its *cone* counterpart, a trend that was attributed to differences in molecular length and ability to span the membrane.

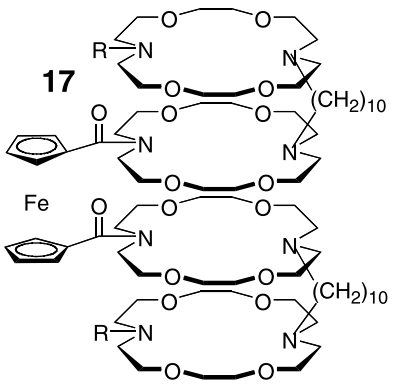


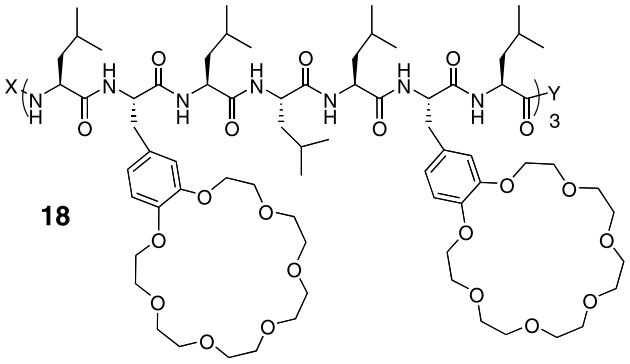




Crown ethers are another common building block in monomeric channel compounds. Gokel and co-workers have continued to refine a class of cation channels they call "hydraphiles." One example is compound **16** which has crown ethers as entry and exit portals, as well as a centrally located relay unit. These mechanistic features are reminiscent of the much larger protein channels [22]. The hydraphiles are synthetically accessible, and studies have extended from Na^+ release measurements in liposomes [23] to electrophysiological studies on living cells [24]. Studies of hydraphiles with different lengths highlighted the advantage of matching the channel's length with the hydrophobic width of the bilayer [25]. Meanwhile, Hall and colleagues have used a similar architecture to prepare a redox-active ion channel, **17** [26]. In this case, the channel is comprised of four diaza-18-crown-6 rings linked by two dodecyl chains, and one centrally located ferrocene. Oxidation of **17** resulted in a compound that was switched to an inactive form, a phenomenon which is still under investigation. The Na^+ transport rate of **17** was observed to be approximately six times faster than the natural mobile carrier, monensin. A third example of crown ether based channels was reported by Voyer, Pucci and colleagues [27]. They prepared various derivatives of a 21-mer peptide unit containing two 21-crown-7 phenylalanines, given as **18**. Each derivative was varied in polarity at the N- and C-terminal groups of the compound. The altered peptide polarity did not affect its conformation. However, the use of polyhydroxylated substituents at the N- and C-termini did increase compound incorporation into lipid bilayers. Sodium transport increased almost 3-fold when the N-terminus was substituted, while C-terminal substitution caused a modest decrease in activity.

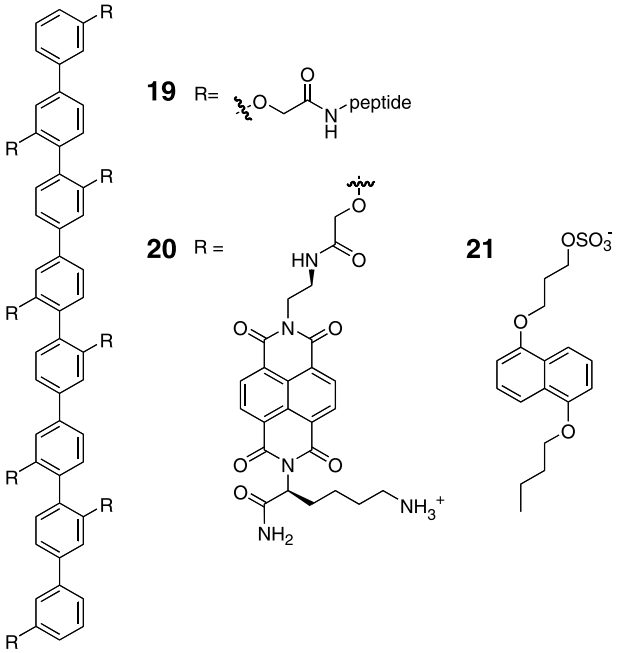






SELF-ASSEMBLED PORES

Designing synthetic molecules to self assemble as pores is an ongoing activity in supramolecular chemistry. The Matile group has continued to produce innovative designs using their rigid-rod β-barrel concept. Each monomer of the barrel is comprised of a *p*-octaphenyl backbone with single pentapeptides branching from each aromatic ring, shown as **19**. When four of these



subunits self associate, the octaphenyl groups form the corners of a rectangular pore. The peptides of each subunit form β-sheets with adjacent monomers, thus becoming the walls of the pore [28]. Matile recently reported a variation of this design in which the hydrogen bonded peptides were replaced by pi stacking naphthalenediimide (NDI) moieties (**20**), which twist the pore into a closed conformation [29,30]. Addition of the electron poor arene dialoxynaphethalene (DAN, **21**) lead to intercalation between the NDI molecules which effectively

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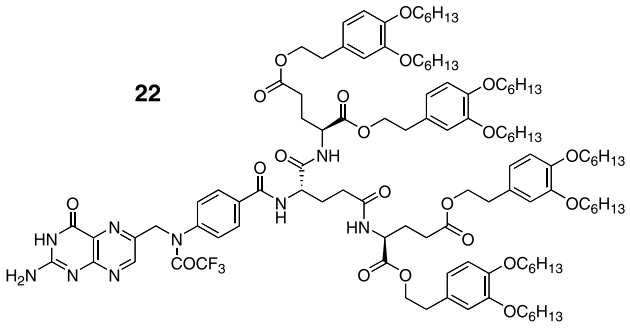

untwisted and opened the pore. This remarkable system can be considered as the first example of a ligand gated synthetic ion channel. In a related design, folate dendrimers (**22**) were shown to self assemble into rosettes that simultaneously underwent aromatic stacking. Each stack has a single cation sandwiched between two rosettes thus forming an ion channel with a 5-fold preference for cations over anions [31].

Peptide derived transporters comprise a significant group of self-assembled pores. Tomich and colleagues have utilized the second transmembrane segment of the glycine receptor (M2GlyR) to transport Cl^- in living cells [32]. The 22-residue sequence, NK4-M2GlyR p-22 (listed as **23**), is thought to insert into a bilayer where it self assembles with other monomers into pore forming "helical bundles." Several derivatives of **23** have been tested for chloride transport across MDCK epithelial layers. In short, N-terminal truncations reduced channel activity whereas C-terminally truncated peptides were virtually unchanged. Increased transport was noted from derivatives containing C-terminal substitutions with combinations of arginine, tryptophan, phenylalanine, and/or tyrosine [33]. Another peptide involved in transport originates from the Gokel group. Their chloride transporter, termed SCMTR (**24**), is a membrane anchored heptapeptide (GGG-PGGG) that was 10-fold selective for anions during bilayer patch clamp studies. Structure-activity relationship studies have demonstrated how the length and terminal residues of the anchor [34] and most recently the peptide side-chains [35], affect its transport ability. These compounds have also been utilized in biological studies to transport Cl^- in epithelial layers composed of primary murine trachea cells [36]. Lastly, the peptide gramicidin A (gA) is a classic pore-forming agent that self-assembles as a dimer to selectively transport cations. Koert and colleagues have recently made a covalent dimer of gramicidin to increase its activity [37]. Another derivative, **25**, was prepared using a biscyclohexylether δ-amino acid linker to alter the pore's ion selectivity [38]. By increasing the number of oxygens at the bilayer surface and interior, selectivity for Cs^+/K^+ was increased from 3:2 to 10:1. Functionalizing gramicidin at the bilayer surface with an aza-18-crown-6 to make compound **26**, reversed the selectivity to K^+ over Cs^+.

23 KKKKPARVGLGITTVLTMTTQS

24 $R_2N\text{-}COCH_2OCH_2CO\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Pro\text{-}Gly\text{-}Gly\text{-}Gly\text{-}OR'$

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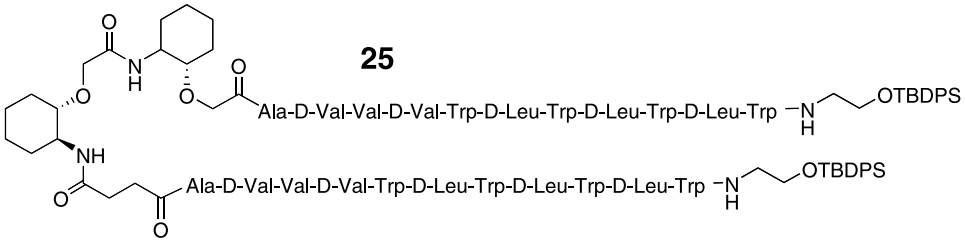

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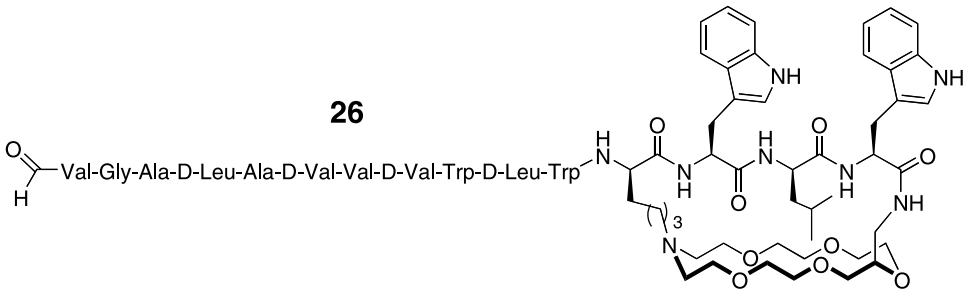
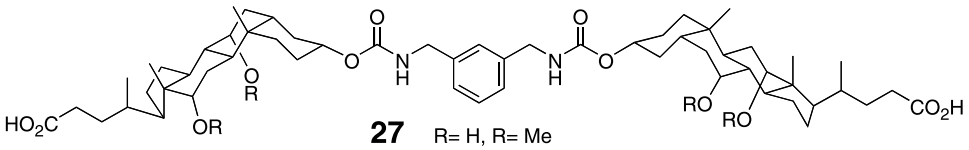
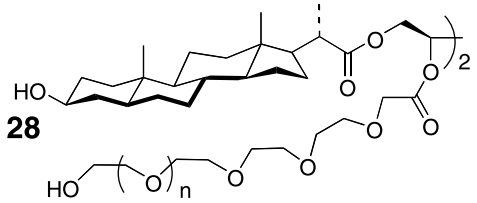


Steroids have also been utilized as non-covalent building blocks to form self-assembled pores. Kobuke and colleagues have studied the pore formation of the cholate dimers, shown as **27**. Each monomer is capable of spanning the bilayer, with two units joining to form the walls of the pore. This class of compounds exhibited open/closed behavior during patch clamp studies with 8-fold cation/anion selectivity and two independent conductance states of approximately 9 and 25 pS [39]. Methylation of the cholic acid hydroxyl groups produced a channel with almost 17-fold cation selectivity, but with numerous conductance states between 5–20 pS. In addition, De Riccardis and co-workers have demonstrated that a C2-symmetric sterol-oligo(ethylene glycol) (**28**) [40] is capable of spanning a liposome membrane and promoting Na^+ transport at a similar rate as its monomer unit (**29**) [41]. However, the C2-symmetric compound did have much higher proton transport rates compared to its monomeric derivative, which was attributed to the stability of the proposed self-assembled pore.



27 R= H, R= Me



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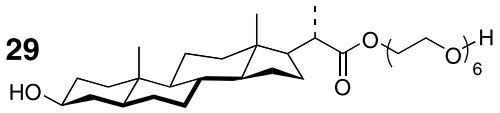

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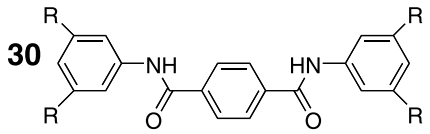
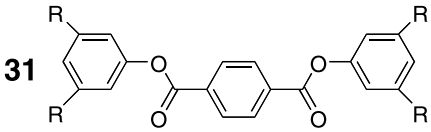
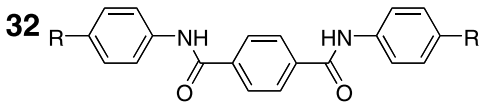
Several other noteworthy self assembling pores have recently appeared. Fyles and colleagues studied three bolaamphiphilic structures (**30**–**32**) that exhibit similar specific conductances and a selectivity of $Cs^+ > Na^+ > Cl^-$ [42]. Interestingly, a change in functionality from an amide (**30**) to an ester (**31**) did not alter the conductive state of the pore. J. T. Davis and co-workers have shown that a partial-cone calix[4]arene (paco-H, **33**) and t-butyl derivative (paco-tBu, **34**) exhibit drastically different chloride transport abilities [43]. Crystal structures identified intramolecular hydrogen bonds between the amide NH protons of the inverted arm and its ether oxygens for paco-H but not for the paco-tBu conformation. Ultimately, paco-H has an amide NH proton available to form a hydrogen bond to Cl^- and pass it through the channel whereas the paco-tBu amide NH protons form intermolecular hydrogen bonds. Lastly, Percec, Heiney and colleagues have continued work on their proton transporting "dendritic dipeptide" pores [44]. Monomer **35** self-assembled to form columns stabilized by π stacking and hydrophobic interactions of the dendritic tails, as well as hydrogen bonding of the peptidyl apex functional group [45]. This unique architecture formed aesthetically pleasing pores, and may have application in water purification technology.



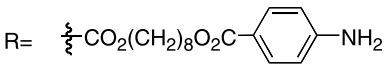
30

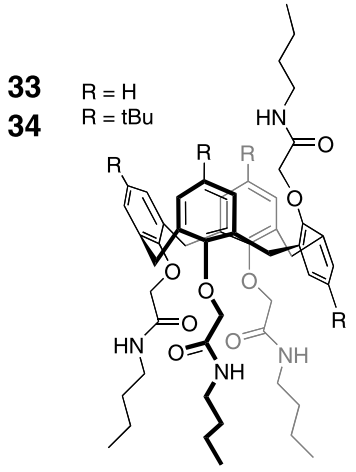


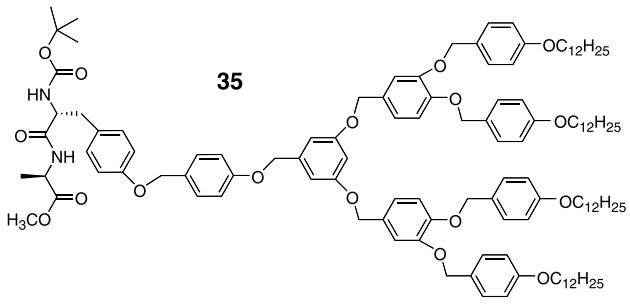
31



32







CONCLUDING REMARKS

It is now 25 years since Tabushi and Nolte independently reported the first examples of synthetic ion channels [46,47]. Today, a structurally diverse population of synthetic molecules is known to facilitate ion and molecule transport across bilayer membranes. A brief scan of the structures in this article shows that the common building blocks are crown ethers, steroids, curcubiturils, cyclodextrins, peptides and calixarenes. Some of these designs are beginning to exhibit sophisticated mechanistic features such as ligand gating, and in the near future it is likely that synthetic transporters will be incorporated into nanoscale assemblies that act as switches and sensors. There is also likely to be progress in pharmaceutical applications such as lead compounds for anti-cancer chemotherapy, antibiotics, or channel replacement therapy.

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