Ion channels and pores, made from scratch

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We elaborate on the structural diversity well beyond the biological limitations that becomes accessible with synthetic ion channels and pores, and on the importance of advanced nanoarchitecture to create significant function.

1 Introduction

No painter would ever dream of doing better than Nature, but no painter would stop painting because of this conclusion. He may mention his feeling that we do not quite understand what we can not create, point out that his objectives are not photographic reproductions but to spotlight isolated aspects that are essential but otherwise difficult to appreciate, or to contribute his distinguishing ability to introduce motifs that are totally new.[1]

For much the same reasons, ion channels and pores have aroused the curiosity of synthetic organic chemists since decades.[1] As contribution to a special issue that focuses on analytical and bioengineering aspects of biological ion channels and pores, we will try to point out selected highlights from leading groups in the field of synthetic ion channels and pores, followed by a similarly brief summary of our own work on the topic. The focus is on more recent progress, and readers interested in the early studies or in more detail are referred to several more comprehensive reviews that appeared recently.[1–8] Moreover, the terms "synthetic" or "artificial" are restricted here to ion channels and pores that (1) form in lipid bilayer membranes and (2) are made from scaffolds that do not occur in biological ion channels and pores.[1,2] This definition excludes *de novo* peptide as scaffolds (although they may be made using synthetic organic chemistry), a rich field inspired by classics from nature such as α-helix bundles formed by melittin, alamethicin or the magainins, as well as the gramicidin β-helix. Other excluded topics such as chemically modified or bioengineered membrane proteins, peptides and natural products as well as pores formed in membranes other than lipid bilayers may be covered in other contributions to this special issue.

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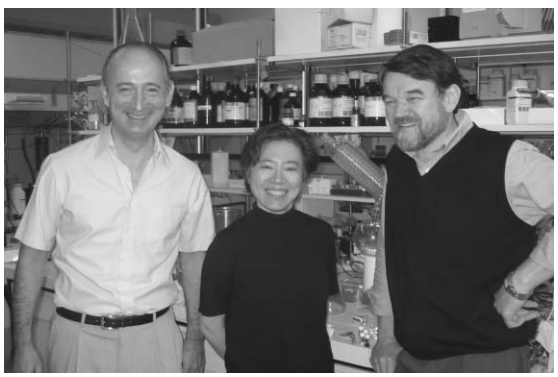
2 The hall of fame

The structural diversity that has become accessible with organic synthesis of ion channels and pores is simply marvelous (Fig. 1). The first synthetic ion channel is commonly attributed to an amphiphilic cyclodextrin from the group of the late Tabushi.[9] It appeared at a time when gramicidin A mimics[10] and the barrel-stave model for ion channels formed by macrolide antibiotics like amphotericin[11] were already attracting considerable attention. The cyclodextrin motif was recently revisited in the synthetic ion channel **1**.[12] Here, a β-cyclodextrin macrocycle, whose inside is hydrophobic and outside hydrophilic, is envisioned as an ion channel scaffold at the membrane–water interface. A ring of amines is placed right below the macrocycle to introduce anion selectivity and sensitivity toward pH. This cationic filter is followed by oligoalkyloxy tails that are long enough to span a lipid bilayer to provide a unimolecular ion-conducting pathway.

Calixarenes are another family of macrocycles that have attracted



Stefan Matile, Naomi Sakai and Jiri Mareda

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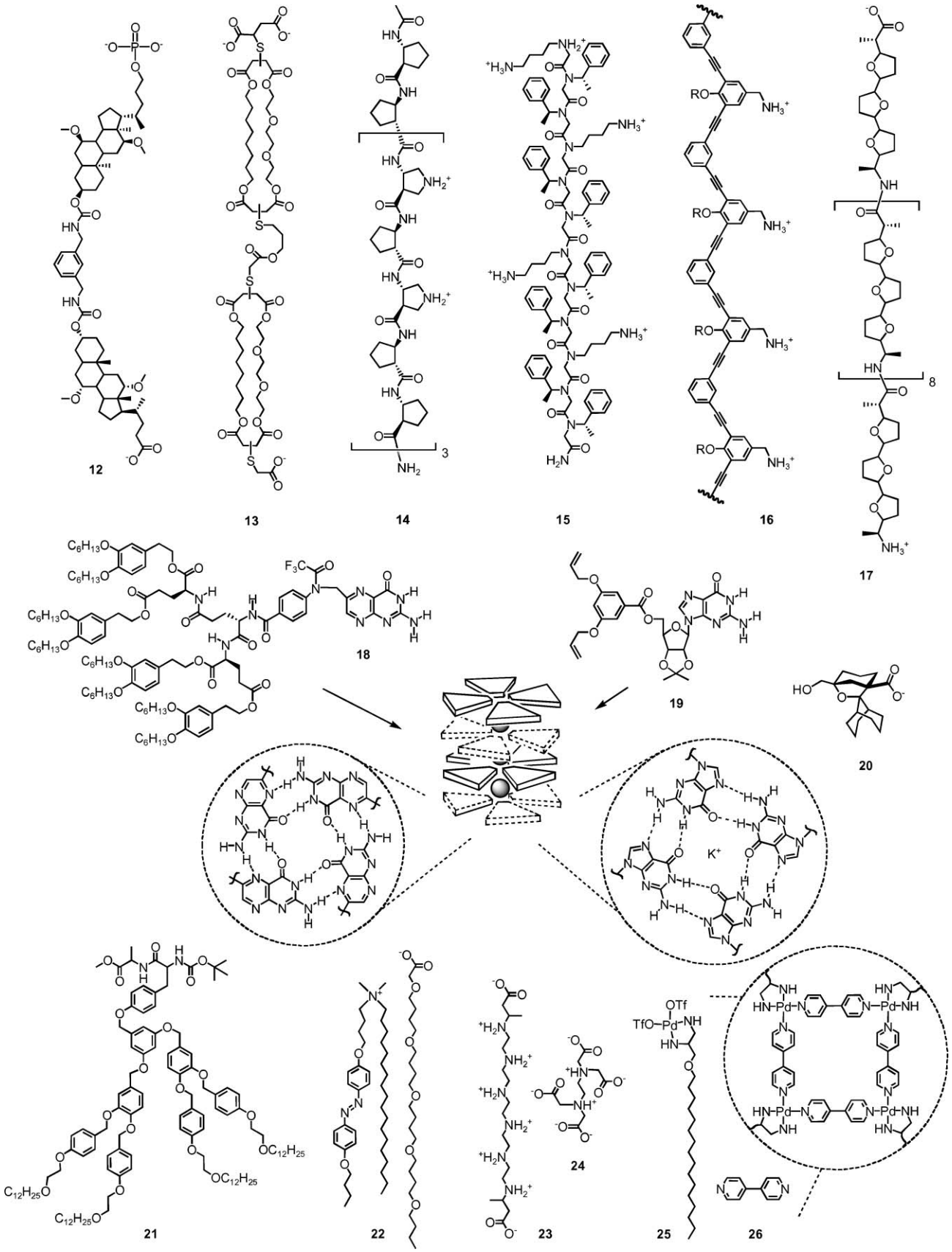
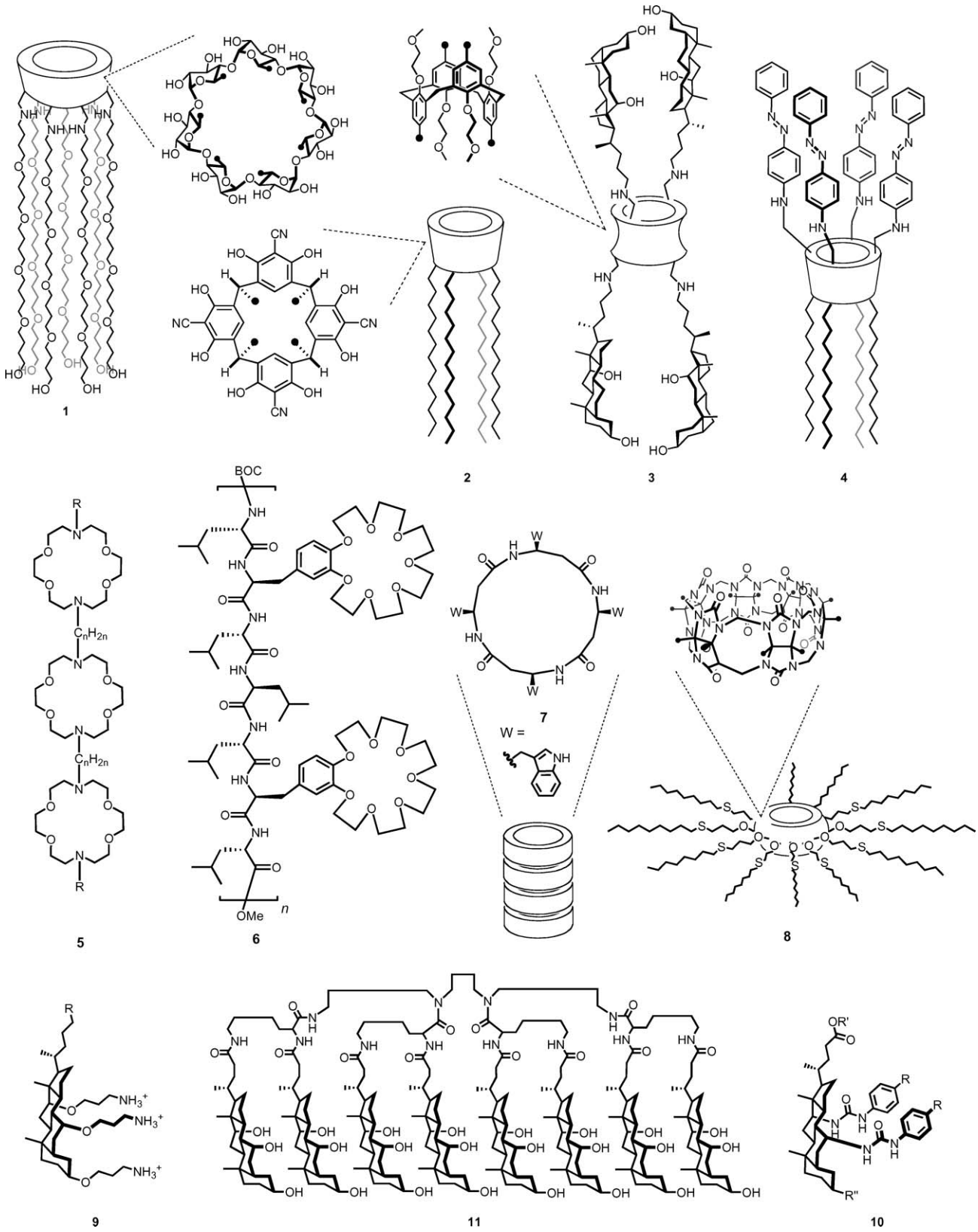


Fig. 1 Structure of selected synthetic ion channel and pores.



considerable attention in the field of synthetic ion channels. They offer a robust scaffold and the possibility of introducing ion selectivity by cation–π interactions during passage of the cation through the macrocycle. Early breakthroughs included the use of calix[4]-arenes as a selectivity filter that selects for potassium.[13] Recent progress includes the introduction of π-accepting cyano groups to lower the pK_a of the phenols in the macrocycle for pH gating around physiological pH.[14] In ion channel **2**, the macrocycle is envisioned as a selectivity filter at the interface. The

length of four alkyl tails attached on one side of the macrocycle matches the thickness of one leaflet of a lipid bilayer, the active structure is expected to be a tail-to-tail dimer.

To create unimolecular ion channel **3**, a calix[4]arene in 1,3-alternate conformation was envisioned to serve as a macrocyclic scaffold in the middle of the bilayer that positions a dicholate sandwich on each side to form a hydrophilic pathway across the bilayer membrane.[15] A third example of recent progress with calixarene macrocycles is dimeric channel **4** with diazobenzenes placed at the interface to achieve responsiveness to light.[16]

Crown ethers are classical macrocycles that recognize matching cations by coordination to the oxygen lone pairs. Monomeric crowns act as ion carriers in lipid bilayers. The Gokel group proposed early on the concept that covalent alignment in linear oligocrowns such as **5** would transform monomeric ion carriers into ion channels.[17] A transmembrane active structure is envisioned, with cations hopping along central and peripheral crowns. Activity naturally depends on the size of the crowns, the length of the spacers between the crowns and the terminal anchors R at the membrane–water interface. Recent developments focus on activity in live cells, particularly bacteria.

Other scaffolds explored for oligocrowns include polyisocyanates,[18] *p*-oligophenyls (below) and α-helices such as **6** from the Voyer group.[19] Formally derived from phenylalanine, the artificial crown-ether amino acids are placed in position 2 and 5 of the heptad repeat. In an α-helical conformation, this sequence places the crowns on top of each other to form an ionophoric channel for multiion hopping across a lipid bilayer.

Peptide macrocycles have been explored as synthetic ion channels and pores in several groups. All L-repeats were envisioned to act as monomers or assemble into artificial β-barrels,[20,21] L,D-repeats were introduced as mimics in between the closely related gramicidin A β-helix and macrocycles such as gramicidin S or valinomycin ion channels.[10,22,23] This approach was further expanded to mixed L,L,L,D-repeats to functionalize, as with refined β-helices,[10] the interior of the ion channels formed by the stacked macrocycles.[24] Peptide macrocycle **7** is a unique example in this series that uses β-peptides to form a scaffold that does not occur in similar form in biology.[22] β-Peptides were of interest because the uniform orientation of the backbone carbonyls in stacked macrocycles suggested that the formed ion channels could be voltage gated, an interesting concept that was not confirmed experimentally. Peptide macrocycles have also been studied as selectivity filters at the membrane–water interface with attached alkyl tails as in calixarenes **2** or **4**.[25]

Cucubituril macrocycles have been introduced more recently in the field of synthetic ion channels and pores.[26] In clear contrast to cyclodextrin, calixarene or peptide macrocycles such as **1–4**, the molecular pumpkin **8** carries alkyl groups in the equatorial rather than the axial position. This equatorial ring of alkyls was expected to introduce micellar defects in the lipid bilayer around the macrocycle. The carbonyl oxygens at both rims of a single molecular pumpkin sitting in the center of the micellar channel should then select for cations. Interestingly, this synthetic ion channel could be blocked efficiently by acetylcholine.

The facially amphiphilic cholate appeared in many variations as a privileged scaffold in ion channels and pores. Monomeric cholates with cations (*e.g.*, **9**)[27] or ureas (*e.g.*, **10**)[4] on the hydrophilic face are under intense investigation as antimicrobials or chloride transporters, respectively. Oligocholates up to octamer **11** were proposed to form bundles in one leaflet with a hydrophilic channel in the middle, with the active ion channel being a dimer.[28] Similarly dimeric active structures were expected with cholates attached to one face of a calix[4]arene.[13,16] Only cholates at both rims of the macrocycle may move the calix[4]arene scaffold to the middle of the membrane to give unimolecular ion channel **3**.[15] A transmembrane scaffold with two covalently linked cholates was also envisioned for **12**.[29] The facial amphiphilicity was then expected to stimulate the self-assembly into transmembrane bundles with a central hydrophilic channel. Transmembrane cholate dimers such as **12** with differently charged termini exhibited current rectification. Earlier, voltage gating was also demonstrated with synthetic ion channel **13**, which comprises a more flexible amphiphilic transmembrane scaffold with differently charged termini.[30]

Mimics of biological or *de novo* α-helix bundles are naturally attractive scaffolds for the design of synthetic ion channels and pores. The cyclopentane constraints in β-peptide **14** are known to direct folding into 2.5-helices, their replacement with hydrophilic pyrrolidines in positions 1 and 3 of the pentad repeat would thus provide access to the cationic facial amphiphile that is often expected to selectively form pores in the anionic, highly polarized plasma membranes of bacteria.[31] Similar magainin mimics with cationic and hydrophobic faces were accessible with scaffolds such as the 3.0-helical peptoids **15**[32] or poly(1,3-phenyleneethynylene)s **16** that may self-assemble into pleated sheets and beyond.[33] Peptide **17**, finally, a masterpiece in asymmetric multistep synthesis, is composed of ten amino acids that contain three tetrahydrofurans between acid and amine.[34] These oligo-THFs were expected to capture cations within a unimolecular helix that is somehow reminiscent of the gramicidin β-helix. Recent research in this area focused on the introduction of THF amino acids and crown ethers into the gramicidin scaffold.[6]

Several approaches to the self-assembly of synthetic ion channels and pores with more complex architecture became accessible recently. Folate dendrimers **18**, for example, self-assemble into planar cyclic tetramers that can coordinate cations with the carbonyl lone pairs pointing towards the center (sodium fits best).[35] Face-to-face π-stacking of these ionophoric folate quartets provides access to attractive ion channel architecture. The corresponding π-stacked G-quartet architecture is accessible from guanine **19**.[36] In contrast to folate, however, G-quartets do not cyclize without potassium templates because of otherwise dominant polymerization. Two double bonds were added to each guanine to covalently crosslink the final active ion channels by Grubbs metathesis. Similarly complex "barrel–rosette" architecture[1] has been observed in the solid state for membrane-active hydroxyacids such as **20** and dendritic dipeptides such as **21**.[37,38] Both

suprastructures have a hydrophobic interior reminiscent of some (but not all) biological ion channels, and dipeptide nanotubes similar to **21** have been studied before in several groups for various purposes.[39,40]

"Minimalist" approaches to synthetic ion channels focus on small, readily accessible monomers. Often, they are single- or double-chain amphiphiles reminiscent of detergents or lipids.[1] However, the complexity and heterogeneity of the active structure of synthetic ion channels usually increase with decreasing complexity of the monomer structure, and so minimalist approaches often result in complex behavior. Facially amphiphilic ion pairs are the first synthetic ion channels that were systematically studied by single-channel measurements in planar bilayers.[41] In the more recent version **22**, a diazobenzene is added for sensitivity toward light.[42] Minimalist systems have also been considered for ion channels and pores that respond to chemical stimulation. Fuhrhop's pioneering polyamine channel **23**, for example, can be closed with EDTA **24** and reopened with divalent metal cations that remove the blocker.[43] Attractive coordination chemistry was recently considered by the Fyles group to assemble amphiphilic ethylenediamine palladium(II) complexes **25** with bipyridine ligands **26** into ion channels with metallosupramolecular squares at the membrane–water interface.[44]

3 Rigid rods

Despite this impressive structural diversity of the channels and pores developed so far and the pioneering examples on ion selectivity, membrane recognition, sensitivity to light, voltage gating, ligand gating and blockage discussed in the preceding section, the creation of advanced function "beyond the simple hole" remains challenging. For modular access to such advanced multifunctional bionanoarchitectonics, we have introduced rigid-rod molecules as privileged scaffolds.[45] Somehow the antithesis to foldamers,[46,47] these simple rods bypass all folding problems because they do not fold.[48] Interestingly, rigid, *i.e.*, (1) unbendable, (2) incompressible, (3) unfoldable and (4) ununfoldable rods do not exist in biology. They are, however, common and useful in the materials sciences.[48–60]

Oligoacetylenes **27** are the simplest rods but clearly not the most rigid ones (Fig. 2).[50] *p*-Oligophenyls **28** are similarly pure, more rigid, blue fluorescent, often chiral and always non-planar because of the biphenyl torsion between proximal phenyl rings.[45,51,52] The mixture of these two modules in OPEs **29** [*i.e.*, oligo(1,4-phenyleneethynylene)s] is of interest as they are fully conjugated colorful *p*-semiconductors with adjacent phenyl rings oriented either parallel or perpendicular to each other.[53–55] Oligo- and poly(1,3-phenyleneethynylene)s such as **16** are not rigid-rod molecules because they can roll up into helices,[46] and nor are polyenes such as carotenoids. Whereas monomeric and not overly substituted *p*-oligophenyls **28** can rotate almost freely around their carbon–carbon single bond, oligonaphthalenes **30** are an emerging class of rigid-rod molecules of exceptional stereochemical complexity because this rotation is blocked.[56]

Oligocubanes **31** are one out of many existing non-aromatic rigid rods.[57] Oligonaphthalenediimide (O-NDI) and oligoperylenediimide (O-PDI) rods **32** and **33** are attractive in optoelectronics because they contain stable organic n-semiconductors that can be colored without global structural changes.[58,59] With a length of l = 106 nm, the longest existing rigid-rod molecule is a *meso–meso* oligoporphyrin **34**.[60] For more comprehensive collections of rigid-rod molecules realized so far, the interested reader is referred to pertinent reviews of the topic.[48,49]

4 Ion channels and pores à la baguette

To create ion channels and pores from rigid-rod scaffolds, we originally selected *p*-oligophenyls **28** as model rods.[45,61] Today, ion channels made from O-NDIs **32**[62] and O-PDIs **33**[63] exist as well, and the introduction of the OPE scaffold **29** is in progress. Initial focus on *p*-oligophenyls **28** was meaningful

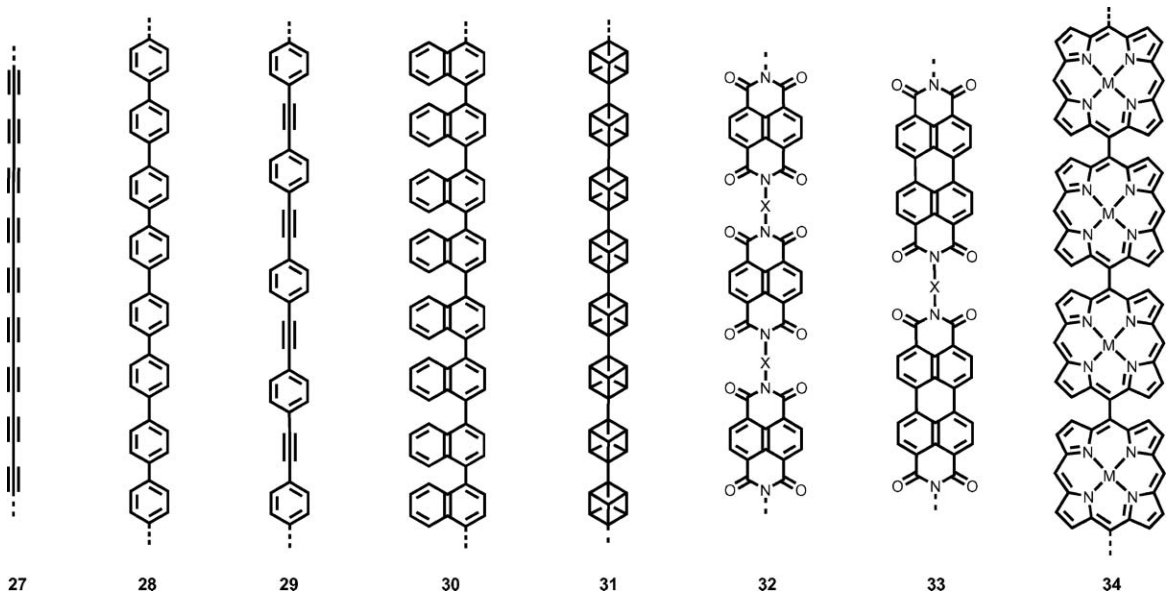


Fig. 2 Structure of selected rigid-rod molecules.

because these rods are not only quite easy to synthesize but also because they are non-planar, chiral and fluorescent, characteristics that are of use as means to control supramolecular architecture and as intrinsic probes for structural studies in lipid bilayers.

Rigid-rod polyol **35** was made to act as transmembrane proton wire (Fig. 3).[61] For this purpose, a hydrogen-bonded chain (HBC) was established along the membrane-spanning *p*-octiphenyl scaffold. To move across the membrane, all a proton has to do is to bind to the terminal oxygen lone pair of the HBC. Then, all hydrogen and O–H bonds flip to formally shuttle the proton along the HBC (a). Then, the proton can be released at the other end of the HBC on the other side of the membrane. Rotation around the C–O bond of all involved alcohols returns the HBC to the resting state and prepares for the transport of the next proton (b). This hop-and-turn HBC mechanism was proposed early on by Onsanger to play a central role in bioenergetics; the introduction of rigid-rod scaffolds provided access to the presumably first functional model of this key process.

The recently reported anion–π slide **36** is exceptional for two reasons.[62] First, it introduces with the π-acidic, shape-persistent oligo-(*p*-phenylene)-*N*,*N*-naphthalenediimides (O-NDIs) a rigid-rod molecule different from *p*-oligophenyls. Second, the O-NDI rod is expected to play not only a structural but also a functional role. Dynamic cation–π interactions along π-basic *p*-oligophenyl scaffolds have been confirmed previously to provide access to cation–π slides that exhibit the biologically relevant potassium selectivity (Eisenman IV topology).[64] The introduction of anion–π interactions to expand approaches to anion selectivity beyond ion pairing and hydrogen bonding was of scientific interest because these less obvious interactions are attractive theoretically, poorly explored *in vitro*, and inaccessible with ion channel proteins. Rigid O-NDI rod **36** was found to transport anions across lipid bilayer membranes with a rare halide VI selectivity ($Cl^- > F^- > Br^- > I^-$) and a substantial anomalous mole fraction effect (AMFE). This AMFE confirmed the existence of the multiple binding sites expected for a π-slide **36**. Moreover, it demonstrated the occurrence of "Newtonian" multiion hopping, a mechanism of choice in biological ion channels to solve the problem of how to be fast and selective.

Rigid push–pull rods such as **37** were introduced as shape-persistent α-helix mimics to explore the role of dipole–potential interactions and transmembrane charge translocation for voltage gating.[65,66] This was of particular interest with regard to Merrifield's pioneering proposal on the mechanism of action of natural antibiotics[67] and led to considerations of the role of counterions to regulate charge translocation, thoughts that today finally start to make their predicted appearance in discussion on the mechanism of action of cell-penetrating peptides[68] and the structural basis of voltage gating in biological channels.[69] The axial dipole in push–pull rod **37** is

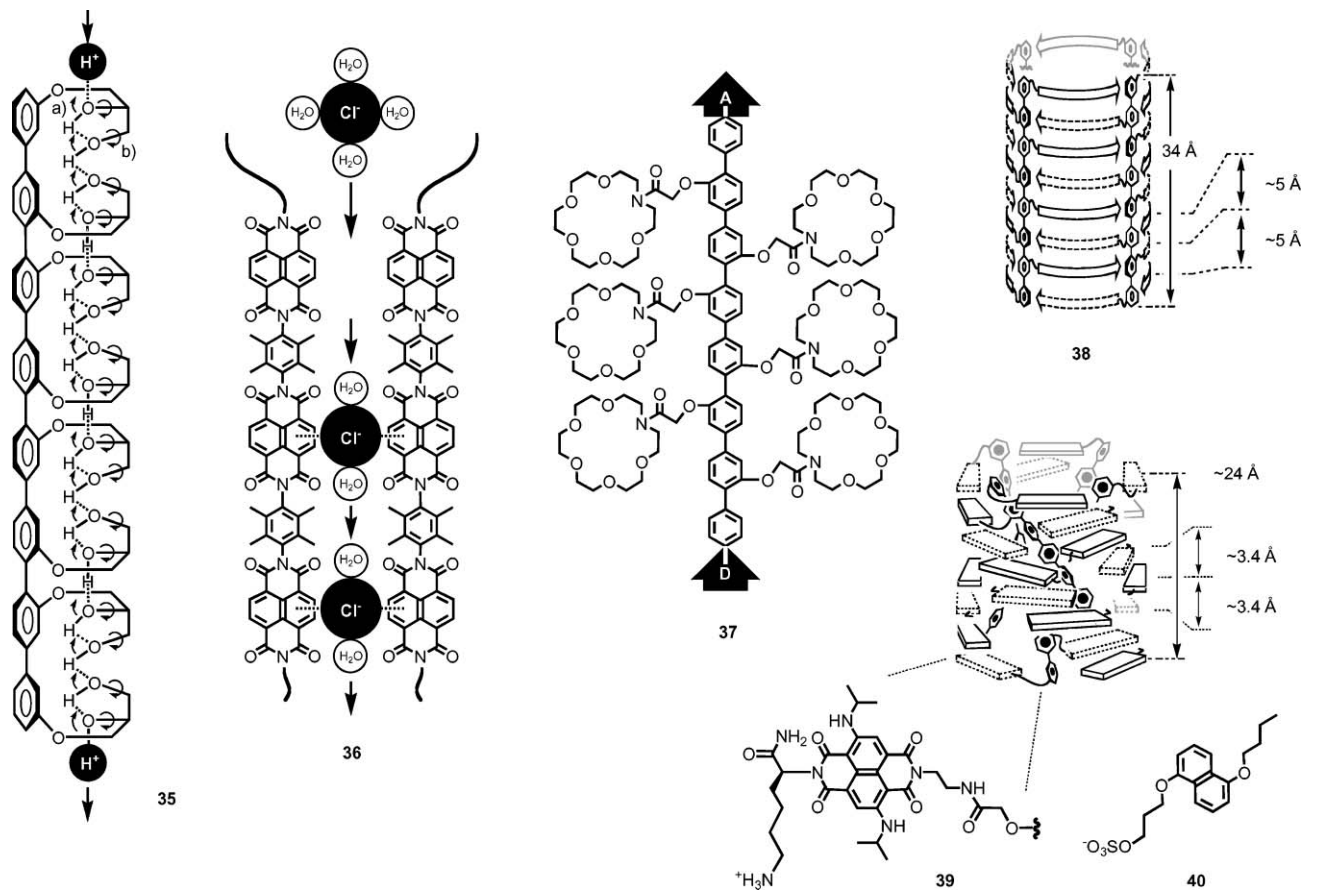


Fig. 3 Selected synthetic ion channels and pores constructed from rigid-rod scaffolds.

introduced with a π-donor D at one rod terminus and a π-acceptor A at the other. Unlike α-helical macrodipoles, the macrodipole of the push–pull rod is always there (independent of conformational changes) but can be turned off on demand without major structural changes. Fluorescence depth quenching of the intrinsic *p*-octiphenyl fluorescence readily reports structural changes (*e.g.*, rod reorientations) in response to membrane polarization under meaningful conditions.[66] Crown ethers are added in push–pull rod **37** to report the functional consequences of dipole–potential interactions.

Rigid-rod β-barrels **38** were originally introduced to explore unexpected behavior of rigid-rod HBCs **35** in black lipid membranes.[70,71] These barrel-stave supramolecules self-assemble from *p*-octiphenyls that carry short peptide strands along their rigid-rod scaffold. Interdigitation of peptides from neighboring rods produces eight-stranded antiparallel β-sheets in-between. The non-planarity of the *p*-octiphenyl staves is then essential to turn the planar β-sheets around, promoting cylindrical self-assembly into supramolecular oligomers and preventing the linear self-assembly into the supramolecular polymers known from protein misfolding. Tetramers, the smallest oligomers accessible without excessive internal crowding around the *p*-oligophenyl turns, are found most frequently. Rigid-rod β-barrels **38** are attractive because the chemical and physical properties of the outer and inner barrel surface can be rationally selected and changed simply by varying the peptide sequence. To create synthetic multifunctional pores, the outer surface was made hydrophobic to maximize pore–membrane interactions. Various active sites were installed at the inner pore surface to catch and possibly convert molecules that are passing by, through the pore and across the membrane.

Because of this facile introduction and variation of internal and external function, the concept of synthetic multifunctional pores could be introduced and developed with rigid-rod β-barrels. Realized examples cover many variations of ion selectivity, voltage-gated push–pull barrels,[72,73] pore opening and closing in response to chemical stimulation by pH, cations, molecules, macromolecules and supramolecules,[45,71,74] and catalysis.[45,71,75,76] The use of synthetic multifunctional pores as optical transducers of chemical reactions was particularly attractive because of broad applicability in different fields such as drug discovery (*i.e.*, enzyme inhibitor screening), diagnostics (*i.e.*, multicomponent sensing), and so on.[77–79] For this purpose, synthetic pores that respond to small changes in bulk and/or charge of as many substrates and products as possible are best. For multicomponent sensing in complex matrices, optical transduction by synthetic pores is combined with enzymes as specific signal generators. As an illustrative example from the supermarket, synthetic multifunctional pores capable of discriminating between ATP as good and ADP as poor pore blockers were implemented as sucrose sensors.[78] Soft drinks such as Coca-Cola or Red Bull were incubated first with invertase and hexokinase as uncoupled signal generators, and consumption of the ATP blocker during sugar phosphorylation was visible by the "naked eye" as pore activation in fluorogenic vesicles. Details on sensing with pores have been reviewed recently in a special issue of *Topics in Current Chemistry* on Chemical Sensors.[79]

As far as progress toward advanced rigid-rod β-barrel architecture is concerned, examples include multiple peptide sequences for voltage sensitive "in-depth" molecular recognition,[80] internal artificial amino acids for π-clamping of elusive analytes,[81] programmed assembly with mismatched rods,[82] and so on. Extensive insights on the structural level do exist despite clear emphasis of this research on advanced function.[83] Highlights include evidence for active tetramers from Hill plots,[84] transmembrane rods from fluorescence depth quenching,[85] also during blockage,[74,86] or AFM snapshots that show a single polymer blocker entering and moving through a single pore **38**.[87]

Replacement of the β-sheets in rigid-rod β-barrels **38** by π-stacks produces rigid-rod π-helices **39**.[88–91] This barrel → helix transition occurs because the repeat distance of the π-stacks is clearly shorter than that of the β-sheets. The "hyperboloidal" barrel → helix transition that takes place with sticky rigid rods closes the internal pore of rigid-rod π-helix **39** (Fig. 4A). This closed transmembrane rigid-rod π-stack architecture is thus incompatible with the transport of ion and molecules but perfect for the transport of electrons.[91] Unidirectional charge mobility in π-stacks can be better than in

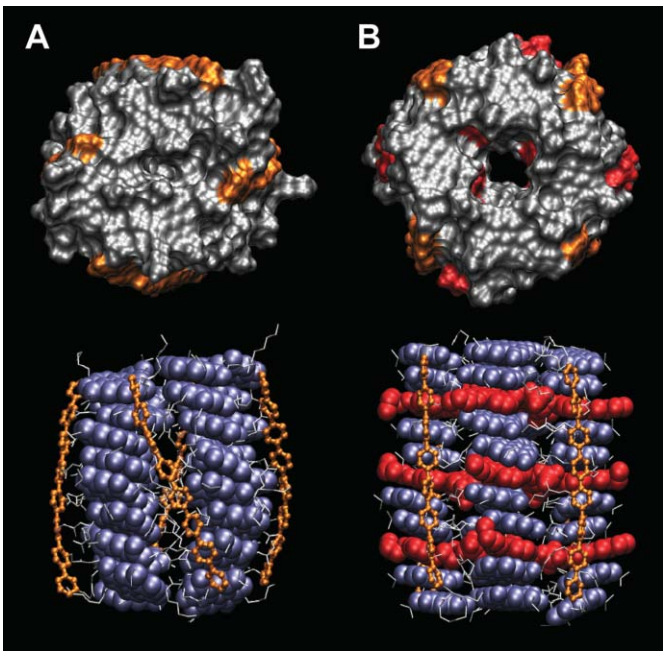


Fig. 4 Molecular dynamics simulations of photosystem **39** in the absence (A) and in the presence (B) of 12 ligands **40** (red) in top and side view. Reproduced from ref. 91, copyright © 2006 by the American Association for the Advancement of Science.

conjugated polymers, with precise architecture being able to overcompensate the weaker electronic coupling between monomer units. NDIs were selected as exceptionally compact, organizable and colorizable π-acidic[62] n-semiconductors to create photosynthetic activity with rigid-rod π-stack architecture **39**. Photosynthetic activity in vesicles was measured with internal quinone as electron acceptor and external EDTA as electron donor. Internal pH sensitive fluorescence probes (HPTS) were added to monitor proton consumption during quinone reduction with light. Time-resolved fluorescence and transient absorption spectroscopy provided direct experimental evidence that, upon irradiation of **39**, a charge-separated state characterized by a relatively long lifetime (61 ps) is populated almost quantitatively on an ultrafast timescale (<2 ps).

The closed photosystem **39** was designed to open up into an ion channel in response to chemical stimulation. Intercalation of the π-basic ligand **40** into the rigid-rod π-stack architecture **39** (just as we all know from the chemistry and biology of DNA duplexes) was expected to increase the π-stack repeat distance. This increase in π-stack repeat should initiate a "hyperboloidal" helix → barrel transition to finally match the repeat of the rigid-rod stave and give a barrel-stave supramolecule with an open pore in the middle (Fig. 4B). Highly selective and highly cooperative formation of small, ohmic, anion selective, and surprisingly homogenous single channels was found in response to the addition of ligand **40** to π-helices like photosystem **39**.[88–91]

5 Tongues and leaves

In summary, the rich collection of synthetic ion channels and pores available today is an impressive demonstration of the distinguishing ability of organic chemists to create new molecules from scratch. It also keeps us wondering about the enormous structural variably far beyond the limitations of biology that is waiting to be explored. The introduction of rigid-rod molecules as privileged scaffolds has provided modular access to the sophisticated bionanoarchitectonics that is needed to create significant function. The obtained highlights include motifs such as rigid-rod barrels, helices, stacks, slides and wires that can act as smart, stimuli-responsive photosystems, pores, ion channels, hosts, sensors and catalysts. As far as perspectives are concerned, some speak of drugs,[1,4,27,31–33] while others consider artificial tongues[79] and, of course,[91,92] artificial leaves.

Acknowledgements

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