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Synthetic Ion Channels: From Pores to Biological Applications

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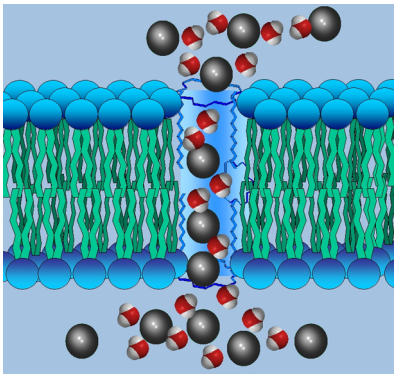
CONSPECTUS

In this Account, we describe the development of several diverse families of synthetic, membrane-active amphiphiles that form pores and facilitate transport within membrane bilayers. For the most part, the compounds are amphiphiles that insert into the bilayer and form pores either on their own or by self-assembly. The first family of synthetic ion channels prepared in our lab, the hydraphiles, used crown ethers as head groups and as a polar central element. In a range of biophysical studies, we showed that the hydraphiles formed unimolecular pores that spanned the bilayer. They mediated the transport of Na^+ and K^+ but were blocked by Ag^+. The hydraphiles are nonrectifying and disrupt ion homeostasis. As a result, these synthetic ion channels are toxic to various bacteria and yeast, a feature that has been used therapeutically in direct injection chemotherapy.



We also developed a family of amphiphilic heptapeptide ion transporters that selected Cl^- >10-fold over K^+ and showed voltage dependent gating. The formed pores were approximately dimeric, and variations in the N- and C-terminal anchor chains and the acids affected transport rates. Surprisingly, the longer N-terminal anchor chains led to less transport but greater Cl^- selectivity. A proline residue, which is present in the ClC protein channel's conductance pore, proved to be critical for Cl^- transport selectivity.

Pyrogallol[4]arenes are macrocycles formed by acid-catalyzed condensation of four 1,2,3- trihydroxybenzenes with four aldehydes. The combination of 12 hydroxyl groups on one face of the macrocycle and four pendant alkyl chains conferred considerable amphiphilicity to these compounds. The pyrogallol[4]arenes inserted into bilayer membranes and conducted ions. Based on our experimental evidence, the ions passed through a self-assembled pore comprising four or five amphiphiles rather than passing through the central opening of a single macrocycle. Pyrogallol[4]arenes constructed with branched chains are also amphiphilic and active in membranes. The pyrogallol[4]arene with 3-pentyl sidechains formed a unique nanotube assembly and functioned as an ion channel in bilayer membranes.

Finally, we showed that dianilides of either isophthalic or dipicolinic acids, compounds which have been extensively studied as anion binders, can self-assemble to form pores within bilayers. We called these dianilides tris-arenes and have shown that they readily bind to phosphate anions. These structures also mediated the transport of DNA plasmids through vital bilayer membranes in the bacterium *Escherichia coli* and in the yeast *Saccharomyces cerevisiae*. This transformation or transfection process occurred readily and without any apparent toxicity or mutagenicity.

Introduction

The discovery of crown ethers in the late 1960s[1] led to an explosion of activity involving these remarkable molecules.[2] The interest was manifested first in the synthesis of a vast array of structures that represented variations in ring sizes, ring heteroatoms, heterocyclic subunits, and even multiple macrorings.[3] The second phase involved the study of ion complexation in an effort to determine both ion binding strengths and selectivities.[4] The contemporaneous discovery of natural ion transporters such as valinomycin[5] encouraged emulation of membrane transport by amphiphilic macrocycles. Within two decades, the literature encompassing these areas was vast.[6]

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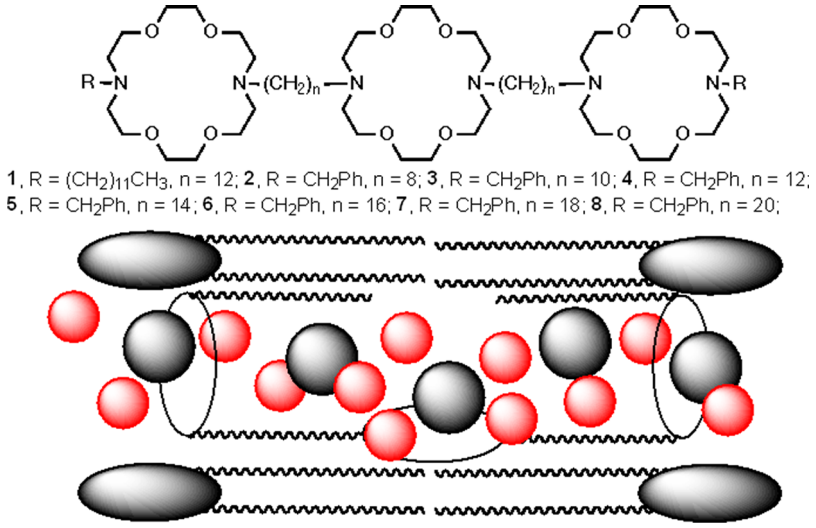

FIGURE 1. Top panel: General structure of hydraphiles. Bottom panel: Schematic of the membrane-active conformation. The larger spheres represent cations and the smaller spheres represent water molecules.

Nature uses ion channels more extensively than it does carriers for transmembrane ion transport.[7,8] The incredible importance of ion channels in physiologic function and in diseases resulting from defective function is now well-recognized.[9] Our initial interest in ion channels arose, in part, because synthetic channels that transported the common physiological ions Na^+ and K^+ were unknown. In the 1980s, the challenges to mimic a natural channel with a synthetic amphiphile were legion. At that time, the peptide sequences of many natural channels were known, but the only solid state structure of a membrane protein that had been reported was bacteriorhodopsin.[10] Synthetic ion channels designed de novo required guesses or estimates of several properties. Despite the need for guesses, the approach taken in our lab[11] was conceptually similar to that taken independently by other chemists. Lehn and Jullien[12] and Fyles et al.[13] were simultaneously working to develop synthetic ion channel systems, unknown to us at that time.

The Design of Tris(macrocycle) Hydraphiles

Our synthetic ion channel design involved extensive use of crown ethers as structural elements. It is interesting, but perhaps not surprising, that, in all three laboratories, the independently conceived designs involved a central macrocycle. In our approach, the central macrocycle was included to provide a polar residue at the midplane of the bilayer, where membrane polarity is lowest. Chemical intuition suggested that it would be difficult for ions to traverse a 30−35 Å hydrophobic span without some energy-lowering element. A macrocycle was incorporated for this purpose and two similar ("distal") macrocycles were incorporated at a distance of about 15 Å on either side to serve as amphiphilic head groups.

The structure of the first synthetic ion channel developed in our laboratory is shown in Figure 1 as **1**.[11] The *n*-dodecyl side chains were linked only to the distal macrocycles and were intended to align with fatty acid chains within the bilayer. They were not covalently connected to the central macrocycle or to each other in the hope that they would adapt structurally within the bilayer to achieve a functional channel conformation. This flexibility proved to be important because the original concept was that the three macrorings would be parallel within the membrane. Extensive biophysical studies ultimately showed that the central macrocycle was perpendicular to the distal macrocycles. In retrospect, the initially imagined conformation would have presented the central macrocycle as an obstacle to transport. The functional conformation inferred from experimental studies is illustrated schematically in Figure 1.

The following is known about the compounds we have called hydraphiles, so-called because they are amphiphiles and they are two-headed and reminiscent of the mythical hydra serpent. They are selective for Na^+ over K^+ by ~4:1.[14] Hydraphiles show classic open-close behavior when studied by using a planar bilayer conductance voltage clamp apparatus.[15] The ion-conductance pathway is unimolecular.[15] Hydraphiles having covalent connectors of 8 carbon atoms do not conduct ions in dioleoylphosphatidylcholine (DOPC) bilayer membranes. The optimal spacer length for hydraphiles in such membranes is 12−16 methylenes. Longer chain hydraphiles function, but are poorer transporters.[16] Passage of ions through the bilayer mediated by hydraphiles

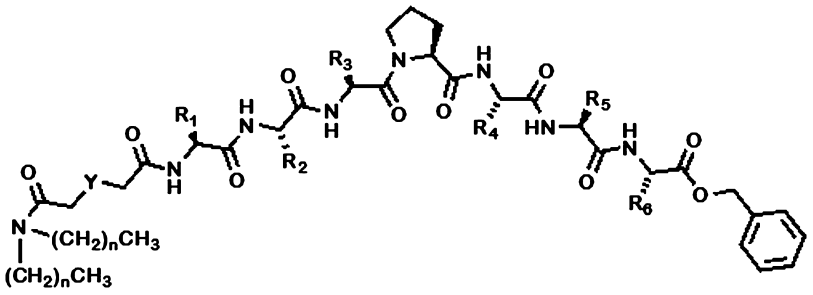

FIGURE 2. Generalized structure of a synthetic anion transporter. The alkyl chains are the *N*-terminal anchor ($n = 0-17$). Benzyl is shown as the *C*-terminal anchor. R_1-R_6 represent variations in the amino acid structures; in some cases, Pro was varied as well. The linker chain varied with $Y = (CH_2)_{0,1}$, O, S, or NH.

can be blocked either by strong complexation of Ag^+ or a side chain that can H-bond across the distal macrocycles.[17] Use of fluorescent side-chained hydraphiles showed that they experienced a dielectric constant (ε polarity) of ~25, which corresponds to the glyceryl regime of the bilayer.[15] Fluorescence depth quenching showed that the side chains are separated by ~30 Å, a distance corresponding well with the insulator regime of the bilayer. The head groups of hydraphiles interact with the head groups of the amphiphiles that comprise the bilayer.[18]

Synthetic Anion Transporters (SATs)

After extensive study of the hydraphile cation conductors, we turned our attention to the development of a synthetic anion-conducting channel. By this time, the Nobel prize-winning structure of the KcsA voltage gated potassium channel had been reported.[19] There was also increasing information about channel structures and the sequences of ClC family proteins[20] and Cl^--conducting C-peptide were known.[21] Our design was intended to mimic a phospholipid monomer.[22] We considered that the earliest channels must have borne a structural resemblance to early membranes. Absent any fossil record of such early structures, we decided to model portions of modern membrane structures. We would use a dialkylamine to replicate the twin fatty acyl chains and diglycolic acid [$(HO_2CCH_2)_2O$] to approximate the glyceryl regime in length and polarity. The head group would be $(Gly)_3Pro(Gly)_3$. This heptapeptide was inspired by sequences in ClC and C-peptide. A benzyl group comprised the C-terminal residue; it was chosen in part because it can be removed by hydrogenolysis. The initial concept was that the synthetic anion transporters (SATs) would function as dimers within the bilayer.

Figure 2 shows a generalized structure of amphiphilic heptapeptides. We have called these compounds "synthetic anion transporters" or SATs. Many structural variations were made in which the *N*-terminal chain lengths, the *C*-terminal anchor (shown as benzyl), the connecting diacid, and the peptides (sequence and length) were all varied.[23] They exhibit classic open-close behavior and they are selective for Cl^- over K^+ by more than 10-fold.[24] FRET studies confirmed aggregation in the bilayer.[25] Hill plots[26] using data from planar bilayer conductance or Cl^- release from liposomes[27] suggested that the pores were, as designed, approximately dimeric. When two SAT molecules were connected at either the C- or N-terminus to form *pseudo*-dimers, either compound was a more effective Cl^- transporter than twice the concentration of monomer.[28]

Changing the peptide sequence from $(Gly)_3Pro(Gly)_3$ to $(Gly)_3Leu(Gly)_3$ dramatically reduced Cl^- release from liposomes.[29] Altering the C-terminal ester from benzyl to *n*-heptyl increased efficacy; replacing benzyl by *n*-octadecyl obviated function.[30] A particularly interesting finding was that the presence of a carboxylate (glutamic acid) in the peptide sequence reduced Cl^- transport.[31] SATs that aggregate in the bulk aqueous phase fail to form pores, while those that do not aggregate are effective transporters.[32] Only about 30% of the available SAT partitions into the bilayer.[31] Finally, experiments conducted using an Ussing chamber showed that SATs function as Cl^- transporters in vital airway epithelial cells.[33]

Aplosspans

Work reported by both Kobuke[34] and Davis[35] and their coworkers suggested to us that the macrocyclic headgroups to which we attributed both efficacy and selectivity might be replaced by much simpler modules. Extremely simple amphiphilic structures such as the one that is shown in Figure 3, span the bilayer and transport ions.[36] We called them "aplosspans" from the Greek $\alpha\pi\lambda o\sigma$ = "simple" plus "span." We found that Na^+ was released from DOPC liposomes in a dose-dependent fashion. Ion release experiments detecting

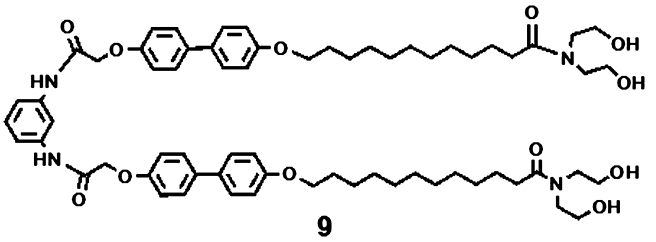

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FIGURE 3. Aplosspan built from simple molecular components as a two-headed amphiphile (a "bola-amphiphile").

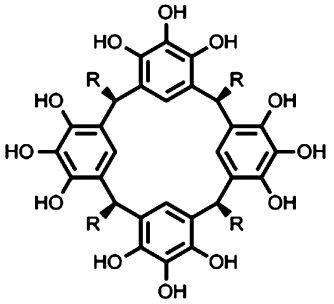
either Na^+ or Cl^- showed that compound **9** favored release of NaCl > NaBr and NaCl > KCl.[37] The mechanism by which this compound operates may be related to the oligoesters reported by Fyles.[38]

Pyrogallo[4]arenes

The success of the aplosspan studies piqued our interest in other structural types. Our criteria generally were that membrane-active compounds would at least need to be amphiphilic and be able to insert in bilayer membranes. The pyrogallol[4]arenes (Pgs) represent a type of amphiphile that has been studied more extensively in the solid state than in the solution or within bilayer membranes. In the solid state, Pgs often crystallize as infinite bilayers. These compounds may also crystallize as dimeric or hexameric capsules. The latter have been extensively explored by Atwood and co-workers.[39] These capsules are of inherent interest as they enclose a significant volume (~1500 $Å^3$).[40]

Our interest was in the Pgs that had either fairly long normal or branched alkyl chains.[41] The former crystallize less readily, which is critical because the preparation of these compounds involves heating pyrogallol with an aldehyde in ethanolic aqueous HCl solution, giving a complex mixture. Pure Pgs are usually obtained by crystallization. Representative structures are shown in Figure 4.

Our initial finding was that Pgs having *n*-undecyl side chains (**10**) did, in fact, form pores in bilayer membranes. These pores had the interesting property that they remained open and showed similar conductances at either positive or negative potentials between 0 and ±30 mV, after which the membranes failed. The conductances suggested a pore size of about 13 Å, probably resulting from the aggregation of six Pgs. When cholesterol was added to the bilayer, a similar "always-open" behavior was observed. In this case, transport was observed and the membranes were stable to ±60 mV. The pore size calculated from the conductance values was only 5 Å and appeared to result from aggregation of four Pgs.[42]



10, R = $(CH_2)_{10}CH_3$
11, R = $CH(CH_3)_2$
12, R = $CH(CH_2CH_3)_2$
13, R = $CH(CH_2CH_2CH_3)_2$

FIGURE 4. Straight- and branched-chain pyrogallol[4]arenes.

The work of Kim[43] and Atwood[44] and their co-workers suggested to us that metal–organic nanocapsules or MONCs[45] could mediate the flow of ions through bilayers. This proved to be the case.[46] These C_{12}Pg MONCs showed $Na^+ > K^+ \gg Cs^+$ selectivity and a permeability ratio for K^+ over Cl^- of 2.4:1. We understood the ion selectivity to reflect the capsule's internal openings, which are ~3.7 Å across. Unsolvated Na^+ and K^+ have diameters of ~2.0 and ~2.7 Å, respectively. Cesium (~3.6 Å) is about the same size as the opening.

The cation/anion selectivity may seem more surprising, but it can be understood in similar terms. Unsolvated Cl^- has a diameter of ~3.4 Å. It is significantly larger than K^+ and absent any other effect, should be less readily passed through the capsule. Of course, the metallorganic nanocapsule is seamed together by copper ions, which may have an affinity for the Cl^- ion, even though each copper is linked to three oxygen atoms.

The mechanism by which this MONC transports ions is unclear. It is certain that the MONC inserts in the bilayer and that open-close behavior indicates pore formation. The gating of the channel could result from a rocking motion of the capsule within the bilayer, which would interrupt transport in a column of water and ions. It is also possible that two capsules may insert into the bilayer and combine to form a pore. In such a case, gating could result from slippage of the two capsules relative to each other. Absent clear evidence, the latter explanation seems more complex than the former and therefore less appealing.

Even more interesting behavior was observed with the branched chain derivatives. Isopropylpyrogallolarene **11** was found to form a stable monolayer on the Langmuir trough. Considered as an amphiphile, its nonpolar chain is remarkably short. The amphiphilic behavior of these

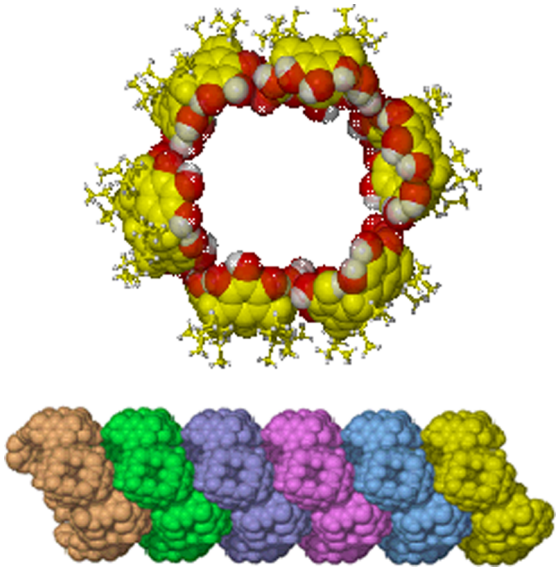


FIGURE 5. Nanotube structure formed from **12**. Top panel: single hexameric unit. Bottom panel: nanotube formed from stacked, self-assembled hexamers.

compounds was investigated further,[47] but our main interest was to see how the branched chain compounds differed in their behavior from the normal-chained analogues.

The branched chain Pgs were screened for the ability to form pores in the bilayer. The studies were conducted in reconstituted, natural soybean asolectin membranes. Both 3-pentylPg, **12**, and 4-heptylPg, **13**, showed membrane activity.[48]

Pyrogallol[4]arenes having 3-pentyl (**12**) and 4-heptyl (**13**) side chains form nanotube[49] and bilayer arrangements in the solid phase, respectively. The unique interlocked nanotube formed by six monomers of **12** is connected via an extensive hydrogen bond network resulting in a macrocyclic hexamer, Figure 5, top panel. These hexameric doughnut shaped units stack one upon the other fostered by solvent exclusion and interlocking of ethyl side chains to form nanotubes, Figure 5, bottom panel. Both compounds form functioning channels within the asolectin membrane although they behave differently, as judged by planar bilayer conductance measurements. From the most dominant conductance states, we calculated the pore size for the nanotube formed from **12** to be about 17 Å, which corresponds well to the diameter of the individual hexamers based on the crystal structure. The formation of the hexameric units was further confirmed by using the Langmuir trough technique.[50] We assume the same stacking happens in the membrane as it does in the solid phase. Lateral movements of the stacked hexameric rings would provide a gating mechanism. The conductance trace for **13** on the other hand, suggests an aggregation mechanism as was proposed for *n*-undecylPg, **10**.

Biological Applications of Synthetic Pore-formers

The synthetic amphiphiles that we prepared showed an affinity for membranes.[11,14] We thus began to consider the potential for using synthetic ion binders, transporters, and pore-forming compounds in membrane applications that we had previously not considered. Evidence for channel function by these compounds in vital organisms[51] further encouraged these studies. Examples that show the versatility of synthetic, amphiphilic pore-formers and some potentially important new applications of them are discussed in the following sections of this Account.

Hydraphile Biological Activity

The hydraphiles were designed to transport alkali metal ions across bilayer membranes. The extensive studies described above demonstrate that they do so. They are symmetrical molecules and may insert into the bilayer from either end. The corollary to this is that these channels cannot be rectifying. If the ion flow is rapid and uncontrolled, it is expected that their presence will lead to rapid equilibration of internal ions with the surrounding medium. This disruption of ion homeostasis is inimical to the survival of the affected cell. We thus explored the potential of hydraphile channels to function as antimicrobials.[52] It should be noted, however, that at sufficiently low concentrations, hydraphiles function safely as channels in vital mammalian (HEK 293) cells.[51]

Two types of experiments were undertaken once it was confirmed that *Escherichia coli* were adversely affected by the presence of hydraphiles.[53] The first was to measure the minimum inhibitory concentration (MIC) for hydraphiles of different lengths. Previous work had shown that the ion transport ability varied as a function of channel length.[16] These studies were done with the family of hydraphiles having benzyl side chains and identified herein as **2**–**8**. Figure 6 shows the relative release of Na^+ ions from DOPC vesicles as a function of length. The second type of experiment done was to confirm by fluorescence using a hydraphile having dansyl side chains that after insertion of the hydraphiles, they were essentially localized in the *E. coli* bilayer. This was readily demonstrated.[53] Additional fluorescent probes also proved to be revealing as described below.

The efficacy of different length channels and their ability to kill Gram negative *E. coli* or Gram positive *Bacillus subtilis* was assayed by determining MIC values in the presence of

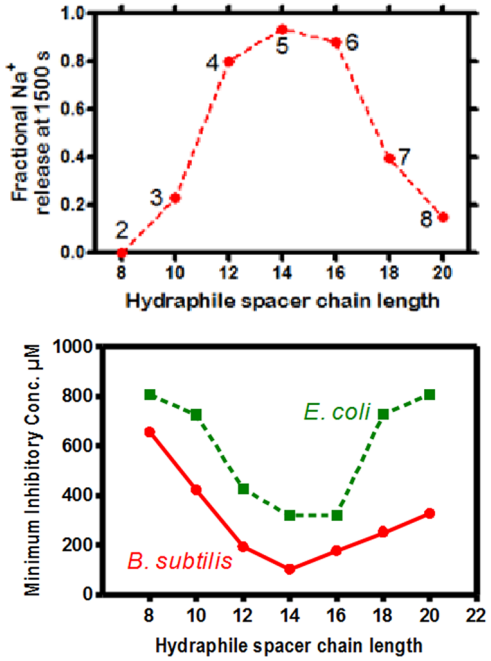


FIGURE 6. Upper panel: Ion release from DOPC vesicles as a function of channel length in compounds **2**–**8**. Lower panel: Toxicity of **2**–**8** to *E. coli* and *B. subtilis* as determined from MIC values.

varying concentrations of hydraphiles **2**–**8**. The results are shown in the lower panel of Figure 6 and are remarkably complementary to the length dependence shown in the top panel of Figure 6. Although the ordinates are obviously different, there is essentially a direct correlation between channel function and cellular toxicity.[54] Additional studies showed that although hydraphiles of appropriate length were toxic to various microbes and less so to mammalian cells, the therapeutic index was not sufficient to recommend hydraphiles as a practical antibiotic.[52] Two tangential applications for hydraphiles emerged from these studies. These are described in the following sections and both are currently under active investigation.

Hydraphile–Antibiotic Synergy

Our understanding of hydraphile toxicity was that the nonrectifying synthetic channels disrupted ion homeostasis.[55] It occurred to us that the formation of pores at nontoxic levels might permit the transport of other substances, particularly antibiotics into various microbes. If so, the efficacy of known antibiotics might be enhanced. We therefore attempted a straightforward screening experiment. We determined first by experiment that the hydraphiles of interest showed no toxicity at concentrations such as 1 μM. The toxicity to bacteria observed in prior studies occurred at levels at least 5-fold higher than this (see Figure 6). We established 1 μM as the approximate concentration for a range of experiments. We selected four FDA approved antibiotics for the synergy experiments: erythromycin,[56] kanamycin,[57] rifampicin,[58,59] and tetracycline.[60]

The four compounds shown in Figure 7 are unrelated either structurally or by mechanism of action. The compounds rifampicin and kanamycin were of particular interest to us because they are primary and secondary therapeutics against *Mycobacterium tuberculosis*.[61] Initial studies, however, were conducted with *E. coli*, *B. subtilis*, and *Pseudomonas aeruginosa*. The MIC values observed for *E. coli* and these four antibiotics were measured and found to be as follows: erythromycin 200 μM, kanamycin 25 μM, rifampicin 50 μM, and tetracycline 3.1 μM. When benzyl hydraphile **4** (dodecylene spacer chains) was coadministered (1 μM **4**) with the four antibiotics shown in Figure 7, the MIC values diminished: erythromycin from 200 to 25 μM; kanamycin from 25 to 12.5 μM; rifampicin from 50 to 3.1 μM; and tetracycline from 3.1 μM to 800 nM. The enhancements in activity produced by the presence of a nontoxic level of hydraphile were, for the four antibiotics, 8-fold, 2-fold, 16-fold, and 4-fold, respectively.[62]

Work is currently in progress in this area. There are at least two hypotheses concerning the mode of action to be tested. Based on the ability of hydraphiles to pass ions through the bilayer, it may be possible to assist the passage of small drug molecules. Initial experiments using planar bilayer conductance methods have failed to confirm this possibility, but these results are so far preliminary. An alternate hypothesis is that the hydraphile is acting to block efflux pumps.[63] Microbes use natural efflux pumps to eject such foreign substances as antibiotics. If the hydraphiles interfere with the normal function of such pumps in some way, antibiotic efficacy would be increased without any change in the concentration of administered drug. The latter possibility may not reflect channel function per se, but the chemistry involved here remains to be resolved.

Hydraphiles as Chemotherapeutic Agents

The excision of tumor cells has been accomplished by a variety of methods. These include surgery, radiation, and chemotherapy. Chemotherapy usually involves administration of a drug that is especially toxic to fast growing cells. Thus tumor cells are susceptible and side effects are manifested typically in the hair and gut cells. An alternative to surgery is direct injection chemotherapy, which uses a chemical to directly attack a tumor site.[64] Both ethanol and acetic acid have proved to be therapeutic in this context.

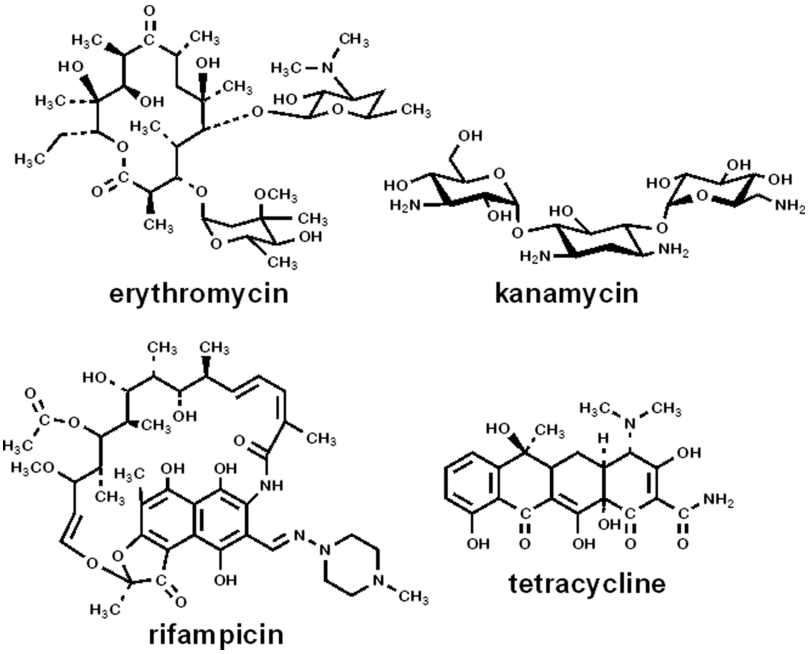


FIGURE 7. FDA approved antibiotics used in the hydraphile synergy studies.

The relatively high diffusivity of such small chemical agents, however, leads to collateral cellular damage. The toxicity of hydraphiles to microbes is extensible to all cells at high enough concentrations. The hydraphiles do not rapidly diffuse through tissues and they do exhibit a generalized toxic effect on cells at high enough concentrations. Very recent studies have shown that the hydraphiles can be used effectively as a direct injection chemotherapeutic agent.[65,66]

Tris-arenes and Transport of DNA

The Cl^- binding ability of tris-arenes such as **14** and **15** (see Figure 8) has inspired extensive study. The range of structures that has been prepared is impressive. Early studies emphasized solid state interactions with anions such as F^- and other halides. More recently, tris-arenes were shown to complex and transport halides,[67] carboxylates,[68] phosphates,[69] and so forth. For the most part, the mechanism of transport has proved to involve a carrier mechanism. Recently, attention has focused on the details of transport, especially with respect to the antiported ions. The tris-arenes have become anion binding modules incorporated into various ditopic receptor systems. It should also be noted that peptide side-armed (not tris-arene) isophthalic acid derivatives have exhibited channel function,[70] albeit by an unspecified mechanism.[71]

Our own work with dianilide derivatives of isophthalic acid and 2,6-dipicolinic acid demonstrated both solid state complexation and transport. In an especially interesting

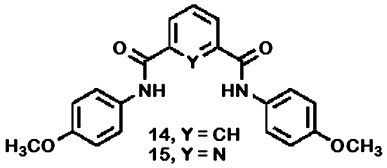


FIGURE 8. Tris-arene transformation agents based on isophthalic acid **14** and 2,6-dipicolinic acid **15**.

case, 4,4′-dinitropicolinanilide, evidence was obtained by planar bilayer conductance studies for pore formation.[72] Our surmise was that the tris-arenes stacked face-to-face within the bilayer and provided a semiorganized array of H-bond sites that could mediate conduction. Sliding or rotation of the individual tris-arenes could account for the open-close behavior that was observed. Although stacking of individual monomers to form a pore within a bilayer is well documented, the mechanism suggested remains speculative.

We recognized, however, that H-bond interactions could also form with phosphate anions. A stack of tris-arenes might form around the external "ladder" of the sugar–phosphate chains in DNA. If so, a continuous stack of tris-arenes would surround the DNA molecule, diminishing the surface charge and enhancing the hydrophobicity of the surface. The nucleobases in DNA are spaced closely but the phosphates are not. If complexation of phosphate led to a stacked exterior, the DNA ladder would not only have a more hydrophobic surface, it would be compressed. In such

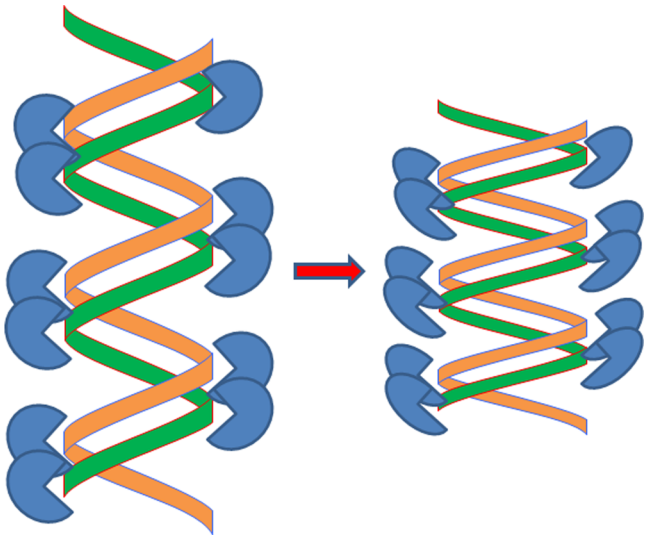


FIGURE 9. Schematic representation of the postulated interaction between DNA and tris-arenes.

a case, it seemed possible that tris-arenes could serve either as transformation or transfection agents. This is illustrated schematically in Figure 9.

Initial experiments with **14** and **15** were conducted with commercial JM-109 *E. coli* cells. These cells are treated to be "competent". That is to say that their inherent permeability to DNA transformation has been enhanced relative to untreated cells. Transformation was assessed by using *E. coli* having no resistance to ampicillin. After treatment with a plasmid containing an ampicillin resistance gene, the bacteria were grown on an antibiotic rich medium. If the gene entered the bacteria and was expressed, colonies of *E. coli* would be present on the medium. The number of colonies compared to controls would give an indication of efficacy.

The results of these transformation experiments showed that 2.6 kilobase (2.6 kb) plasmid DNA was transported through bacterial membranes about 3-fold more effectively than solvent controls by isophthalic acid 4,4′-dimethoxydianilide.[73] Similar results were obtained for the corresponding 2,6-dipicolinanilide derivatives. More remarkable results were obtained for a 20 kb plasmid, which normally is not capable of passing into *E. coli*. Indeed, the typical plasmid size limit for most methods is 13−15 kb. When *E. coli* were treated with either of the dimethoxyanilide derivatives, transformation was approximately 10-fold that observed in the absence of tris-arene.

Conclusion

It is interesting that initial efforts to prepare a synthetic ion channel were met with considerable skepticism. It was thought by many that synthetic models could not mimic any of the complex and remarkable functions of protein channels. As the field evolved and was enhanced by capable participants reporting clever and creative work, the focus changed to understanding the implications and potential of synthetic channels. In our own work, we have become convinced that early channels must have been simple but capable structures that likely played multiple biological roles. The remarkable versatility of relatively simple membrane active amphiphiles suggests that chemistry will play a significant role in the increasingly important biological applications of membrane-active synthetic molecules.

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BIOGRAPHICAL INFORMATION

George Gokel earned his B.S. in chemistry at Tulane University and Ph.D. at the University of Southern California. He did postdoctoral work with Donald Cram at UCLA and is currently Distinguished Professor of Science and Director of the Center for Nanoscience at the University of Missouri—St. Louis.

Saeedeh Negin earned her B.S. in chemistry at Shiraz University in Iran and Ph.D. at the University of Missouri—St. Louis, where she is currently a postdoctoral fellow. She has studied a variety of membrane active amphiphiles by a range of analytical techniques including planar bilayer conductance. She is currently studying amphiphile synergy in drug delivery.

FOOTNOTES

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The authors declare no competing financial interest.

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