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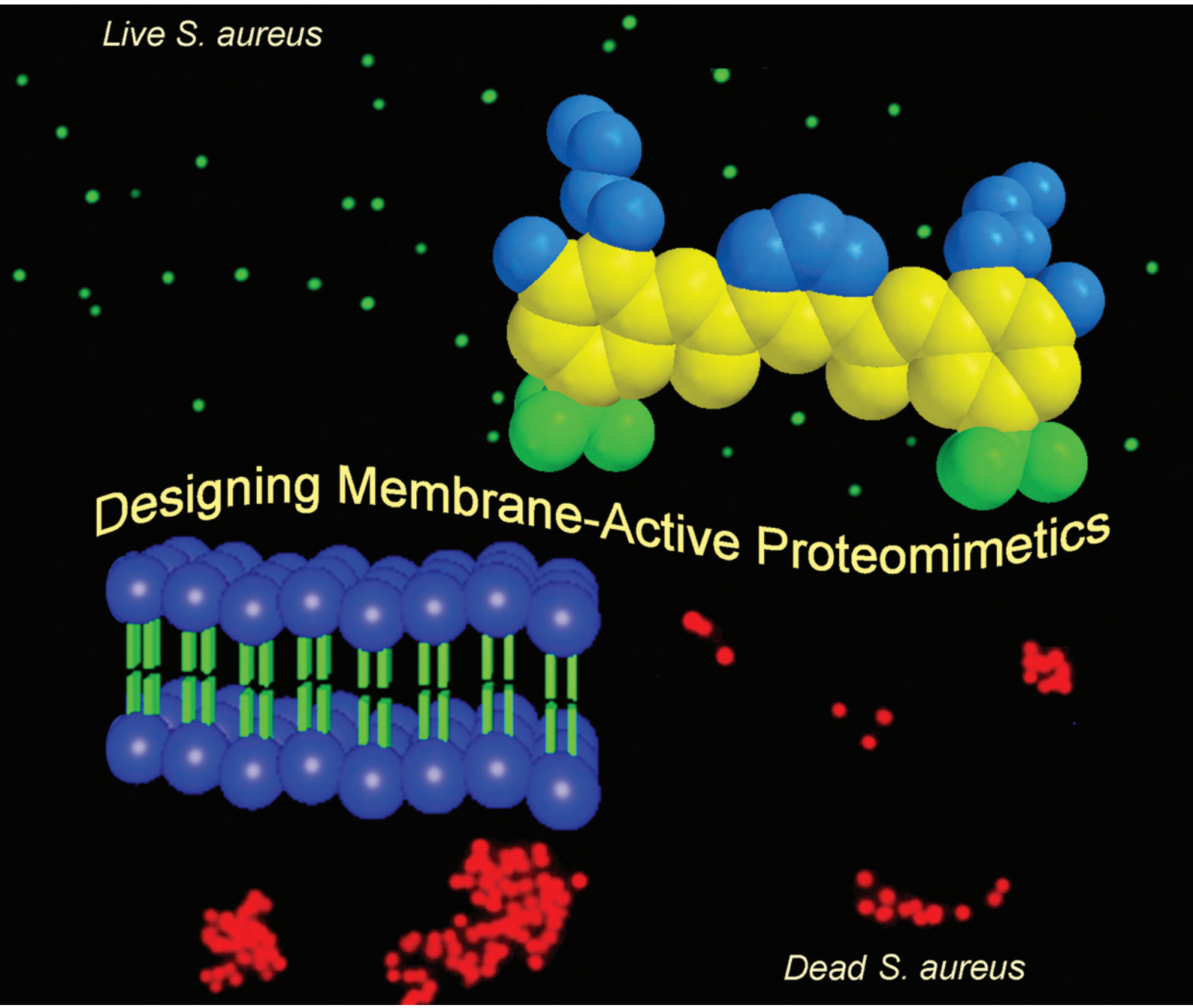

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Conformationally rigid proteomimetics: a case study in designing antimicrobial aryl oligomers

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The promise of proteomics to provide a vast library of protein structural data is exciting to scientists desiring an unprecedented understanding of the relationship between protein structure and function. This powerful knowledge will provide insight into the design rules for proteomimetics which are oligomers and polymers that can be more stable and inexpensive to produce than natural proteins, but still emulate the main biological function of the natural molecule. This Emerging Area article is intended to stimulate discussion on innovative strategies to design the next generation of proteomimetics. Specifically we will examine the design evolution of facially amphiphilic aryl oligomers, compounds that act as synthetic mimics of antimicrobial peptides (SMAMPs) and are known to interact with lipid bilayers. An increasingly important goal in the field of antimicrobial polymers is to develop strategies to rationally design membrane-binding SMAMPs, that are highly cell-selective, from any preferred backbone and molecular weight. It is expected that lessons learned from studying these oligomers can be applied to other systems where mimics are desired to interact with extended surfaces and where it would be most productive to consider mimicking the protein of interest with a large molecule. Obvious examples include disrupting protein–protein interactions or binding long tracts of DNA to control gene expression.

A. Macromolecular approach to protein-like activity

Ongoing efforts in the area of structural proteomics are producing the three-dimensional structures of natural proteins at an unprecedented rate.[1] As the number and quality of structures in this database increases, it should be possible to define commonalities underlying the shared biological properties of functionally related proteins. The result of this vast database will allow one to relate the function of proteins to their structures. In turn, this structural understanding can then be used to design oligomers and polymers that are much more stable and inexpensive to produce than natural proteins, but nevertheless mimic their key biological and

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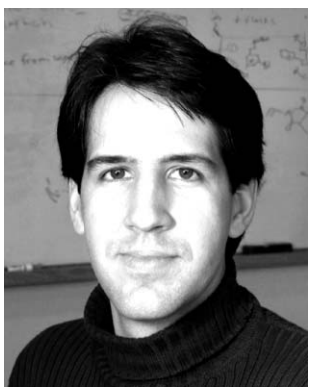
Gregory J. Gabriel



Gregory N. Tew

Gregory N. Tew received a BS in Chemistry from North Carolina State University in 1995 and performed undergraduate research with Professor D. A. Shultz. In 2000, he earned his PhD from the University of Illinois-Urbana under Samuel Stupp after which he joined the Faculty at the Polymer Science and Engineering Department at the University of Massachusetts, Amherst. Before starting there, he spent one year in William DeGrado's laboratory at the University of Pennsylvania Medical School. Current research interests include bioinspired and biomimetic macromolecules, supramolecular polymer science, molecular self organization, and materials for regenerative medicine. This work has lead to Young Investigator awards from the National Science Foundation (CAREER), the Office of Naval Research, the Army Research Office, 3M, DuPont as well as the Presidential Early Career Award for Scientists and Engineers in 2002. Most recently, he was selected as the first American Chemical Society Polymer Chemistry Division Herman F. Mark Young Scholar.

physical properties. For example, one important activity in the pharmaceutical industry has been designing mimics of small (<5 amino acids) peptides. While this approach has been successful and has resulted in small, orally active compounds for peptides such as Arg-Gly-Asp,[2] it has been much more difficult to achieve comparable success for longer peptides or proteins that interact with their targets over more extended surfaces.[3]

When the functional groups that define the binding epitope are distributed over a larger surface area, as is generally the case in proteins that engage in protein–protein, protein–DNA (or RNA) and protein–membrane interactions, it might be most productive to consider mimicking the protein of interest with a large molecule. Thus, the finding that oligomers formed from a variety of monomers other than α-amino acids are able to adopt well-defined secondary structures has generated considerable interest.[4,5] As interest continues to swell, reports that use larger molecular weight (MW) oligomers to interact with or capture the activity of peptides and proteins are becoming more and more available.[6–9]

In the three major classes of protein interactions described above, examples of designed oligomers that interact with proteins,[10] DNA,[11] and lipid membranes[7,9,12–17] have been reported (Fig. 1).[4] Antimicrobial peptides (AMPs),[18,19] which exemplify how specific protein–membrane interactions can be exploited to target different cells with high selectivity, are an attractive class of natural molecules to mimic. Thus, emulating this activity with synthetic mimics of antimicrobial peptides (SMAMPs) has been enthusiastically pursued in recent years to develop novel antibiotic candidates, inexpensive antimicrobial materials, and to learn how these molecules interact with cell membranes.[20]

This Emerging Area article will be confined to these SMAMPs which are built from non-amino acid derivatives to highlight the use of intramolecular interactions and their influence on biological activity. In particular, the design evolution of antimicrobial aryl oligomers over the past several years will be discussed to illustrate the refinements that have led to a novel class of selective antimicrobial proteomimetics. Data shows that designed oligomers are more potent than polymers; however, the growing number of polymer structures with antimicrobial, yet non-hemolytic, activity suggests that the macromolecular approach has significant potential.[7,8,20,26,27] Moreover, learning how to program macromolecules with specific biological activity is an extremely tantalizing idea.

B. Antimicrobial peptidomimetics: how essential is the helix?

The natural AMPs span a rather large collection of primary sequences and a prototypical subcategory of these AMPs are the magainins which display helical conformations that position their charged cationic groups and non-polar groups on opposite sides lengthwise along the helix.[19] This facially amphiphilic (FA) arrangement of residues (Fig. 2) appears to be important in the membrane-disruption activity of these peptides and several mechanisms including pore-formation have been elucidated.[18] In the early stages of foldamer research the design of abiotic oligomers that adopt stable secondary structures was an important quest and, not surprisingly, structurally diverse oligomers displaying helical conformations were targeted fervently.[5] One class of foldamers based on β-amino acids was shown to be helical and appeared to provide mimics for an endless number of natural helical peptides with the added benefit of providing resistance to endogenous proteases.[28] As expected, several antimicrobial β-peptide systems with outstanding biological activities were subsequently reported.[29–31]

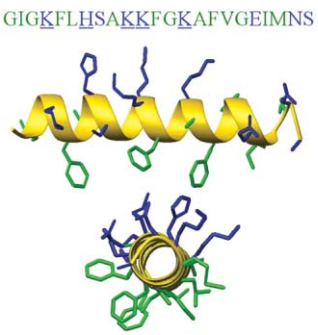


Fig. 2 Primary sequence of magainin-2 with side and end-on representations based on structures in the protein database. Blue and green side groups represent polar and hydrophobic non-polar amino acids, respectively, with the cationic amino acids underlined. The secondary structure illustrates the facially amphiphilic (FA) arrangement of polar and non-polar residues along the helical backbone, which is in yellow.

An interesting question arose in the field of antimicrobial foldamers: could proteomimetics (structurally far from the α- and β-peptides) possess antimicrobial properties if they were designed to attain the FA conformation *without* the benefit of a secondary structure such as a helix? The SMAMP introduced above (Fig. 1C) utilized a thioether moiety providing weak bonds to both amide hydrogens that rigidifies the conformation.[9,25] This conformation holds the amine groups on the same side of the backbone in longer oligomers with non-polar *tert*-butyl groups relegated to the opposite side.[9] A crystal structure of a model arylamide containing a thioether, plus molecular dynamics (MD) simulations in an octane–water interfacial system supported the FA conformation.

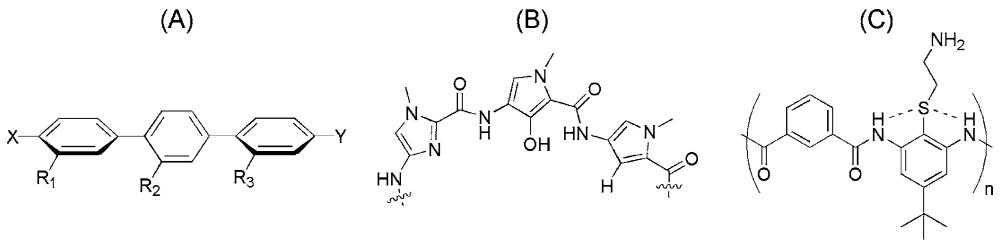


Fig. 1 (A) Terphenyl based α-helical proteomimetics.[10,21] (B) Portion of a programmable DNA-binding oligomer.[6,11] These types of pyrrole polyamides have also been previously studied as antimicrobial agents that operate *via* DNA-interactions.[22–24] (C) Amphiphilic arylamide SMAMP shown to have membrane-disruption activities.[9,25]

Polymers with an average degree of polymerization (n) of eight AB units possessed excellent antimicrobial activity with an MIC (minimum inhibitory concentration) of 7.5–15 μg mL^{-1} against *Escherichia coli*. (For simplicity, all MIC values stated in this article will be based on the growth inhibition of *E. coli* although various strains were used by different researchers). Discrete oligomers, where $n = 2$ or 3, also showed antimicrobial activity (MIC ~19 μg mL^{-1}) while polymers with an average n of ~60 had an undesirably high MIC of >200 μg mL^{-1}. This seminal report demonstrated that short polymers, if they display a FA conformation, could indeed match the antimicrobial efficiencies of natural AMPs and the helical β-peptides without the need to posses a helical structure.[9] In the β-peptide literature, this independence on helicity for antimicrobial oligomers was later demonstrated with 'scrambled' antimicrobial β-peptides that showed no evidence of helix formation.[32] In the α-peptide literature, diastereomers (D/L α-amino acid derivatives) of the bee venom, melittin, were shown to have significantly decreased helicities, but still possessed antimicrobial activity.[33]

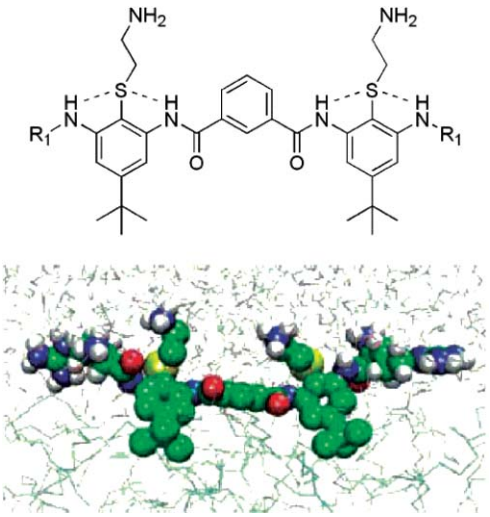


Fig. 3 Arylamide oligomers with thioether units and MD simulation snapshot at the octane–water interface for the compound in which R = arginine (water is top layer).[25] (Simulation snapshot reproduced with permission.)

C. Novel SMAMPs: The evolution of the aryl oligomer design

Several oligomer derivatives based on the arylamide SMAMP backbone (Fig. 1C) were synthesized and evaluated.[25] The end groups of these derivatives were varied while holding the central core constant to develop a structure–activity relationship (SAR) (Fig. 3). MD simulations with this series of compounds was also a useful tool for pre-screening structures and a snapshot from one MD simulation at the octane–water interface is shown for a compound in which R = arginine (Fig. 3). By visual inspection, the two terminal rings were nearly perpendicular to the octane–water interface forcing the *tert*-butyl groups far into the octane layer and the amine groups into the water layer. In fact, when R was arginine, rather than a number of other charged side groups, this separation of charged and non-polar groups at the interface was more pronounced. This led to the assertion that such a conformation would enable the molecule to bind favorably at the lipid bilayer–water interface. When oligomer-induced dye leakage from phospholipid vesicles was studied, the data supported membrane-disruption activity for the arginine arylamide SMAMP.

The most notable feature of this oligomer was its exceptional antimicrobial activity (MIC = 6.25 μg mL^{-1}) coupled with its remarkably high and desirable 50% hemolytic concentration ($HC_{50} = 715$ μg mL^{-1}), one measure of human cell toxicity. (Studies reporting toxicity with regard to other human cell types will be mentioned later as well.) Therefore, selectivity between bacterial and human red blood cells (Selectivity = HC_{50} divided by MIC) is ~110, an order of magnitude greater than a magainin analogue (9.6 measured by the authors) and most of the other SMAMPs studied to that point. This promising biological data coupled with MD simulations and a crystal structure of a model thioether arylamide[9] thus set the stage for rational refinements on the aryl oligomer design.

Consideration of urea-linked aryl oligomers, rather than the amide-linked oligomers, led to the synthesis of a new model compound (Fig. 4A) and its crystal structure revealed that the two urea linkages resided in the same plane as the central benzene ring containing the thioether. This structure suggested that if a molecule was synthesized in which all three rings contained a thioether then each N–aromatic carbon bond would be confined

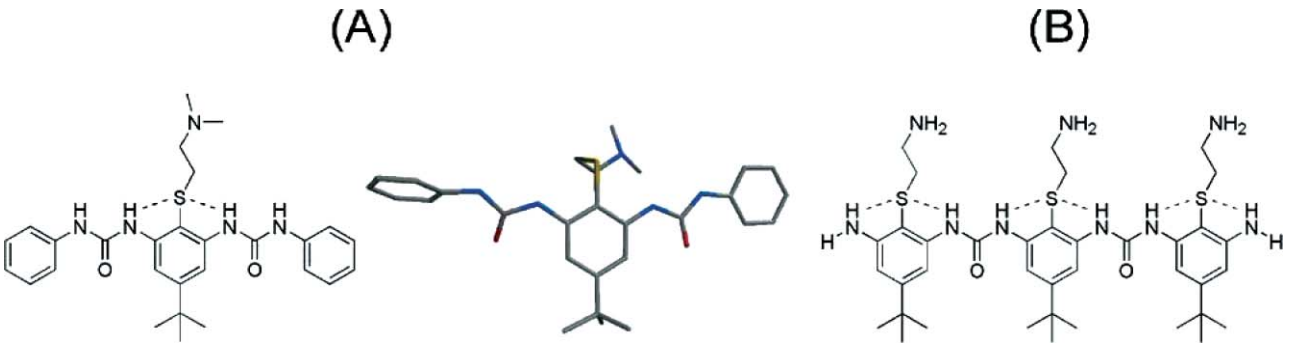


Fig. 4 (A) Aryl oligomer used as a urea-linked model compound and its crystal structure. (Hydrogens omitted for clarity.) (B) Highly active urea-linked SMAMP studied.[34]

due to an NH · · · S interaction and this would place all three rings in the same plane. Also the crystal structure revealed that the lowest energy conformation for the urea linkage was an all-*trans* conformation which was important because the urea group is more flexible than the amide (Fig. 4A).[34]

Therefore, a tri-aryl urea-linked oligomer was synthesized (along with its two and four ring analogues) for comparison to the arylamide SMAMPs previously studied (Fig. 4B).[34] When their antimicrobial activities were investigated, significant improvement in the MIC was observed for all three of these oligomers over the arylamides. For the three and four ring versions, the MIC was measured to be extremely low at 0.7 μg mL^{-1}. However, these oligomers were also hemolytic at or near their MIC, possibly due to the additional *tert*-butyl groups and the resulting increase in hydrophobicity. Despite this increased hemolysis, it was suggested that the 'stiffening' of the backbone from the intramolecular interactions increased the potency and that if some of the *tert*-butyl groups were removed, more selective SMAMPs would be generated.

Another augmentation to the conformational rigidity of the original arylamide oligomers involved replacement of the central benzene ring with a pyrimidine (Fig. 5).[12] In this design the two additional nitrogen atoms provided new hydrogen bond acceptors, resulting in a 3-centered hydrogen bond,[35,36] that limited rotation around the aromatic carbon–carbonyl bond which was not confined in the first set of arylamide oligomers studied (Fig. 3). Two model compounds, that are drawn below according to their crystal structure conformations, were synthesized to demonstrate this point (Fig. 5A and B).[12] It is obvious that the structure without the central pyrimidine ring (Fig. 5B) was not confined to the linear conformation. These model compounds suggested that a pyrimidine central core could provide an excellent scaffold for SMAMPs, if decorated appropriately. Thus, an FA oligomer with

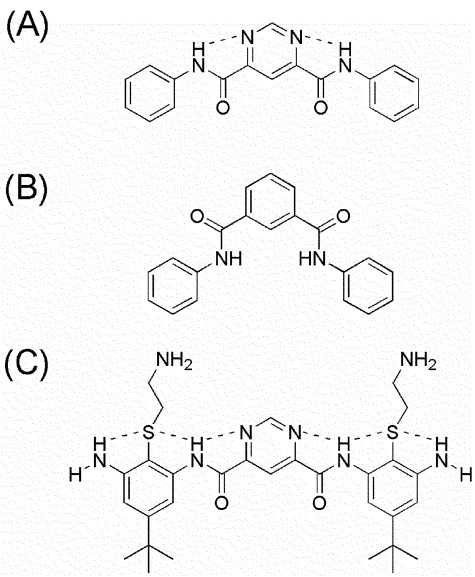


Fig. 5 (A) Model arylamide with central pyrimidine ring. (B) Model arylamide without pyrimidine. (C) SMAMP with incorporated thioether and pyrimidine design elements.[12] These structures are drawn in accordance with their crystal structure conformation.

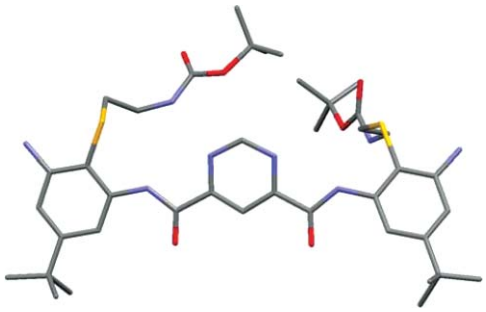


Fig. 6 Crystal structure of the tri-aryl pyrimidine oligomer in Fig. 5C (Boc-protected).[12] (Hydrogens omitted for clarity.)

a pyrimidine core installed was prepared (Fig. 5C) and the crystal structure (Fig. 6) showed that the charged, polar and the *tert*-butyl groups were on opposite sides of the oligomer and that the aryl backbone was nearly all planar.

In-depth comparisons between calculated gas-phase geometries and the crystal structures of several pyrimidine derivatives was also reported.[12] One distinction between the two was that while the extent of planarity differed between calculations and the crystal structures, the computed results agreed well with the X-ray conformations with regard to the presence of intramolecular hydrogen-bonded rings. In addition, solution conformations were investigated using 1D-NMR chemical shift analysis and 2D-NOESY NMR spectroscopy. In another report studying pyrimidine oligomers, sum frequency generation vibrational spectroscopy was used to examine their conformation with regard to the phospholipid membrane–water interface.[14] Here, it was shown that these SMAMPs were indeed membrane-interacting embedding perpendicular to the lipid bilayer surface.

The reported biological activity of the pyrimidine tri-aryl oligomer shown above supported the overriding hypothesis that stiffening the conformation of the backbone would afford more antimicrobial and less hemolytic compounds than an analogous arylamide without the pyrimidine ring.[12] The pyrimidine arylamide with three rings (Fig. 5C) had an MIC of 0.8 μg mL^{-1} compared to its non-pyrimidine analogue which had an MIC of 12 μg mL^{-1}. The selectivity (with respect to HC_{50}) improved as well from 1.0 to 17.5 with the replacement of the center benzene ring with a pyrimidine ring.

From the computational and X-ray structures shown above, a slight curving of the oligomers within the backbone aromatic ring plane was observed due to the five membered hydrogen bonded rings in each of the structures (see Fig. 3, 4A and 6). This curving resulted in a visually obvious splaying of the *tert*-butyl groups. One could imagine that this spreading of the non-polar groups outward (but still within the backbone aromatic ring plane) coupled with the compression of the charged amine groups towards each other would be more pronounced in longer oligomers. At some length it is possible that a coplanar or near coplanar arrangement of the rings would *not* be the most favorable conformation and would destabilize the FA conformation. This may explain why longer oligomers of these series are not significantly better than the tri-aryl oligomers. A better understanding of these cooperative interactions remains an important key in realizing more effective designs and elucidating stronger SARs.

D. Facially amphiphilic SMAMPs without hydrogen-bonding

The SMAMP examples discussed thus far clearly showed that rigidifying the FA conformation led to oligomers with superior antimicrobial activities and in some cases outstanding selectivity (HC_{50}/MIC) values. The SMAMP examples also demonstrated that a helical conformation, or a 'formal secondary structure' for that matter, was not necessary to emulate the membrane-disruption and antimicrobial activity of natural AMPs. Could the structural requirements be 'relaxed' even further expanding the molecular space to completely abiogenic oligomers, in particular oligomers without any hydrogen-bonding amide motifs along the backbone?

Strictly hydrocarbon-based phenylene ethynylene (PE) backbones have been shown to adopt a FA conformation when properly designed and have exhibited novel properties including the ability to stabilize oil–water interfaces and to self-assemble from aqueous solutions into ordered layers.[37] Therefore SMAMPs based on PE backbones (Fig. 7) were synthesized and their conformational behaviors[16,37,38] as well as their biological activities[15,27,39] were thoroughly investigated.

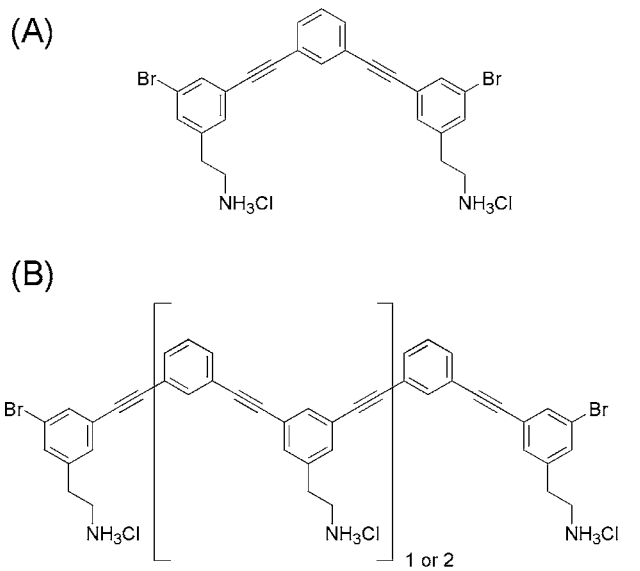


Fig. 7 (A) Highly active and selective phenylene ethynylene SMAMP.[39] (B) Derivatives of different lengths.[27,39]

The tri-aryl PE oligomer (Fig. 7A) afforded impressive results and showed potential as a new clinical treatment for antibiotic-resistant bacterial infections.[39] This particular tri-aryl SMAMP was screened against a large set of bacteria and other microorganisms giving an MIC value against *E. coli* of 0.1 μg mL^{-1}, clearly the most potent aryl oligomer reported thus far. The MIC of the longer PEs were higher but still reasonable (MIC = 25–50 μg mL^{-1}). The measured selectivity, with respect to hemolysis, of the tri-aryl PE was 880, an extremely encouraging result. This SMAMP demonstrated good activity against antibiotic resistant bacterial strains such as MRSA (methicillin-resistant *Staphylococcus aureus*) and VRE (vancomycin-resistant *Enterococci*) and showed no indication of inducing resistance. Results from in-depth cytotoxicity experiments on other mammalian cells besides red blood cells (3T3 fibroblasts and HEPG2 cells) and initial *in vivo* studies were promising as well.[39]

Studies on the membrane-interacting behaviors of these PE oligomers were performed recently.[17] Synchrotron small-angle X-ray scattering showed that the observed antibacterial activity correlates with an induced transition of small unilamellar vesicles into an inverted hexagonal phase, in which hexagonal arrays of 3.4 nm water channels are formed. Also, polarized and fluorescence microscopy was employed to demonstrate selective permeability of phospholipid vesicles treated with the tri-aryl PE SMAMP.

Overall, studies on the PEs proved that even oligomers without the benefit of designed intramolecular interactions to impose conformational rigidity, but with other design elements, can make superior SMAMP candidates. It appears that favorable energetics at the water–lipid interface orients the PE oligomer so that the polar cationic amines are displayed on the same side of the phenylene ethynylene backbone resulting in a FA conformation.[16] Even with these successes (with short oligomers) there are still important challenges ahead in the design of longer proteomimetics able to interact predictably with large areas of proteins, long tracts of DNA, and domains within lipid membranes.

E. Towards selective antimicrobial polymers: two different approaches

Although the PEs are rigid, rotation around their single bonds along the backbone enables the structure to adopt a FA conformation. Therefore, flexible polymers may still make good SMAMPs if the correct balance and orientation of hydrophilic and hydrophobic groups is attained.

There are numerous examples of biocidal polymers, but the pursuit of selective polymers that kill bacteria *and* are non-toxic to humans has only recently started to garner increased interest.[20,26] No doubt, activity in the field of non-toxic antimicrobial polymers and materials will continue to expand as an aging population requires increasingly more biomedical devices such as orthopedic implants, stents, and catheters which are highly susceptible to bacterial biofilm formation.[40–42]

Antimicrobial amphiphilic polymethacrylates have been recently reported (Fig. 8A).[8] In this case, amphiphilicity of the polymer was adjusted through copolymerization, at different feed ratios, of butyl and amino derivatized monomers. In this study the smallest polymer series (1.3–1.9 kDa) afforded the best antimicrobial results, with the polymer having a 30 mol% butyl moiety composition giving an MIC of 16 μg mL^{-1}.

In contrast, amphiphilic polynorbornenes (Fig. 8B) were produced using a different synthetic strategy where the monomers themselves are FA (the non-polar alkyl group, X, and the polar amine charge are on opposite sides of the bicyclic frame).[7] Interestingly, the MIC of the most potent polymer ($X = CHCH(CH_3)_2$) was not as sensitive to MW as the polymethacrylates or the aryl oligomers, with both its 1.6 kDa and 10.3 kDa sized versions possessing an MIC of 25 μg mL^{-1}. The MIC increased to 80 μg mL^{-1} when that particular polymer was made at 57.2 kDa. Interestingly, when the activity is considered on a molar basis, the 57.2 kDa polymer was more active at 1.4 μM compared

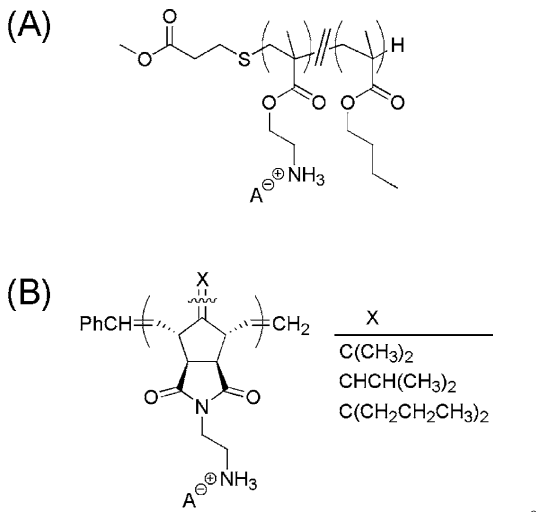


Fig. 8 (A) Amphiphilic polymethacrylate SMAMPs.[8] (B) Polynorbornenes that are FA at the monomer level.[7]

to the 1.6 kDa sample (15.0 μM). This clearly showed that the mechanisms for cell death are cooperative and implies that larger MW macromolecules can provide unique advantages when properly designed. Quite satisfyingly, copolymerization of the most potent (yet toxic) monomer with the most selective (but only slightly potent) monomer resulted in a copolymer having high selectivity (>100) and modest activity (MIC = 40 μg mL^{-1}). Although this MIC is modest compared to the smaller MW oligomers, it represents one of the more potent polymer values to date. Therefore, at least in this system, a 'best of both worlds' situation was observed and underscored the advantage of using controlled copolymerization and monomer design to tune biological activity. This is also one of, if not, the clearest example of how controlling the hydrophobic to hydrophilic balance enables the ability to 'dial-in' selectivity.

F. Outlook

The aryl SMAMPs represent a robust platform to design shape-persistent proteomimetics. At this point it does appear that the more potent and selective SMAMPs are short oligomers although there are strong indications that longer aryl systems approaching the weight of natural AMPs (2–4 kDa) can be tuned to have more attractive biological properties. Computer simulation, X-ray structures, and physical studies examining conformation at the water-lipid interface will all play key roles in determining the course of action in designing larger macromolecules that interact with membranes. Polymers as SMAMPs will continue to be attractive as potential self-sterilizing materials with the challenge being to significantly decrease activity towards mammalian cells yet still have potent antimicrobial activities.[41] Designing polymers increases the landscape complexity enormously but the benefits of learning how to program these synthetic macromolecules is well worth the challenge.

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