

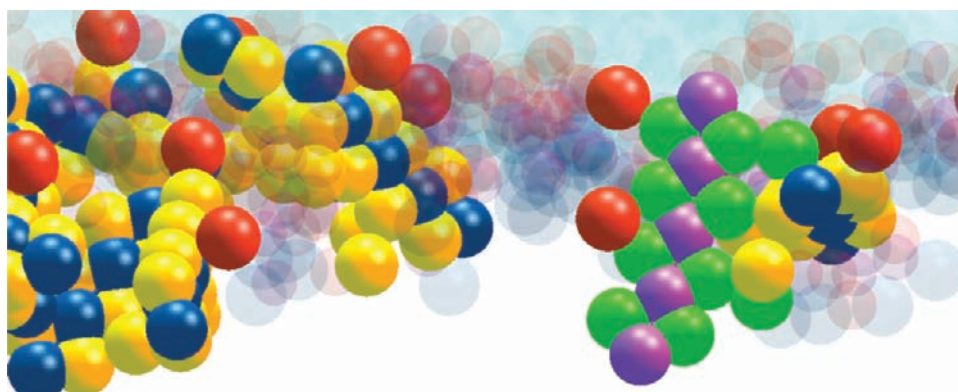
De Novo Design of Antimicrobial Polymers, Foldamers, and Small Molecules: From Discovery to Practical Applications

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CON SPECTUS



Antimicrobial peptides (AMPs) provide protection against a variety of pathogenic bacteria and are, therefore, an important part of the innate immune system. Over the past decade, there has been considerable interest in developing AMPs as intravenously administered antibiotics. However, despite extensive efforts in the pharmaceutical and biotechnology industry, it has proven difficult to achieve this goal. While researchers have solved some relatively simple problems such as susceptibility to proteolysis, more severe problems have included the expense of the materials, toxicity, poor efficacy, and limited tissue distribution.

In this Account, we describe our efforts to design and synthesize “foldamers”—short sequence-specific oligomers based on arylamide and β -amino acid backbones, which fold into well-defined secondary structures—that could act as antimicrobial agents. We reasoned that small “foldamers” would be less expensive to produce than peptides, and might have better tissue distribution. It should be easier to fine-tune the structures and activities of these molecules to minimize toxicity.

Because the activities of many AMPs depends primarily on their overall physicochemical properties rather than the fine details of their precise amino acid sequences, we have designed and synthesized very small “coarse-grained” molecules, which are far simpler than naturally produced AMPs. The molecular design of these foldamers epitomizes the positively charged amphiphilic structures believed to be responsible for the activity of AMPs. The designed oligomers show greater activity than the parent peptides. They have also provided leads for novel small molecule therapeutics that show excellent potency in animal models for multidrug resistant bacterial infections. In addition, such molecules can serve as relatively simple experimental systems for investigations aimed at understanding the mechanism of action for this class of antimicrobial agents. The foldamers’ specificity for bacterial membranes relative to mammalian membranes appears to arise from differences in membrane composition and physical properties between these cell types.

Furthermore, because experimental coarse-graining provided such outstanding results, we developed computational coarse-grained models to enable molecular dynamic simulations of these molecules with phospholipid membranes. These simulations allow investigation of larger systems for longer times than conventional molecular dynamics simulations, allowing us to investigate how physiologically relevant surface concentrations of AMP mimics affect the bilayer structure and properties. Finally, we apply the principles discovered through this work to the design of inexpensive antimicrobial polymers and materials.

Introduction

Biological macromolecules including proteins and RNA generally adopt unique, folded conformations that are responsible for their remarkable properties. Until recently, the process of folding was considered a mystery, but as the fields of protein folding, RNA structure, and molecular organization have advanced, it has become increasingly possible to design non-biological molecules that fold into unique structures. To mimic natural proteins, various investigators have synthesized *oligomers* by sequentially coupling individual monomeric units to provide homogeneous linear molecules of entirely uniform sequence and chain length. An early short list of such oligomers would include poly(pyrrrol/imidazole) DNA-binding oligomers,⁴ pyrrolinone peptide mimetics,⁵ arylamides,^{6–10} *N*-alkylglycines (peptoids¹¹), polyurethanes,¹² and phenylene–ethynyls.^{13,14} Oligomers that fold into well-defined secondary structures have come to be known as *foldamers* (see refs 15–22 for reviews). In the past decade, the area of foldamer research has blossomed in manifold directions, providing a rich diversity of backbone structures. The structural simplicity and relative ease of synthesis of many foldamers allow them to be used as three-dimensional scaffolds for molecular recognition, which, in iterative steps, can be downsized to the dimensions of small molecules for various biological applications.

Already there are multiple examples of functional foldamers that target a number of molecular and biological targets including RNA, proteins, membranes, and carbohydrates, often with affinities approaching or equaling those of natural α -peptides (for recent reviews, see refs 19 and 23). It is, however, also important to identify applications of foldamers to address problems that cannot be solved by use of conventional peptides composed of *D*- or *L*- α -amino acids. Along these lines, we focused on antimicrobial foldamers that mimic the host defense peptides.

Host Defense Peptides, Innate Sources of Antibiotics?

Antibiotic resistance is now one of the most pressing global healthcare problems facing society.^{24,25} Although hospital-acquired, or nosocomial, infections in the United States have gradually declined, approximately 70% of them are resistant to at least one antibiotic, and the trend is increasing. For example, of the approximately two million people who will acquire nosocomial infections this year in U.S. hospitals, 99 000 will die from the infection.²⁶ Antimicrobial peptides (AMPs) have provided a new approach to developing antibiotics because they play a central role in the innate immunity

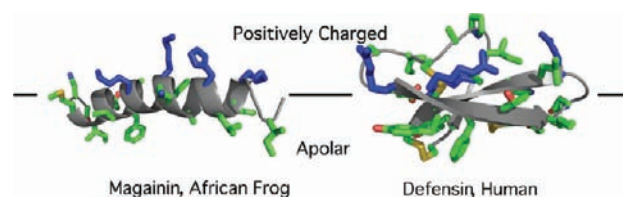


FIGURE 1. Structure of an α -helical magainin (pdb code 2MAG) and a β -sheet defensin peptide (1BNB) in which the cationic groups are colored dark blue and the nonpolar groups are colored green. The facially amphiphilic nature of the overall conformation is highlighted by the segregation of these groups.

system of many organisms.^{1–3,27–29} In some primitive organisms that lack a humoral response AMPs and a few enzymes provide the main defense against bacteria, yeast, fungus, and even viruses. Ribosomally encoded AMPs are typically 12 to approximately 80 residues in length and adopt various active conformations, including α -helices (magainin and cecropin), disulfide-rich β -sheets (bactenecin and defensin) (Figure 1), and other tertiary structures.

Most AMPs adopt highly amphiphilic conformations in which the cationic hydrophilic and hydrophobic side chains segregate onto distinctly opposing regions or faces of the overall folded conformation. This amphiphilic topology appears to be important for insertion into and disruption of the cytoplasmic membrane, leading to bacteria death.^{1,30} This simple physical mechanism of action has resulted in a relatively low propensity for the development of bacterial resistance. However, AMPs can also interact in multiple ways with other components of the innate immune system (reviewed in ref 31), many AMPs can act by additional mechanisms,^{3,32–34} and bacteria are able to respond to AMPs^{27,35,36} and even evolve novel resistance to their toxic affects.^{37,38}

From Natural Host Defense Peptides to Antimicrobial β -Peptide and Peptoids

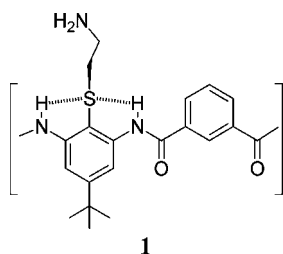
Previously, antimicrobial peptides have been designed by idealizing the amphiphilicity of natural AMPs,^{2,39–41} introduction of *D*-amino acids^{42,43} or long acyl chains,^{44,45} and cyclization.^{42,46} The availability of β -peptides provided another avenue to probe the requirements for activity, because they can adopt distinct secondary structures such as “12-helices” and “14-helices”.^{15,17–20}

Our group,^{47,48} as well as those of Gellman⁴⁹ and Seebach,⁵⁰ independently showed that β -peptides capable of forming amphiphilic 14- or 12-helices had potent antimicrobial activity (Figure 2). Oligomers with lengths of 10–15 residues that achieved an appropriate hydrophilic/lipophilic balance were selective for killing bacteria vs mammalian cells. Oligomers that were too short were inactive, and they also

failed to adopt the desired conformation, while those that were too long or hydrophobic showed unacceptably high toxicities toward human erythrocytes. While these studies were in progress, Gellman and co-workers also described a potent and highly selective antimicrobial peptide based on cyclic β -amino acids. These studies were subsequently extended to a variety of different helical types formed by β -peptides and α/β -peptides.^{51–55} In a similar manner, Patch and Barron designed amphiphilic, helical, antibacterial N-substituted glycine oligomers (peptoids),²² while Guichard and co-workers have synthesized enantiomerically pure antimicrobial foldamers based on a urea backbone.⁵⁶ It was further demonstrated that charge, facial amphiphilicity, and an appropriate hydrophilic/hydrophobic balance were generally important for obtaining selective, nontoxic compounds, although there seems to be no absolute requirement for any one molecular feature.⁵⁷

Antimicrobial Arylamides and Arylureas

The diversity of structures and molecular frameworks employed in the above studies led us to ask whether these principles could be extended to design much simpler oligomers, such as aromatic arylamides,^{6–10} which have been examined extensively in fundamental studies of hydrogen bonding and molecular recognition. Given their relative ease of synthesis, they appeared excellent candidates to initiate the structural simplification or “synthetic coarse graining” of antimicrobial compounds. We prepared compounds related to the core structure **1**, which contains alternating 1,3-phenylene diamine units connected by an isophthalic acid.



A thioether provided a convenient point for attachment of basic groups while also rigidifying the molecule through the formation of intramolecular hydrogen bonds. The segregation between the polar aminoethyl-thioether from the hydrophobic *t*-butyl group provided facial amphiphilicity to the overall structure. Quantum mechanical calculations,⁵⁸ molecular dynamics simulations,⁵⁸ and crystallographic analysis of model compounds (Figure 3) confirmed that the thioether indeed hydrogen bonded with the neighboring amide. In both amides and ureas, the planar arrangement between the cen-

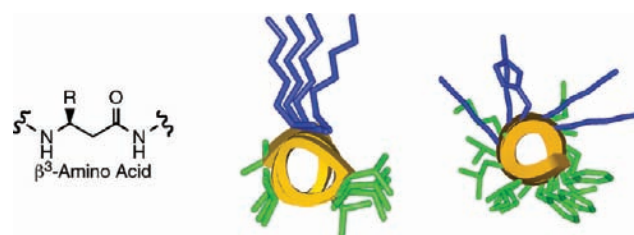


FIGURE 2. Structures of a β^3 -amino acid (left), an antimicrobial β -peptide, $(\beta^3\text{HAla}-\beta^3\text{HLys}-\beta^3\text{HVal})_4\text{-CONH}_2$ (middle), and the natural α -helical peptide magainin (right). Hydrophobic residues are in green and basic side chains in blue.

tral ring and the carbonyl is enforced by NH-thioether hydrogen bonding and possibly a nonconventional CH-hydrogen bond.⁵⁹

Initially we synthesized oligomers of repeating structure **1**.⁶⁰ Compounds with two to three repeats had antibacterial activity with minimum inhibitory concentrations (MICs) as low as ~ 15 $\mu\text{g/mL}$, although they lysed human red blood cells (RBCs) at similar or lower concentrations. Longer polymers showed lower antibacterial activity. Interestingly, the simple three-ring structure, **2** (Table 1, Figure 4), showed reasonable activity and served as a core fragment for elaboration of more active compounds.⁶¹ Addition of amino acid substituents to this core structure resulted in compounds with very good potency and high specificity for bacteria over mammalian cells. Positively charged residues, particularly arginine (**3** in Table 1), increased the potency and the safety of the compounds.⁶¹

Within this initial design, containing a central isophthalic acid group, the two backbone ring-carbonyl single bonds remained rotatable.^{58,62} The addition of internal hydrogen bonds within arylamides can effectively limit these torsional degrees of freedom,^{63–65} which we reasoned might decrease conformational flexibility and increase potency.

Introduction of a pyrimidine in compound **4**⁶⁶ or dialkoxy-groups in **5**^{58,67} allowed the desired hydrogen bonding (Table 1, Figure 3c). Another strategy involved the design of an arylurea scaffold⁶⁸ (**7**), which can form a planar, fully hydrogen-bonded array. All three of these modifications led to marked improvements in antimicrobial activity.

Optimization of both the total charge and the hydrophobic content proved to be particularly important to the design of compounds that are highly active and nontoxic in animals. The introduction of fluorinated amino acids into antimicrobial peptides can lead to increases in potency.⁶⁹ Similarly, we have found that the replacement of *t*-butyl groups with trifluoromethyl groups in these arylamides leads to increases in both potency and safety in compounds such as **8** and **9**. These compounds, like most of those in Table 1, are significantly

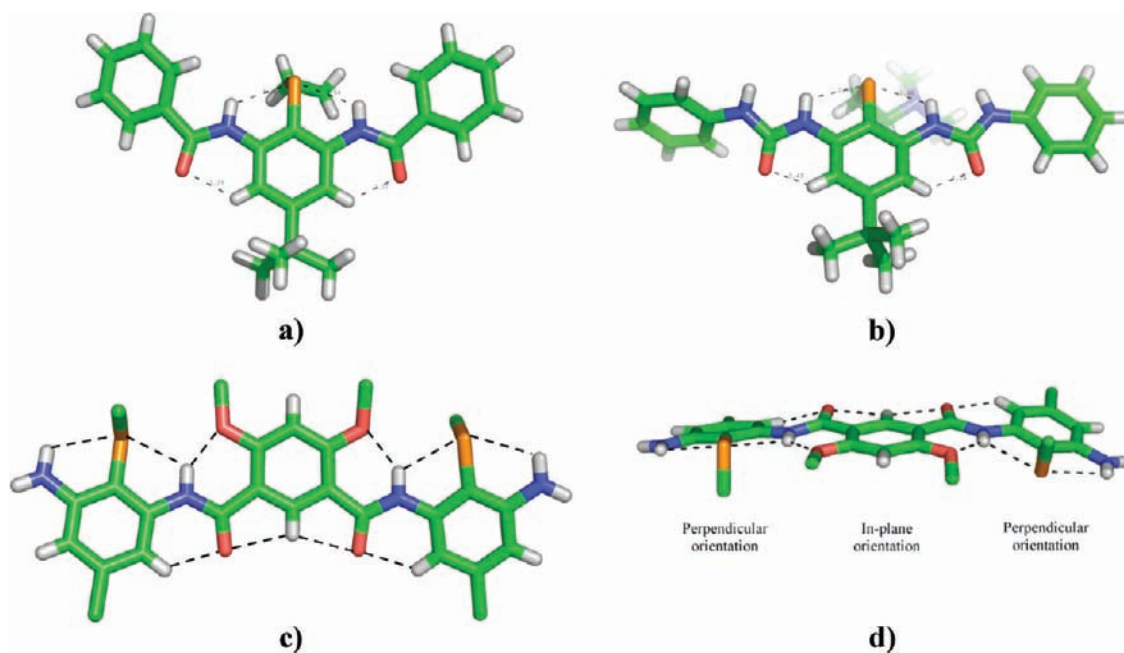


FIGURE 3. Crystal structures of model thioether-containing arylamide (a), arylurea (b), and a dialkoxy-substituted arylamide (c, d).

more potent than the magainin derivative, **MSI-78**, which has a MIC against these two bacterial strains of 12.5 $\mu\text{g}/\text{mL}$.

Highly Active Short Antimicrobial Phenylene Ethynylene

Tew and co-workers dispensed with the amide bond altogether in their design of a phenylene–ethynylene scaffold⁷⁰ with outstanding antibacterial activity and selectivity.⁷¹ Both polymeric materials and short oligomers were investigated. The most active compound (structure **10** shown in Table 1) contains three aromatic rings. Antibacterial screening showed clearly that the short three-ring oligomer, **10**, was highly potent against a large panel of pathogenic and potential bio-warfare bacteria.

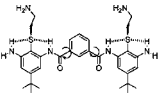
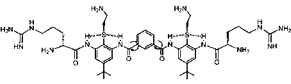
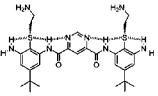
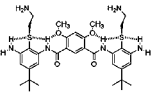
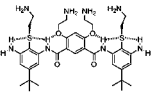
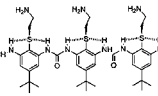
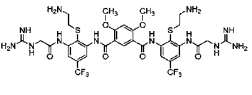
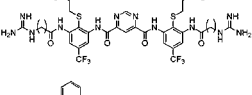
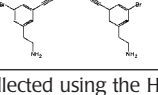
Biological Mode of Action

AMPs generally act directly on the cytoplasmic membrane, although this might not be the primary target of some peptides. Indeed, the phenylene–ethynylene derivative, **10**,^{71,72} is able to cause leakage of dyes from phospholipid vesicles at concentrations similar to those required to kill bacteria. A similar time course is also seen for the loss of the membrane potential in bacteria. The selectivity of AMPs for bacterial membranes is believed to result from differences between the phospholipid compositions of mammalian and bacterial membranes. Bacterial membranes tend to be more negatively charged and lack cholesterol. In many cases,¹ more subtle effects relating to phospholipid composition are involved; primary phospholipids in mammalian membranes include zwitterionic phosphatidylcholine (PC) and negatively charged phosphatidylserine (PS) headgroups, while bacterial membranes are rich in zwitterionic phosphatidylethanolamine (PE) and negatively charged phosphatidylglycerol (PG) lipids including cardiolipin. The differences in the physical properties of these various lipids can be as important as the overall charge of the membrane.^{51,52,54,73} In particular, the area covered by the headgroup of PE is less than that of its hydrophobic tail, causing this phospholipid to be less stable in planar bilayer phases than PC. This feature appears to be particularly important for the high selectivity of compound **10**,^{72,74} which is much more effective at inducing leakage of PG–PE than PS–PC vesicles. X-ray scattering suggests that this compound induces structural changes favoring hexagonal phases in PE-rich membranes.⁷⁴ Epand and co-workers have observed similar results for antimicrobial foldamers and polymers, which also require PE for activity.^{51,52,54,73} Although the phenylene–ethynylene compounds showed a good relationship between membrane-perturbing effects and activity, some of the most potent arylamides cause complete membrane depolarization of *Staphylococcus aureus* at concentrations somewhat higher than those required to cause rapid cell death. This finding might reflect a mechanism of action that is distinct from membrane perturbation, or it might simply indicate that only a small degree of perturbation is required to ultimately trigger cell death.

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TABLE 1. Conformational Tuning of Properties of Antimicrobial Oligomers^a

Compound	Structure	MIC (μM)		
		<i>S. aureus</i> ^b	<i>E. Coli</i> D31	HC ₅₀ (μM) ^c
2		50	12.5	14
3		7.8	3.9	445
4		0.80	0.80	18
5		0.87	0.87	145
6		0.66	5.3	593
7		0.70 ^c	0.70	5
8		0.2	2.8	63-90
9		0.20	0.1	440
10		0.20	0.10	440

^a Data were collected using the Hancock method; numbers quoted here may differ somewhat from those in the original publications if a different method was originally used to determine MICs. ^b Tetracycline- and streptomycin-resistant *S. aureus*. ^c The concentration required to cause 50% lysis of a suspension of red blood cells.

length of the bilayer, so they presumably work by a mechanism resembling the “carpet” mechanism of AMP.⁷⁵ What is critical for this mechanism is that the compounds bind with a sufficiently favorable free energy of association and penetrate the outer leaflet of the bacterial membrane during the initial steps of the process. Furthermore, the compounds must have sufficient polar character to provide water solubility with which to reach the host membrane. Additionally, if the compounds are too hydrophobic, they will bind indiscriminately to mammalian membranes leading to high toxicity. Our data clearly shows that there is no unique combination of molecular features that is absolutely required to satisfy these provisions. Flexible peptides frequently adopt more ordered conformations upon binding; in these structures appropriately placed hydrophobic or charged groups can easily mitigate any loss in

conformational entropy required for binding. Thus, for each scaffold there exists a delicate balance between charge, hydrophobicity, and rigidity that must be fine-tuned to optimize both potency and selectivity.

Antimicrobial Polymers

Studies with antimicrobial foldamers have also informed the design of a variety of arylamide, phenylene–ethynylene, acrylate (Figure 5), and hydrocarbon-based polymers and materials. While an exhaustive review of other antimicrobial polymers would be beyond the scope of this Account, it is important to note that Gelman and co-workers have also developed polymeric antimicrobial agents whose mechanisms of action have been extensively investigated and compared with more peptidic AMPs.^{73,76} Also, cationic polymers with antibacterial and biocidal activity are well-known,^{77–82} in some cases incorporated into materials or immobilized on surfaces.^{76–78}

Our own work in this area has focused on defining features required for selective antimicrobial activity. The phenylene–ethynylene scaffold was the first polymeric series to demonstrate antibacterial activity and selectivity;⁷¹ interestingly, increasing the MW decreased the selectivity factor. This trend of decreasing selectivity with increasing MW was seen with several types of polymers.^{60,83–85} The decrease in selectivity reflects both increased toxicity to mammalian cells and decreased antibacterial activity, possibly due to poor penetration of the large molecules to the cytoplasmic membrane. This is, however, not universally true because amphiphilic polynorbornenes with MW > 3000 Da have good antibacterial activity and minimal toxicity to mammalian cells.^{86–88}

Coarse-Grained Computational Models

Antimicrobial oligomers represent minimal, coarse-grained models that embody the molecular features required for activity. In a similar spirit, it has been possible to create computational coarse-grained models of the arylamide class of antimicrobial foldamers to allow longer simulations of their membrane-perturbing activities. At the time of our studies, all-atom molecular dynamics (MD) computer simulations had been used to explore the interactions of peptide-based antimicrobials with membranes, but these studies had been limited to relatively short times⁸⁹ and only one or a few antimicrobials.⁹⁰ Modern coarse-grain approaches⁹¹ have resulted in the development of several models for membrane simulations in the past years.^{92–94} In this method, the molecule is considered to be composed of a series of carefully parametrized interconnected units, each encompassing sev-

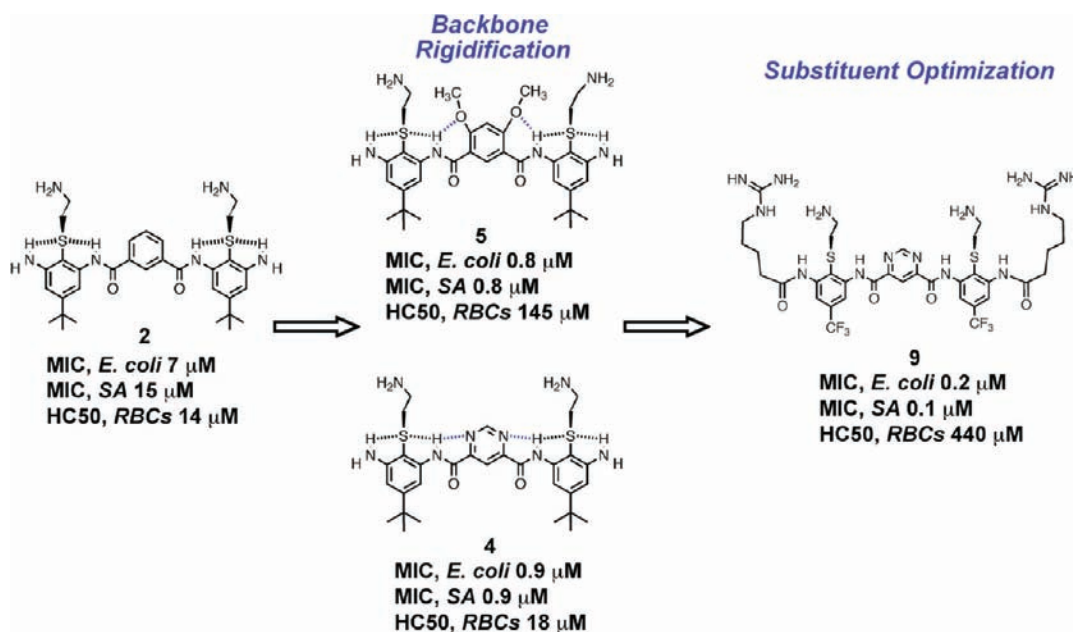


FIGURE 4. Optimization of the activity of arylamide oligomers, including the introduction of hydrogen-bonding substituents and optimization of pendent functional groups.

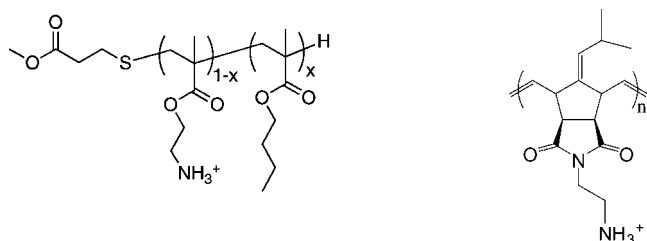


FIGURE 5. Structure of antimicrobial polyacrylamide and polynorbornenyl polymers.

eral atoms. By reduction of the number of atoms, fewer distances need to be calculated at each MD step, making a significant increase in computational speed possible.

Coarse-grain MD allowed microsecond simulations with a relevant number of arylamides per bilayer⁹⁵ at coarse-grained oligomer/phospholipid (CGO/PL) from 1:256 to 1:14, spanning surface concentrations that experimentally give rise to from none to very rapid vesicle lysis. The antimicrobial was initially placed in the aqueous phase just above one side of the membrane to eliminate the requirement for diffusion to the membrane surface, which can be rate-limiting in experimental studies. Different results were observed at the two extreme CGO/PL ratios. At low CGO/PL ratios, the antimicrobial inserts into the bilayer with its long axis parallel to the membrane surface and its apolar groups penetrating into the membrane (Figure 6). By contrast, at the high CGO/phospholipid ratios required for lysis of bilayers in experimental systems,⁹⁵ the drugs initially insert with an ensemble of different angles. The very large imbalance in the concentration of the oligomers between the proximal and the distal leaflets of the

bilayer leads to a metastable state with pronounced buckling of the proximal leaflet of the bilayer. This imbalance provides a strong driving force for translocation of the drug molecules to the opposite side of the bilayer; the buckling and disordering of the bilayer structure might additionally lower the kinetic barrier for translocation. The CGOs frequently diffuse in pairs across the bilayer, often with accompanying ions and water molecules. Following the translocation step, the oligomers are oriented predominantly parallel to the bilayer, although with less extensive ordering than in the simulations at low antimicrobial/phospholipid ratios. In the final configuration the ammonium end of the molecule locates near the glycerol backbone, significantly below the highly polar zwitterionic headgroups. Thus, the polarity gradient of the membrane is altered, with the introduction of charged groups that have a high preference to be hydrated at otherwise relatively nonpolar regions of the bilayer. The result is an increased permeability to water in the simulations.

These simulations provide pictorial detail to prior models inferred from experimental studies. They explain the dependence of lysis on a high order of the peptide concentration; sufficient concentrations of the oligomers must accumulate in the cis leaflet of the bilayer to induce membrane disruption and to provide a driving force for oligomer translocation. Second, the simulations are in agreement with the experimental observation that membrane disruption is a biphasic process. In the initial step, the oligomers bind to and strongly buckle and otherwise asymmetrically perturb the bilayer. The subse-

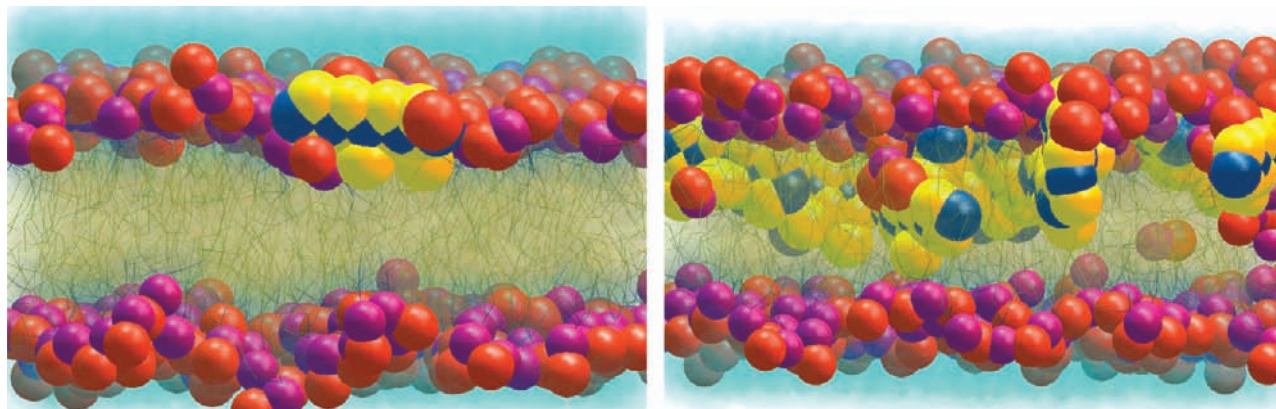


FIGURE 6. Snapshot from a coarse-grained molecular dynamics simulation of the action of an arylamide on the bilayer at an oligomer/lipid ratio of 1:256 (left) and 1:14 (right).⁹⁵ The backbone of the foldamer is shown in blue and yellow, while the headgroups of the membrane and polar groups of the foldamer are shown in purple and red. The lipid chains are shown as sticks. The right panel represents an intermediate time point at which foldamers have inserted deeply and are beginning to translocate across the bilayer.

quent translocation step appears to occur with concomitant formation of pathways for solvent and solute diffusion. Finally, following equilibration of the compounds on both sides of the bilayer, the membrane reaches a state that is intrinsically more permeable than the initial membrane. There are also differences between the coarse-grained and experimental observations. The first is in the time scale of the events, because experimental measurements require an initial diffusion to the membrane surface, which can be rate-determining. The second difference is that the size of our system precludes the observation of large long-lived pores or other openings in the membrane. Thus, the increase in permeability to water and ions observed in our simulations may be a prelude to more deep-seated disruption of the membrane, induced by osmotic imbalances in cellular systems.

Potential of Synthetic Foldamers as Antimicrobials for Fundamental and Applied Research

In summary, beginning with peptides of molecular weights in the range of 2000–5000 Da, it has been possible first to prepare β -peptides with significantly lower molecular weights, followed by arylamides and small molecules with molecular weights in the range of 600–1000 Da.^{67,96} The simplicity of these compounds makes them outstanding candidates for fundamental computational and experimental studies of the mechanism of membrane disruption. Furthermore, proteomic and genomic studies will illuminate the mechanisms by which bacteria respond to these agents compared with natural AMPs.

From a more practical perspective, the lower MW and non-peptidic structures of arylamides have allowed us to address previous problems, including problems with tissue distribution, toxicity, and cost of materials, that plagued the develop-

ment of peptidic analogues of AMPs as intravenously administered antibiotics.¹ Experimental studies *in vitro* have shown that bacteria cannot easily develop resistance to this class of compounds,⁶⁷ suggesting they might not suffer from some of the same problems of resistance encountered in other classes of antibiotics with more specific targets. Indeed, a compound designed by these principles successfully completed the first phase of human clinical trials as an iv antibiotic for treatment of multidrug-resistant *S. aureus*.⁹⁶

We thank our many co-workers for their contributions to these studies and acknowledge Grants GM54616 and AI74866 from NIH for support of this work.

BIOGRAPHICAL INFORMATION

Gregory N. Tew received a B.S. in Chemistry from North Carolina State University in 1995 and performed undergraduate research with Prof. D. A. Shultz. In 2000, he earned his Ph.D. 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 novel hydrogels for regenerative medicine. This work has led to awards from the National Science Foundation (CAREER), the Office of Naval Research, the Army Research Office, 3M, DuPont, and the Presidential Early Career Award for Scientists and Engineers.

Richard W. Scott received his Ph.D. at the University of Pennsylvania in the Department of Microbiology. His postdoctoral training was in molecular biology at the Institute for Cancer Research, Fox Chase, PA. He joined E. I. DuPont as a Principal Investigator in the Central Research and Development Department and then joined Cephalon, Inc., to build and lead the molec-

ular biology department. Over an 11 year career at Cephalon, Dr. Scott became Vice President of Biology where he led discovery teams targeting neurodegenerative disorders, as well as the development of genetically based animal models for Alzheimer's disease and other neurodegenerative disorders. Presently, Dr. Scott is Vice President of Research at PolyMedix, Inc., and has led research teams responsible for the identification and selection of two lead compounds presently in Phase 1 clinical trials, one of which is a small foldamer mimic of the antimicrobial peptides that is being developed as an anti-staphylococcal IV agent. Dr. Scott has over 50 peer-reviewed journal publications and book chapters and is an inventor on six U.S. patents.

Michael L. Klein received his B.Sc. and Ph.D. degrees in Chemistry from the University of Bristol (U.K.). He was a postdoctoral fellow in Italy, U.K., and U.S.A. before joining the Chemistry Division of the NRCC in Ottawa, Canada, where he rose through the ranks from Associate to Principal Research Officer. In 1987, he returned to the United States as Professor of Chemistry at the University of Pennsylvania, where from 1993 he was the Hepburn Professor of Physical Science and Director of the Laboratory for Research on the Structure of Matter. In 2009, he moved to Temple University as the Carnell Professor of Science and Director of the Institute for Computational Molecular Science. His research interests involve probing the structure and dynamics of molecular systems using computer simulation techniques; research topics range from soft matter to chemical biology.

Bill DeGrado received his B.A. in chemistry from Kalamazoo College (1978) and his Ph.D. in organic chemistry from the University of Chicago (1981). He spent the subsequent 15 years engaged in research at DuPont and DuPont-Merck Pharmaceutical Company. He joined the University of Pennsylvania in 1996, where he is the Raiziss Professor in the Department of Biochemistry and Biophysics and an adjunct member of the Chemistry Department. The DeGrado laboratory works on experimental and computational studies aimed at understanding molecular interactions and dynamics, with particular emphasis on the design of proteins, peptides, and peptide mimics. Specific areas of investigation include pharmaceutical chemistry, structural biology, and biochemistry.

FOOTNOTES

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