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PNNL-30503

Functional Biomimetic Polymers with Antimicrobial Activity

September 2020

Jay W. Grate
Kai-For Mo

U.S. DEPARTMENT OF ENERGY

Prepared for the U.S. Department of Energy
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High degrees of specificity and functionality are required of molecules and materials in a variety of applications. Nature achieves these characteristics using sequence-defined macromolecules; these polymers have side chains arranged in sequences, such as the amino acids in peptides and protein, and the nucleic acid bases in poly(nucleic acids) such as DNA. In addition, the backbones structures and noncovalent interactions such as hydrogen bonding lead to folding structures such as helices and sheets, and to secondary and tertiary structure. Such macromolecular architectures can lead to functions as diverse and exquisite as molecular recognition, signaling, biocatalysis, self-assembly into materials, and information storage. There is a basic science need for new ***synthetic*** molecules and materials that provide the same exquisite functions as natural macromolecules, while also affording better ***stability*** in applications.

At PNNL, we have developed a completely new class of synthetic biomimetic sequence-defined polymers based on triazine chemistry, which we call TZPs. PNNL's new polymers offer the opportunity to achieve similar functions to natural macromolecules; specifically we designed and synthesized a diversity of test molecules for antimicrobial activity.

A conceptual basis for how TZPs might lead to amphipathic structures with antimicrobial activity is shown in Figures 1 and 2.

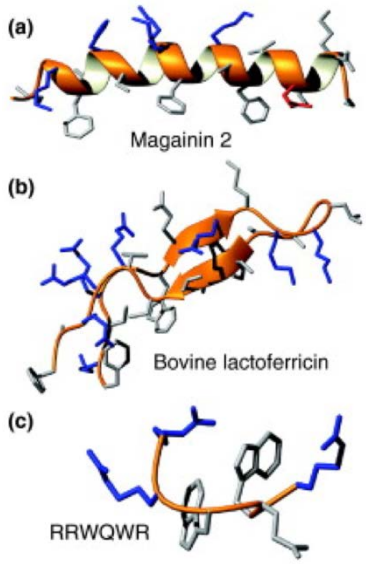

Figure 1. Structures of some antimicrobial peptides showing a) helical, b) beta sheet, and c) extended molecular structures, taken from a portion of a figure in ref. [24] The amphipathic character is particularly evident in Magainin 2 with blue cationic lysine side chains on the top and aromatic lipophilic side chains on the bottom.

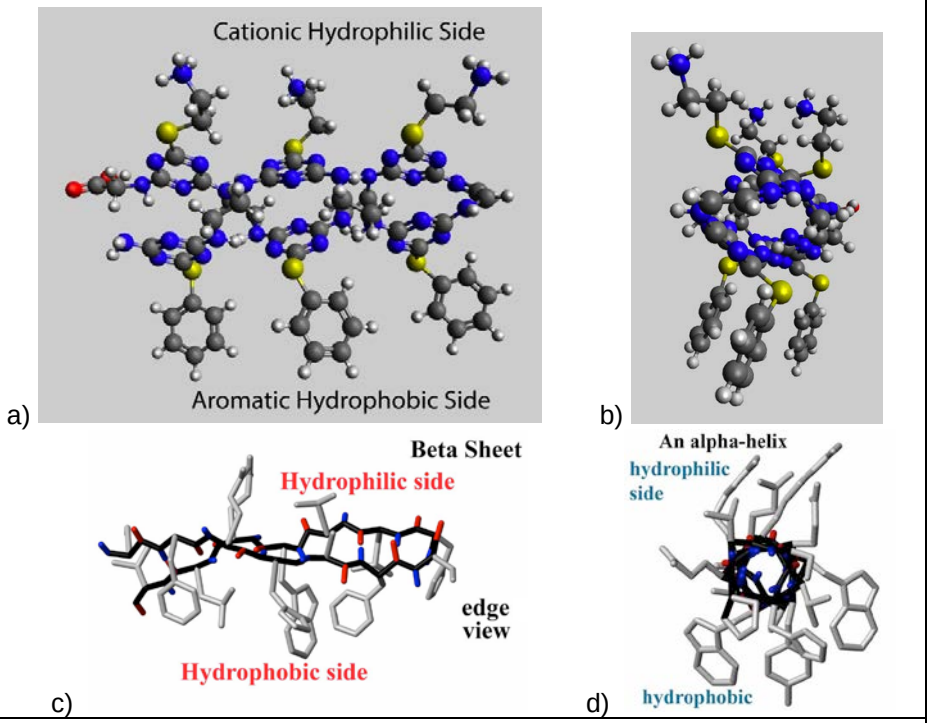

Figure 2. Amphipathic structures of a triazine-based hexamer in folded conformation forming an ordered nanorod, where the nanorod scaffold is derived from molecular dynamics simulation,[1] and side chains have been drawn in as hydrophilic and hydrophobic functional groups. The first image a) shows a side view, reminiscent of a beta sheet, and the second nanorod image b) shows an end-on view of the same rod, with side chains radiating out from the core rod. The mimicry of peptides structures is shown by comparison with generic c) beta sheet side view and d) end-on helix images from Wikipedia(protein structure).

We designed the triazine-based polymers (TZPs) to mimic the structure and function of natural peptide-based antimicrobials. In nature, these ubiquitous natural antibiotics work by membrane interaction and disruption, an activity that arises from foldamer or extended chain structures that arrange side chains in a way that leads to amphipathic properties. We used design principles from the field of antimicrobial peptides to design our stable synthetic polymers, and had them evaluated for antimicrobial activity. In this way, we can begin to understand how to design our new biomimetic synthetic polymers to achieve specific functional objectives.

Working with collaborators, we determined quantitative data on the antimicrobial activity, in the form of Minimum Inhibitory Concentration (MIC) values, of two test sets of stable synthetic TZPs. Antimicrobial activity against a variety of wild type and drug resistant pathogens was found. In this project, we obtained the first data on the activities of TZPs as antimicrobials, while learning what features, such as side chain structures and primary sequence, influenced the observed activity.

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