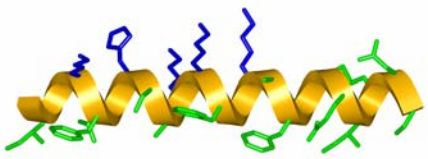
Extended Facially Amphiphilic Molecules

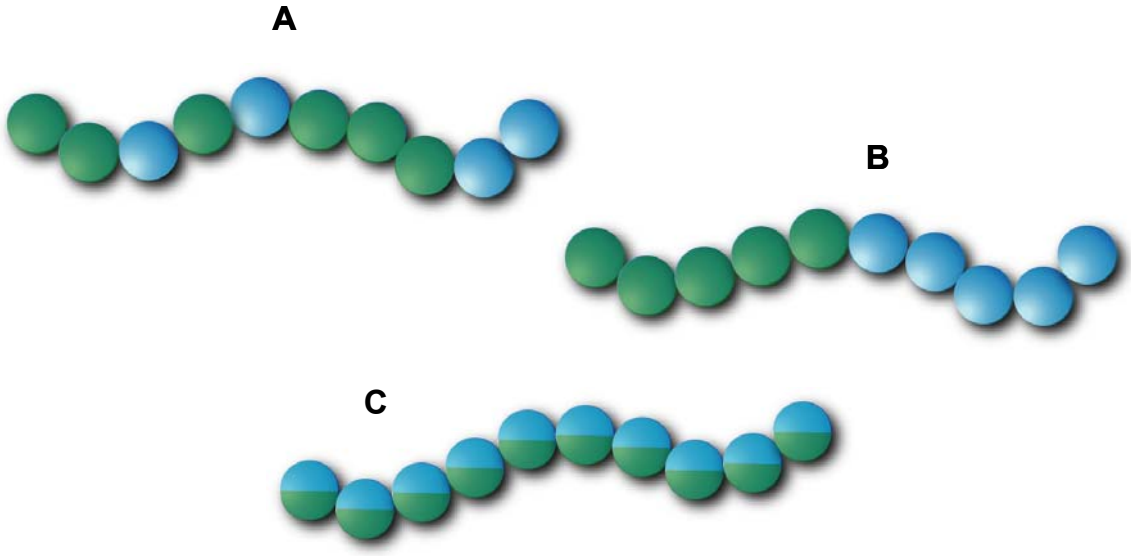
Naturally occurring biomolecules known as host defense peptides display an impressive spectrum of antimicrobial activity. At the same time, these peptides are non-toxic to their host cells and many other mammalian cells. Interestingly, their biological mode of action is through disruption of the bilayer lipid membrane representing a remarkable ability to discriminate between minor compositional differences. There are more than 700 members of this peptide class but most adopt a similar physiochemical architecture which we describe as facially amphiphilic. An example of the naturally occurring Magainin peptide is shown below in which the cationic and nonpolar side chains are shown in blue and green respectively.



The ability to develop simple macromolecules that exhibit similar function and behavior, but are much easier to prepare, will provide fundamental insight into the critical parameters responsible for the biological activity of the naturally occurring peptides. At the same time, it will enable new technologies in materials and pharmaceutical applications. These include permanently anti-septic materials such as catheters.

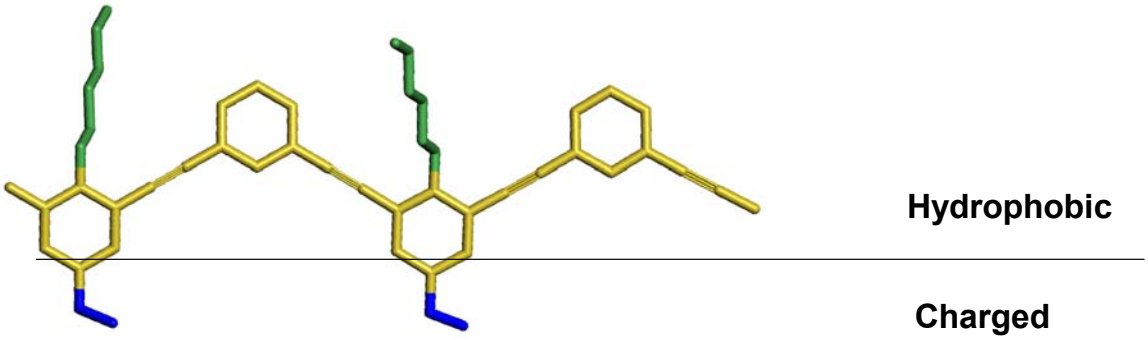
Novel Polymer Architectures

Such polymers also represent a new class of amphiphilic copolymers. Classic amphiphilic copolymers have random or blocky architectures along the backbone (A and B); however, the new polymers we are studying have polar and nonpolar groups segregated lengthwise as shown below. As one looks down the molecular backbone, these new facially amphiphilic molecules (C) have polar and nonpolar functions always on opposite sides.



Cationic meta-Phenylene Ethynylene Polymers:

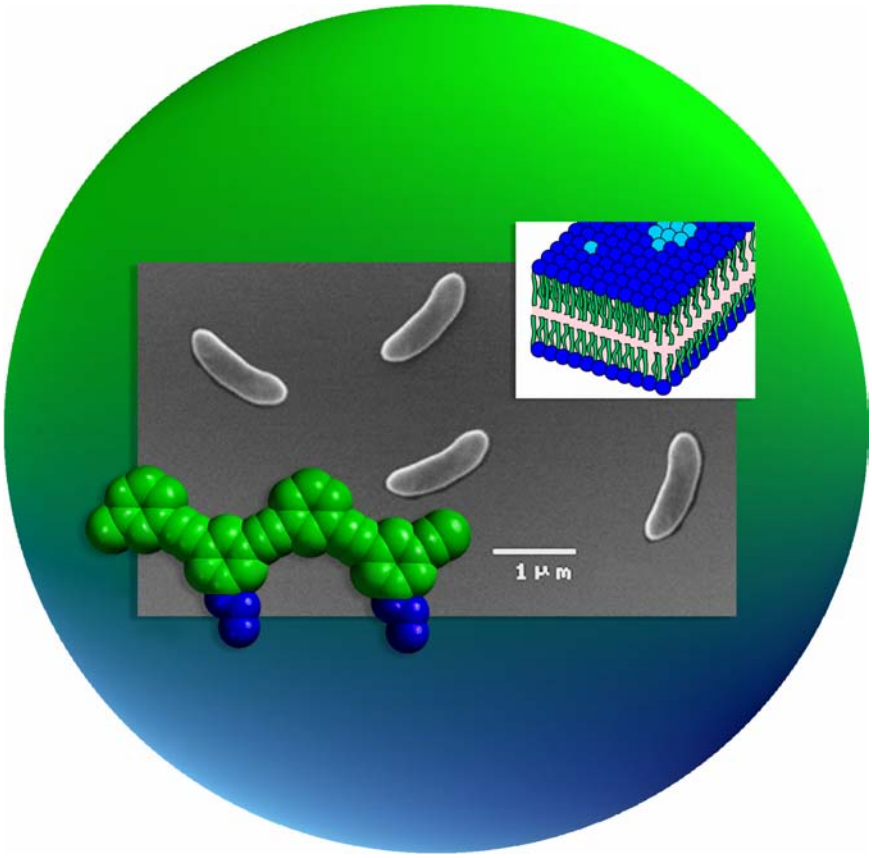
We have designed solely aromatic backbone polymers with polar and nonpolar groups that capture the activity and selectivity of these host defense peptides. One example of these polymers is shown below at a polar-nonpolar interface. This interface is generic and can represent the air-water interface or the lipid-water interface of cells.



The ability of these polymers to kill bacteria but not human red blood cells is shown in the table. As you can see, there are several structures represented. When the m-PE molecules contain a five carbon side chain, they are too hydrophobic and therefore not soluble enough. Removing this side chain leads to C0 structures which prove to be very active. The molecular weight dependence shows that short polymers are most selective. The 1600 molecular weight sample is the first polymer with facially amphiphilic architecture to demonstrate significant selectivity. As the table shows, it has a 10 fold selectivity for *E. coli* and *B. Subtilis* over human red blood cells. The even shorter structure has better selectivity. This work was highlighted on the cover of the Journal of Polymer Science-Polymer Chemistry in August of 2004 with the image shown below.

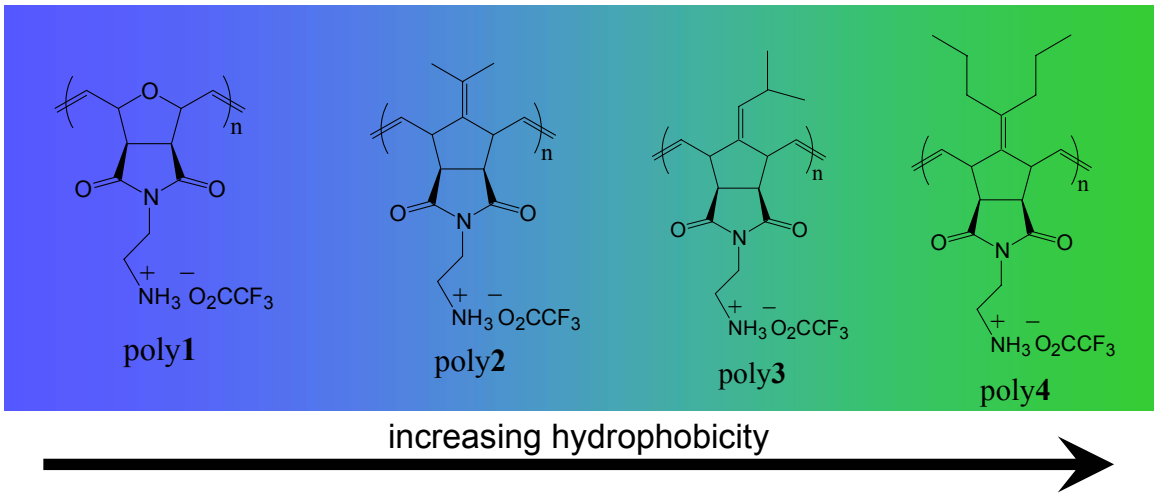
			MIC (μg/mL)			Selectivity
Structure	MW	n	*E. coli*	*B. subtilis*	HC_{50}	$HC_{50}/MIC_{E.\ coli}$
C5	6785	20	-	-	-	-
C0	5380	20	25	25	12.5	0.5
C0	1600	6	50	50	540	10.8
C0	590	1.5	0.85	1.7	75	**88.2**
monomer	315	N/A	>>100	>>100	3400	N/A
MSI-78			12.5		120	9.6

MIC is minimal inhibitory concentration or the least amount of sample need to stop 90% growth. HC_{50} is the amount of sample required to lyse 50% of the red blood cells.



Functionalize Polynorborenes:

A recent collaboration with Prof. Bryan Coughlin has lead to a new series of amphiphilic molecules with similar biochemical properties. The chemical structure of these polymers is shown below.



By tuning the length of the side chain and copolymer composition, both active and selective molecules were discovered. Look for this work which will be published soon!