

Protein Mimicry with Bioinspired Peptoid Polymers

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Introduction

Despite the fact that proteins and bulk polymers share a common linear polymeric architecture, the fields of Structural Biology and Polymer Science are presently separated by a great divide [1]. In fact, there are relatively few non-natural polymer systems that include even the most fundamental of biopolymer attributes: chemical diversity and sequence specificity. The chemical information encoded within the polypeptide chain, by virtue of its linear sequence of chemical functional groups, is sufficient to “instruct” it to fold into a precise 3D architecture, and to exhibit advanced properties, such as molecular recognition and catalysis [2]. We are exploring the concept of building analogous protein-mimetic materials from “information rich” synthetic polymers [3]. The solid-phase submonomer synthesis of *N*-substituted glycine peptoid oligomers has emerged as one of the most efficient ways to synthesize sequence-specific polymers from a highly chemically diverse monomer set [4-6]. We are applying fundamental rules that govern protein folding to the world of polypeptoids, with the aim of folding peptoid polymers into artificial protein-like structures to yield a new generation of robust protein-mimetic materials [7-11].

The *de novo* design of proteins remains a challenging problem despite the availability of a large database of protein structures and sophisticated computational tools. So where do we start when approaching the problem of folding non-natural polymers into atomically-defined architectures? We have simplified the problem by first focusing on mimicry of the two fundamental secondary structural units found in protein structure: alpha helices and beta sheets. We have shown that despite a lack of H-bond donors in the peptoid backbone, peptoids bearing alpha-chiral sidechains can fold into helices [12,13]. This effect was first predicted in 1997, and then demonstrated experimentally in 1998. But the peptoid beta-sheet mimetic was not discovered until over a decade later [10,11]. This is because a helix involves only the local folding of a single chain, whereas folding into a sheet involves chain-chain interactions, a higher level of complexity [14]. Here, we explore the sequence requirements to fold a peptoid chain into an achiral, supra-molecular nanosheet (Figure 1).

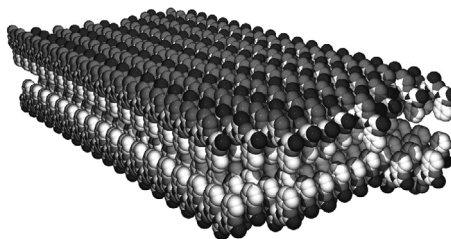


Fig. 1. Polypeptoid nanosheets are a mimetic of peptidic beta sheets, despite a lack of chirality and backbone H-bond donors.

Results and Discussion

We reasoned that the most fundamental rules that govern protein folding should also apply to peptoid polymers. We therefore began our search for peptoid beta-sheet mimetics by considering the visionary ideas of Ken Dill, Michael Hecht and others, who noted the overwhelming importance of the patterning of hydrophilic and hydrophobic groups within the polypeptide chain [15,16]. It was demonstrated that the exact identity of an amino acid was not as important as whether it was polar or non-polar. It was also shown that helices and sheets also exhibit distinct sequence periodicities of polar and non-polar residues.

These observations inspired us to explore the impact of sequence periodicity on peptoid structure. We set out to synthesize repeating patterns of hydrophilic and hydrophobic peptoid sequences using our robotic parallel synthesizers. To enable such a study, we used a minimalist monomer set that included one hydrophobic monomer (*N*-2-phenylethylglycine), and a pair of polar monomers (*N*-2-aminoethylglycine and *N*-2-carboxyethylglycine). This way the number of possible sequence variants could be kept manageable. A systematic set of 36mer peptoids was synthesized consisting of different repeating patterns of these monomers (the two-fold

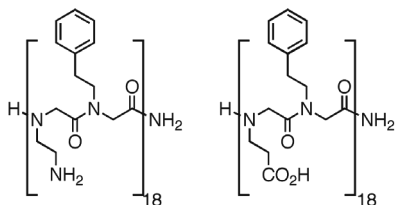


Fig. 2. A 1:1 mixture of oppositely charged two-fold periodic peptoid 36mer amphiphiles forms nanosheets in dilute aqueous conditions at room temperature.

periodic sequences are shown in Figure 2). The purified peptoids were then dissolved in dilute physiological buffers and examined by optical and electron microscopy.

Peptoids containing an alternating two-fold repeating pattern of hydrophilic and hydrophobic sidechains assembled into micron-sized nanosheets in high yield (Figure 3) [10,11]. The nanosheets were further characterized by atomic force microscopy, X-ray powder diffraction, and transmission electron microscopy, and found to be uniformly ~3 nm thick and highly ordered. The data are consistent with a bilayer model (Figure 1), where the hydrophobic groups are buried in the

core, and the ionic groups are exposed to water. The nanosheets often have very straight edges, are stable over a broad pH range (3-11) and can survive in hot water and even drying under vacuum. They spontaneously dissolve in the presence of >50% acetonitrile. Because the nanosheets are comprised of achiral peptoid polymers, the resulting planar structure shows no surface curvature, in contrast to peptidic beta sheets [17].

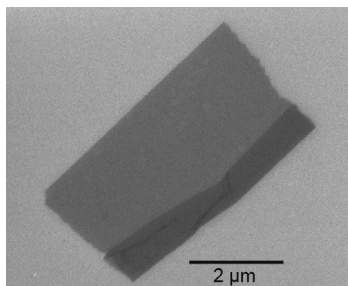


Fig. 3. Scanning electron micrograph of a peptoid nanosheet.

The peptoid nanosheets demonstrate that a non-natural polymer can be folded into a defined structure based on the monomer sequence pattern. The nanosheet structure itself is an excellent two-dimensional platform upon which to display functionality, which may find utility as membrane mimetics, sensors for chem/bio detection, templates for the growth on inorganic materials, and substrates for electron microscopy. More broadly, the ability to introduce chemical sequence information into polymer chains promises to yield a new family of protein-mimetic polymers.

Acknowledgments

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