Mimicry of protein structure with sequence-defined peptoid polymers

T. Yu[a], X. Jiang[b], X. Luo[a], D. Prendergast[a], N.P. Balsara[b], R.N. Zuckermann[a,b]

[a]Molecular Foundry and [b]Materials Science Divisions, 1 Cyclotron Rd., Lawrence Berkeley National Laboratory, Berkeley, CA 94720.

A longstanding challenge in molecular biomimicry is to build synthetic nanostructures with the same architectural sophistication as proteins. One of the most promising ways to do this is to synthesize sequence-defined, non-natural polymer chains that, like in Nature, spontaneously fold and assemble into precise three-dimensional structures. This was originally a synthesis problem, but the automated solid-phase submonomer synthesis method now allows one to efficiently synthesize high-purity, sequence-defined peptoid polymers up to 50 monomers in length[1]. The method uses readily available primary amine synthons, allowing hundreds of chemically diverse sidechains to be cheaply introduced[2].

This tremendous synthetic capability raised the next problem: which sequences of chemical information in a chain encode for precise folding into a 3D structure? This is essentially the protein folding problem extended to the non-natural world. Using our synthesis capabilities in concert with computational modeling and high-resolution characterization techniques, we demonstrate here the design, synthesize, assembly and engineering of a variety of protein-mimetic nanostructures[3]. We show by direct cryo-TEM imaging, AFM, NMR and X-ray scattering, that almost all known crystalline peptoid assemblies share a universal secondary structure motif, the *cis*-Sigma strand, based on a backbone fold containing all *cis*-amide bonds[4]. This unexpected universality of peptoid backbone folding offers a unique opportunity to rationally design and engineer these materials to create robust, nanomaterials capable of protein-like functions, like specific molecular recognition and catalysis.

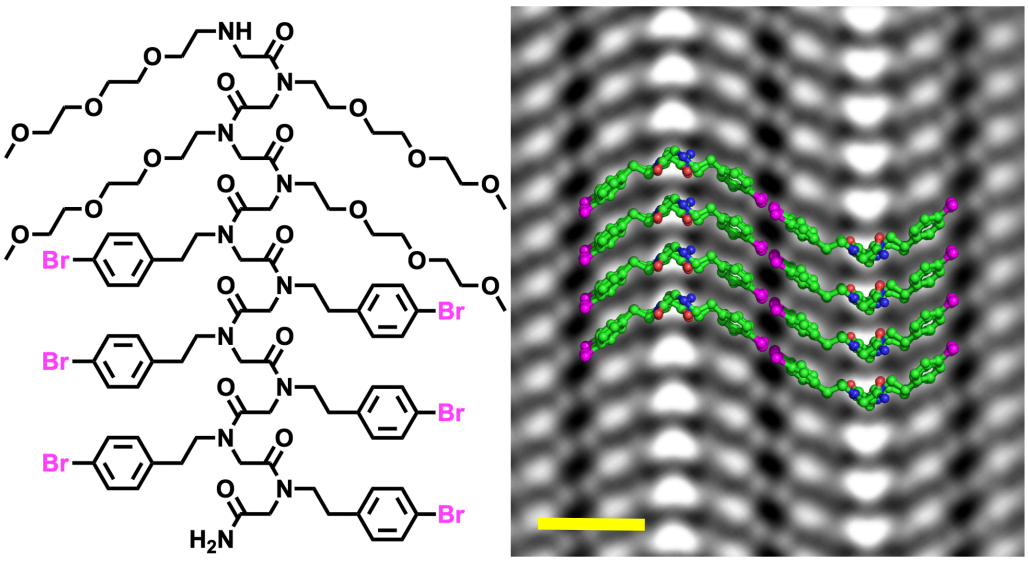

Figure 1. Cryo-TEM imaging of a crystalline peptoid nanosheet assembled from a peptoid decamer (Nte_4-$Nbrpe_6$), showing the rectangular lattice packing characteristic of peptoid *cis*-Sigma strands. The para-bromine atom substituents (show in in magenta on the molecular overlay) can be clearly resolved (scale bar = 1 nm).

References

1. R. N. Zuckermann, J. M. Kerr, S. B. H. Kent, W. H. Moos, Efficient Method for the Preparation of Peptoids [Oligo(N-substituted glycines)] by Submonomer Solid Phase Synthesis. *J. Am. Chem. Soc.* **114** (1992).
2. M. D. Connolly, S. Xuan, N. Molchanova, R. N. Zuckermann, "Submonomer synthesis of sequence defined peptoids with diverse side-chains" in Methods in Enzymology*,* E. J. Petersson, Ed. (Academic Press, 2021), vol. 656, pp. 241-270.
3. S. Xuan, X. Jiang, R. K. Spencer, N. K. Li, D. Prendergast, N. P. Balsara, R. N. Zuckermann, Atomic-level engineering and imaging of polypeptoid crystal lattices. *Proc. Natl. Acad. Sci. U. S. A.* **116** (2019).
4. D. R. Greer, M. A. Stolberg, J. Kundu, R. K. Spencer, T. Pascal, D. Prendergast, N. P. Balsara, R. N. Zuckermann, Universal Relationship between Molecular Structure and Crystal Structure in Peptoid Polymers and Prevalence of the cis Backbone Conformation. *J. Am. Chem. Soc.* **140** (2018).