Taking inspiration from Biopolymers : Foldamers as Protein Mimics

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The discovery that synthetic sequence-specific oligomers can adopt well-defined folded structures – foldamers[1] – has profoundly changed our view of biopolymer mimicry, raising prospects for exploring new chemical spaces and creating novel synthetic architectures with defined functions.[2-4] In this presentation, we will discuss some of our efforts towards this goal, showing how de novo design, careful structural investigation and subsequent sequence engineering of non-peptide helical foldamers may be used to generate effective peptide and protein mimics.
Besides aliphatic and aromatic oligoamide foldamers (β-peptides, peptoids, sulfono-γ-AApeptides, quinoline-based oligoamides,…) which have received much of the attention in the field, a few other backbones that do not contain an amide linkage but similarly show a high folding propensity (e.g. aliphatic urea-based oligomers studied in our group) have emerged. Oligourea foldamers which form well-defined and stable helical secondary structures (Fig. 1) reminiscent of the α-helix combine a number of characteristics – synthetic accessibility, sequence modularity, folding fidelity, and stability to proteolysis – that bode well for their use in various applications.[5]

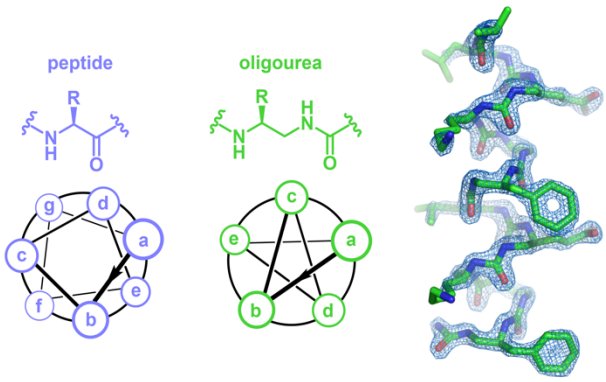

Figure 1. Helical-wheel representations of α-peptide and oligourea backbones and x-ray structure of a helically-folded oligourea foldamer

Applications developed in our group with a focus on molecular recognition include the design of (*i*) bioactive peptide mimics with a reduced peptide character and improved pharmacological properties (i.e. modulators of protein-protein interactions and receptor ligands), (*ii*) foldamer-based organocatalysts as well as more sophisticated architectures like (*iii*) composite proteins and (*iv*) foldamer-based nanostructures.

References

1. S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173-180.
2. G. Guichard, I. Huc, *Chem. Commun.* **2011**, *47*, 5933-5941
3. W. S. Horne, T. N. Grossmann, *Nat. Chem.* **2020**, *12*, 331-337
4. M. Pasco, C. Dolain, G. Guichard, in *Supramolecular Chemistry in Water* (Ed.: S. Kubik), Wiley - VCH Verlag GmbH & Co. KGaA Weinheim, Germany, **2019**, pp. 337-374.
5. S. H. Yoo, B. Li, C. Dolain, M. Pasco, G. Guichard, in *Methods Enzymol., Vol. 656* (Ed.: E. J. Petersson), Academic Press, **2021**, pp. 59-92.