

Folding, dynamics and assembly of helical biomimetic architectures

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The amazing variety of structures and of functions displayed by proteins is attainable with a set of only about 20 amino-acid constituents arranged in a linear sequence. One can only wonder what structures and what functions are attainable by appropriately combining the innumerable non-natural monomers available to chemists. To answer this question, synthetic foldamers –oligomers that fold into well-defined conformations in solution– have been the object of great attention and very active research over the past ten years. It has been shown that the secondary structural motifs of proteins are not restricted to the α -peptide backbone but belong to many classes of oligomers as, for example, the numerous molecular strands reported to wind into helices.¹ Among the most studied families of non-natural oligomers are aliphatic β , γ , and δ -peptides, which bear particular significance because of their similarity to α -peptides.²

This lecture will focus on the promising family of aza-aromatic oligoamide foldamers which, as we will show, feature a remarkable combination of structure *predictability*, *stability*, *tunability* and ease of synthesis, and thus possess a high potential for mimicking the secondary structures of biopolymers. The aryl-amide bond rotation can be restricted through specific attractive and repulsive interactions between amide and functional groups at the ortho position on the aryl moiety. The overall conformation of an oligomer results from the simple linear combination of the local conformational preferences at each amide bond. Thus, by simply changing the relative orientation of the acid and amine units, and by tuning the size of these units, the curvature of the oligomeric strand may be tuned from strictly linear to highly bent, giving rise to helices of controllable diameter and to extended linear conformations.³

The folded states of these oligomers also give rise to large conformational changes and dynamic phenomena. For example, helix–linear strand transitions may be induced upon changing the local conformational preference of aryl-amide bonds using protonation of the endocyclic pyridine nitrogens⁴ or metal ion coordination.⁵ Helical handedness may be induced in solution by chiral groups at the end of a helix, and reversibly switched off in the solid state.⁶ Extension of the double helices like springs allow their hybridization into double helices.⁷ The pitch of these double helices can be increased further upon coordination of metal ions.⁵

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