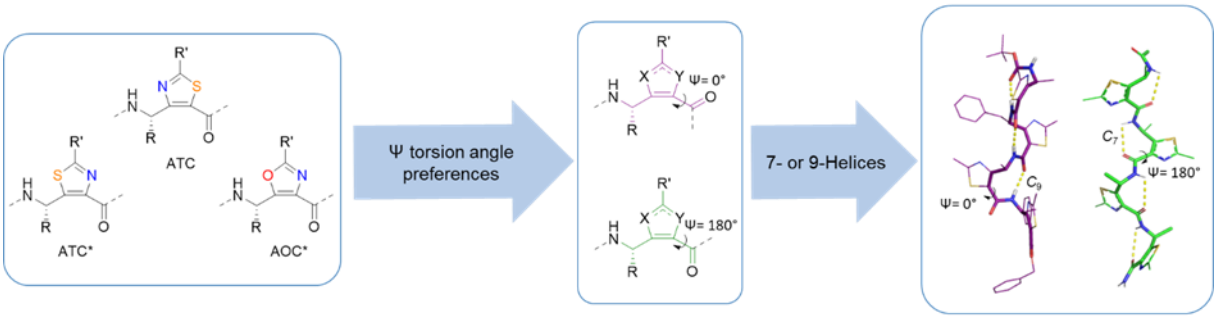
Shaping heterocyclic γ-peptide foldamers by stereo-electronic effects: Towards novel helical architectures

Samantha Chaise [(a)], Young Kee Kang[(b)], Ludovic Maillard[(a)], Baptiste Legrand[(a)]

[a]DAPP, IBMM UMR 5247, Montpellier, France;
[b]Department of Chemistry, Chungbuk National University, Cheongju, Republic of Korea

Heterocycles are widely used in many areas of organic chemistry to develop therapeutics and peptidomimetics.[1] They can orient molecular conformation in different ways since heteroatoms are hydrogen bond donors and acceptors, have negative and positive partial charges, and thus are key players in a wide range of interactions.[2] The last decade, we developed γ-peptide foldamers incorporating highly constrained five-membered heterocyclic γ-amino acids built around a thiazole, named ATC for 4-Amino(methyl)-1,3-Thiazole-5-Carboxylic acid.[3] We showed that ATC induces original 9-helix[4] and 9/12-ribbon[5] in γ- and α/γ-peptides, respectively.

In this study, according to conformational searches, we hypothesized that varying the nature of the heterocycles in γ-peptide backbones may offer new prospects to tune the stability of existing helices and theoretically allows to reach new architectures. We first developed robust synthesis pathways to access to enantiomerically pure thiazole- and oxazole-based analogs of ATC so called ATC* (5-amino(methyl)-1,3-thiazole-4-carboxylic acids) and AOC* (4-amino(methyl)-1,3-oxazole-5-carboxylic acids). We extensively studied the conformational preference of the corresponding oligomers by DFT, FTIR, XRD, CD, and NMR in a wide range of solvent conditions. We obtained a 7-Helix structure never described before whose stability varies with the chain-length. Interestingly, we observed a solvent-dependent conformational switch between the 7- and the 9-Helices.



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