Synthesis, properties and applications of fluorinated helical peptidic foldamers

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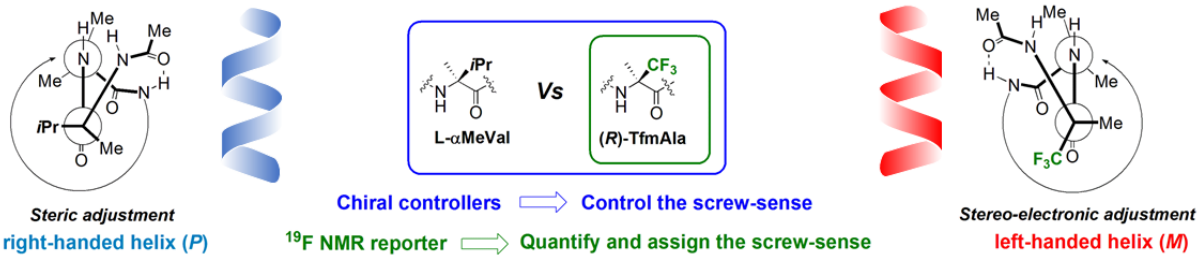
Peptidomimetic foldamers are a class of compounds capable of adopting well-defined secondary structures mimicking protein folding with the advantage of being very stable against proteases. Meanwhile, the use of fluorinated compounds in medicinal chemistry has become widely popular, with the incorporation of fluorine atoms being of major interest to modulate their physicochemical and therapeutic properties[1] but also as NMR probes. However, fluorinated foldamers remain scarcely explored compounds despite their obvious interest in both chemical biology and medicinal chemistry.

Our group is interested in the synthesis of fluorinated peptidic foldamers, in particular those able of promoting and stabilizing helical conformations, such as 3_{10}- or PPII-type helix.[2-5] In the course of our study, we recently investigated oligomers of *α*-aminoisobutyric acid (Aib) due to their ability to form stable 3_{10}-helices.[2,3] The achiral nature of Aib does not allow for a screw-sense preference of the helix and presents equal population of left- and right-handed conformers. However, the incorporation of a single chiral residue into the peptide chain may alter the equilibrium between the two forms, resulting in a screw-sense preference on the overall helical chain.[6]

Here, I will present our main results obtained on original fluorinated Aib foldamers incorporating the *(R)*-*α*-trifluoromethylalanine (*α*-TfmAla). After presenting their synthesis, I will detail driven conformational studies based on NMR, circular dichroism and X-ray crystallography which confirmed their ability to adopt 3_{10} helical structure. In addition, I will show that the introduction of chiral *α*-TfmAla allows to promote, quantify and in some case to assign the screw-sense preference of the helical chain. We Our results demonstrate that the stereo-electronic properties of the CF_3 group and the *C*-terminal unit have a major impact in the control of the helical screw-sense. This thorough structural study opens the field for the development of finely tunable fluorinated helical foldamers towards application in chemical biology.



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