Oral/poster presentation

Exploring the use of fluorine for peptoid structure induction

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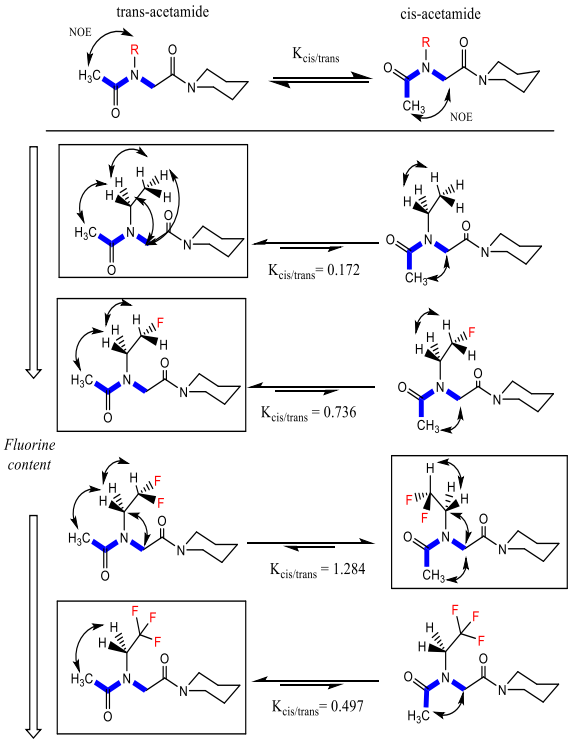
Introduction: Peptoids are oligomers of *N*-alkyl-glycine that are emerging as leading candidates in clinical research overcoming the main disadvantages observed in peptide application, showing strong resistance to bio-degradation and denaturalization[1]. Their biological activity relies on adopting an amphiphilic folded conformation that allows the interaction with different cellular targets. In peptoid structure, the amide bonds exhibit low conformational preference, having small $\Delta G_{cis/trans}$, so strong efforts have been made in order to improve peptoid folding, mainly into helical structures. Here we have investigated the potential application of fluorine in order to control amide bond *cis/trans* ratio in model systems.

Results and discussion: We have synthetized novel *N*-fluoroalkyl monomers as models for peptoid amide bonds[2]. The equilibrium $K_{cis/trans}$ ratio has been analysed by NMR on the basis of specific ^{1}H-^{1}H NOE contacts for each structure. Further analysis of ^{1}H-^{1}H COSY spectra allowed complete signal assignment, and *cis/trans* ratio evaluation from the corresponding integrated signals.



Fluorine substitution into non aromatic systems causes a general increase in the *cis/trans* ratio. In chloroform, the effect did not follow a cumulative trend, being maximal for the di-fluorinated compound, indicating the presence of some electronic effect. This trend was lost in more polar solvents, where calculated $K_{cis/trans}$ increased progressively with the number of fluorine atoms present. Noteworthy, values obtained for the di-fluorinated compound were comparable to those observed for the control *cis* inducting (*S*)-1-phenylethylamine (N*spe*).

In the case of aromatic residues, as proposed in literature, a dramatic electron withdrawing effect was observed stabilizing the *cis* conformation[2]. Interestingly, only one isomer could be found in the case of $-CF_3$ analogous of chiral N*spe* residue.

In order to gain further insights concerning the monomer behaviour in a real system, we synthetized three model peptoid based in *trans* inducting ethylamine residues that were substituted by 2,2-difluoroethylamine residues or by *cis* inducting *Nspe*. Circular Dichroism analysis confirmed the helical and non-helical structures for the control peptoids while the fluorinated derivative showed a new maximum, what may be pointing out that some distinct structure has been stabilized, even though not helical.

1. Dohm, M. T., Kapoor, R. & Barron, A. E., *Curr. Pharm. Des., 2011,* **17**
2. Gorske, B. C., Stringer, J. R., Bastian, B. L., Fowler, S. A. & Blackwell, H. E., *J. Am. Chem. Soc., 2009,* **131**