Artificial Mimics of G-Protein Coupled Receptors built from Conformationallly Switchable Peptidomimetic Foldamers

Jonathan Clayden

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK

Foldamers, by definition, have a well defined conformation. Yet many of the biomolecules (peptides and proteins in particular) that they aim to mimic do not share this feature of conformational uniformity. Indeed, for molecules involved in biological signalling, conformational changes are central to their function. We have been exploring the possibilities offered by loosening the definition of a foldamer to include switchable structures that have more than one accessible conformation.[1,2] This lecture will describe the design and utility of such **dynamic foldamers**[3] in the development of responsive systems that can use conformational change as a means of processing and communicating information. It will discuss the structural limitations of symmetry imposed by an ideally switchable structure, and show how conformational uniformity may be quantified.[4,5] It will outline the application of alternative switching mechanisms in the design of extended molecules that respond selectively to chemical signals in solution and in the membrane phase. Mimicking the the way that G-protein copoled receptors communicate information across impermeabel barriers.[6,7]

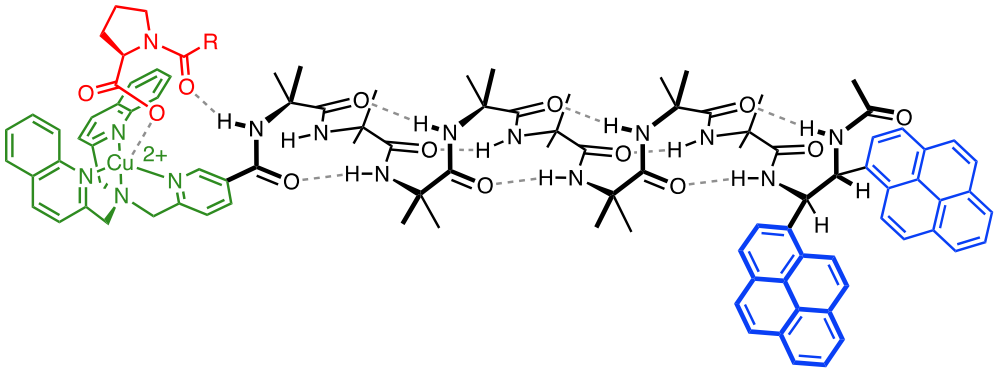

Fig 1: An artificial molecular communication device. A chiral carboxylate ligand (red), bound by a Cu(II) 'cofactor', induces a left-handed screw sense preference, detected by a remote fluorescent reporter (blue), in an otherwise achiral helical chain.

(1) De Poli, M.; Zawodny, W.; Quinonero, O.; Lorch, M.; Webb, S. J.; Clayden, J. *Science* **2016**, *352* (6285), 575.
(2) Lister, F. G. A.; Le Bailly, B. A. F.; Webb, S. J.; Clayden, J. *Nature Chem.* **2017**, *9* (5), 420.
(3) Le Bailly, B. A. F.; Clayden, J. *Chem. Commun.* **2016**, *52* (27), 4852.
(4) Tomsett, M.; Maffucci, I.; Le Bailly, B. A. F.; Byrne, L.; Bijvoets, S. M.; Lizio, M. G.; Raftery, J.; Butts, C. P.; Webb, S. J.; Contini, A.; Clayden, J. *Chem. Sci.* **2017**, *8* (4), 3007.
(5) Le Bailly, B. A. F.; Byrne, L.; Diemer, V.; Foroozandeh, M.; Morris, G. A.; Clayden, J. *Chem. Sci.* **2015**, *6* (4), 2313.
(6) Brioche, J.; Pike, S. J.; Tshepelevitsh, S.; Leito, I.; Morris, G. A.; Webb, S. J.; Clayden, J. *J. Am. Chem. Soc.* **2015**, *137* (20), 6680.
(7) Wechsel, R.; Žabka, M.; Ward, J. W.; Clayden, J. *J. Am. Chem. Soc.* **2018**, *140* (10), 3528.