Synthesis of novel rigid paramagnetic tags for NMR Spectroscopy

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Abstract:

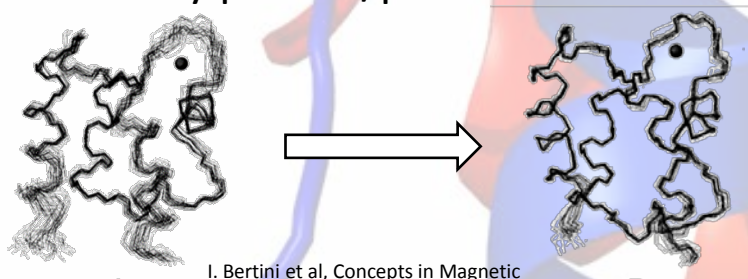
The tagging of proteins with paramagnetic centers provides angular and long-distance restraints for the determination and/or refinement of protein structures using NMR[1].

1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-based cycles are long-known for being strong lanthanide-chelators and those properties have led to the design of DOTA-based paramagnetic tags for NMR spectroscopy[2]. However, in order to maximize the measured effects (namely pseudo-contact-shift (PCS), residual dipolar coupling (RDC) or paramagnetic relaxation enhancement (PRE)) on the NMR spectra, the lanthanide-chelating tags must 1) not release the metal, 2) be present as a single stereoisomer, and 3) be as rigid as possible in order not to cause averaging of the measured effects due to molecular tumbling. Here, we present the synthesis of novel rigid lanthanide-binding tags with increased kinetic inertness and conformational stability.

These molecules are meant to be used as tools for structural studies of difficult and/or neglected medicinally relevant target-proteins in the frame of the MSCA AEGIS-ITN network.

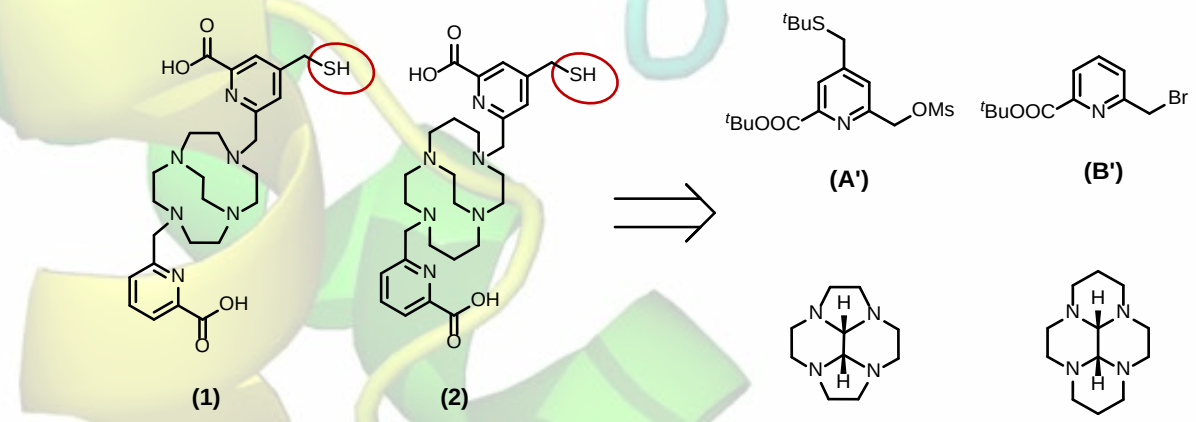
What is a paramagnetic tag?

A paramagnetic tag is a molecule its paramagnetism has distance-dependent effects measurable via NMR that give us information for the determination and/or refinement of protein structures. It also allows us to study protein/protein interactions.



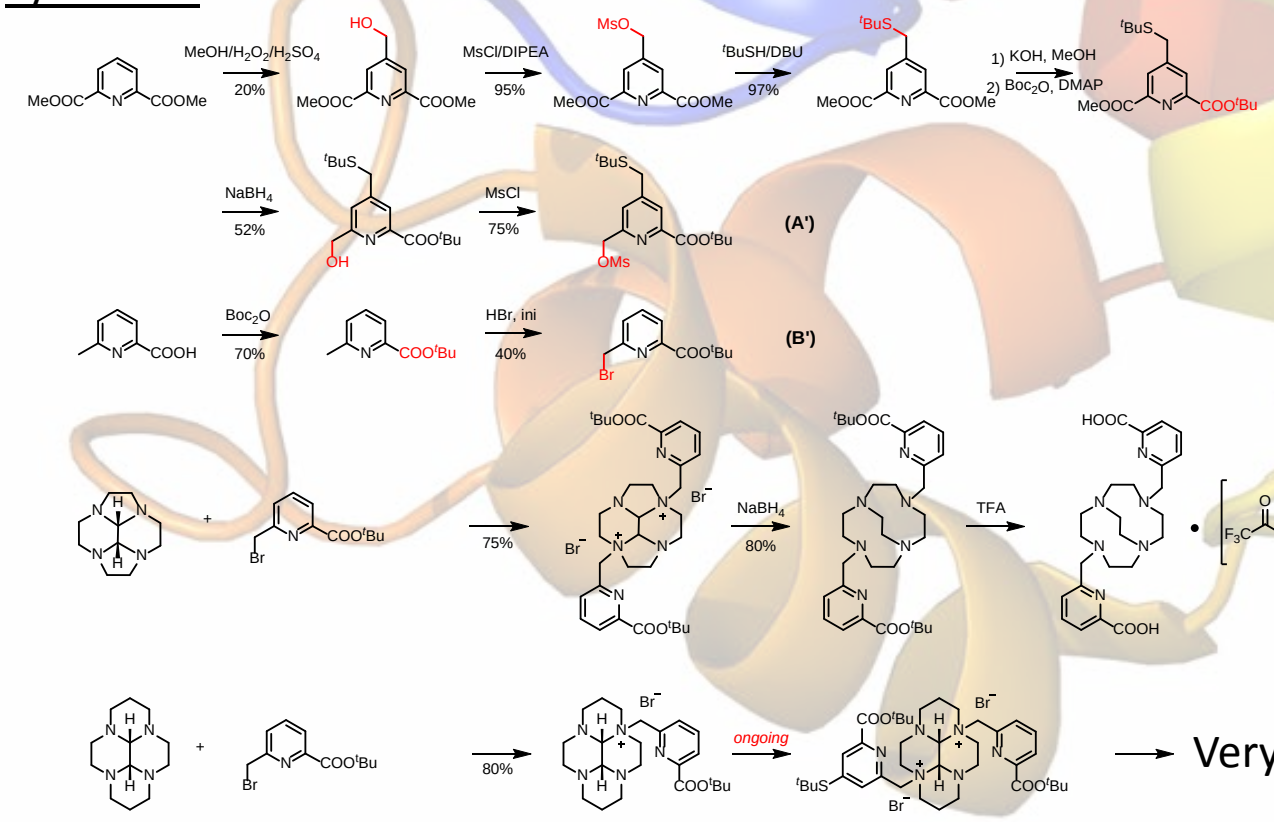
I. Bertini et al, Concepts in Magnetic Resonance, Vol. 14(4) 259–286 (2002)

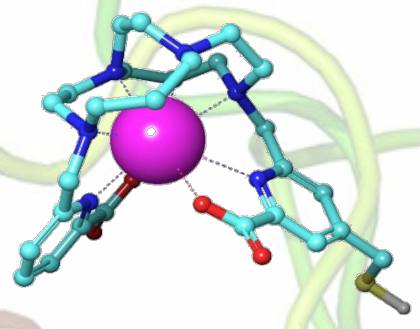
Our tag:



1. Coordination: 8 atoms
2. Enhanced rigidity
3. Single-point attachment

Synthesis:





Our tag's basket-like shape

References: [1]Brath, U. *J.Am.Chem.Soc.* **2015**, *137*, 11391-11398. [2]Liu, W.-M. *Coordination Chemistry Review* **2014**, *2-12*, 273-274. [3]Rodriguez-Rodriguez, A. *J. Am. Chem. Soc*. **2014**, 136, 17954−17957

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