Cu-coordination changes triggered by external ligands

Cu deregulation has been reported in several neurodegenerative diseases. Misplaced Cu is supposed to bind to amyloid-β (Aβ) peptides in Alzheimer's (AD) or α-synuclein in Parkinson's (PD) diseases. Both peptides/proteins belong to the class of the so-called intrinsically disordered proteins (IDPs) and are prone to form amyloids, i.e. beta-sheet rich aggregates. Moreover, these Cu-peptide/protein complexes have been shown to catalyze efficiently in vitro the ROS production in the presence of dioxygen and reducing agents. Hence Cu-bound amyloid peptides became the target of a therapeutic approach aimed at inhibiting the over-production of Cu-induced ROS might lead to the oxidative stress observed in AD and PD.
The coordination chemistry of Cu(II) and Cu(I) bound to Aβ peptides is very different. In Aβ, both Cu(II) and Cu(I) bind to the N-terminal domain (Aβ_{1-16}). Cu(II) is coordinated in a distorted square-pyramidal geometry with 3 nitrogen atoms (two belonging to histidine residues) and 1 oxygen atom, plus an axial O ligand, while Cu(I) has a digonal coordination involving two histidine residues.
In order to explain the relatively efficient ROS production by Cu-Aβ, it has been suggested that the latter is catalyzed by a low populated Cu-state, called an "in-between state that can cycle between Cu(I) and Cu(II) redox states with little atomic rearrangement and hence produce efficiently ROS.

In this proposal, we aimed at trapping and characterizing possible intermediates in Cu-Aβ redox cycling via X-ray Absorption Spectroscopy (XAS) measurements at the Cu K-edge. XAS measurements at the Cu K-edge were performed at the BM30 beamline of the ESRF. In order to identify possible intermediate species appearing during the Cu(II)-Aβ_{1-16} photoreduction process, the spectra of Cu(I)-Aβ_{1-16} and Cu(II)-Aβ_{1-16} resting states were first acquired and best-fit structures were obtained (Figure 1).

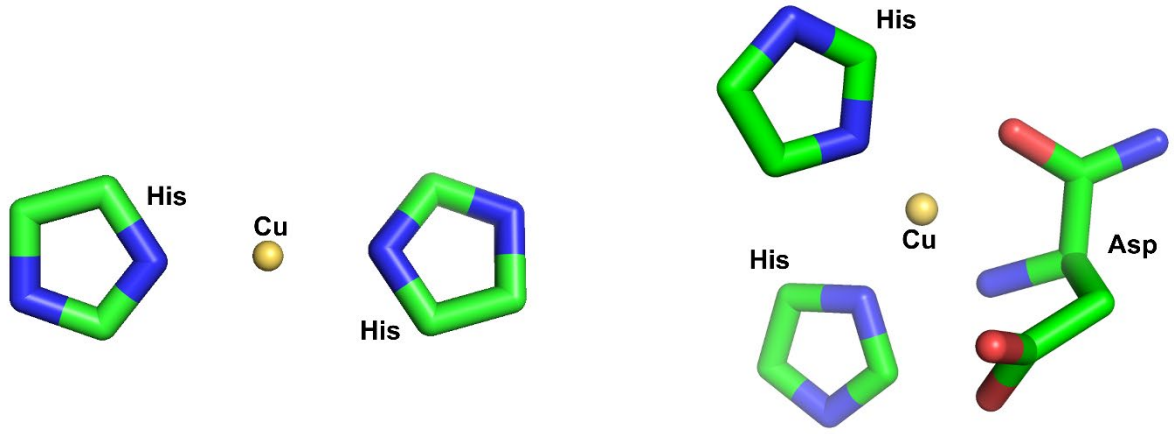

Figure 1 – EXAFS best-fit structures for spectra Aβ-Cu(I) (left) and Aβ-Cu(II) (right) complexes.

It is well known that, in the physical conditions of standard XAS experiments, which are typically performed at a temperature as low as 10 K, a progressive reduction of Cu(II) to Cu(I) is observed in Cu-Aβ peptide complexes. Despite the progressive reduction of Cu(II) to Cu(I), at 10 K the spatial organization of the ligands does not significantly change, yielding a Cu(I) ion in a coordination sphere of the Cu(II) resting state. In these experiments, the samples were irradiated with a high X-ray dose at 10 K. To allow partial relaxation of the ligands around Cu, the temperature was raised up to 200 K with the aim of producing and trapping non-resting states, which were then structurally characterized by XAS and a spectrum of a sample, termed S6$_{10\text{-}200\text{-}10}$, was acquired. Best-fits, obtained for a coordination mode involving one histidine residue and the N-terminal Asp1, are given in Figure 2.

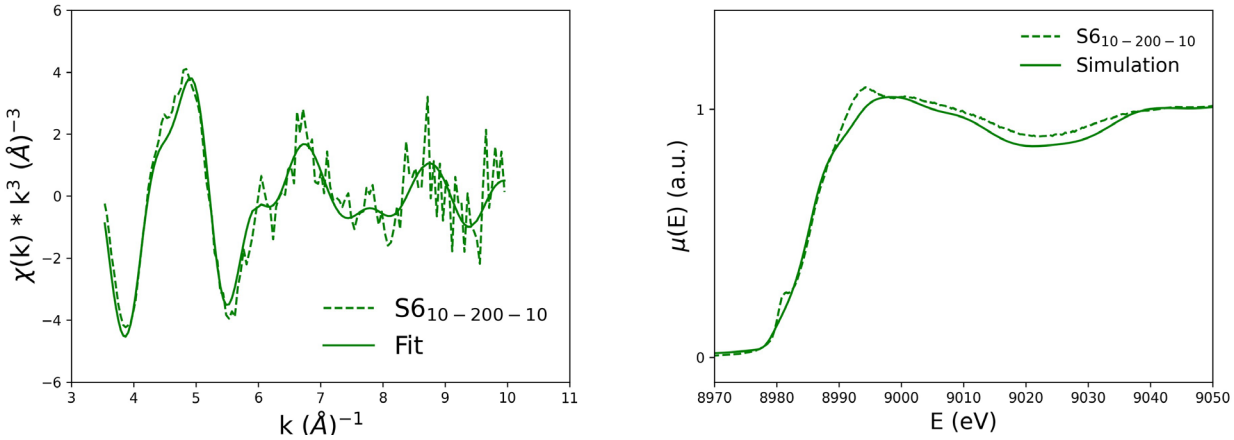

Figure 2 – EXAFS experimental data (dashed line) and best-fit (solid line) for sample $S6_{10\text{-}200\text{-}10}$ (left panel). XANES data (dashed line) and FDMNES simulation (solid line) calculated for the EXAFS best-fit structure (right panel).

The results of our experiments have been published in Falcone *et al.*, [Ang. Chem. Int. Ed. 2023] and provided a structural characterization of an intermediate of Cu(II)-Aβ_{1-16} reduction, supporting the existence and identity of a previously postulated redox-active "in-between" state.

References

Falcone, E., Nobili, G., Okafor, M., Proux, O., Rossi, G., Morante, S., ... & Stellato, F. (2023). Chasing the Elusive" In-Between" State of the Copper-Amyloidβ Complex by X-ray Absorption through Partial Thermal Relaxation after Photoreduction. *Angewandte Chemie International Edition*, e202217791.