



	Experiment title: XAS evidence of Cu(I) coordination in metal complexes of medical interest	Experiment number: 30-02 1044
Beamline: FAME	Date of experiment: from: 14/11/2013 to: 19/11/2013	Date of report: 22/02/2013
Shifts: 12	Local contact(s): Isabelle KIEFFER	<i>Received at ESRF:</i>
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Report:

Objective of the experiment:

This experiment had two main objectives:

1. The confirmation of the XAS results obtained in November 2011 (Exp 30-02-1024) on Cu(I) complexes with cysteine-based tripodal ligands L^{1-3} .¹ Indeed, these molecules are promising Cu chelators to treat metal overload, in particular in Wilson rare disease² and have been targeted to hepatic cells.³ Since we demonstrated in 2011 that the concentration of the complexes was a key-parameter for the speciation, it was necessary to run supplementary experiments with more diluted samples ([CuL] ~ 0.5 mM).
2. The analysis of Cu(I) complexes with novel sulfur-based tripodal ligands, which were developed by Anne-Solène Jullien during her PhD.⁴ The tripods were modified by substituting cysteines by the non natural amino acid D-Penicillamine, which is the currently-used drug to treat WD in $L^{4,5}$ or by neutral sulfur donor (thioethers), which mimic the coordination geometry of CTR1 Cu transporters in T^{1-4} .

Results and conclusion:

Cu K-edge XAS spectra were acquired for more than 20 different samples at low temperature (4-15 K) with cysteine ligands L^1 and L^2 , D-Pen ligands L^4 and L^5 and thioether ligands T^{1-4} .

Thiol derivatives L^1 , L^2 and L^5 .

The total ligand concentration was kept around 3 mM and Cu(I) concentration was varied from 0.5 to 5 mM. The **equilibrium between two different Cu(I) species** was proved in the edge spectra (Fig. 1 for L^1), which show several isobestic points, characteristic of the presence of only two different absorbing species. The first species (at low Cu concentration) is a mononuclear Cu(I) complex and EXAFS data confirm a **perfect trigonal planar CuS_3 environment with three Cu-S bonds of 2.26 Å**. The second species is a cluster complex $(Cu_2L)_z$, with EXAFS data also characteristic of a perfect trigonal planar CuS_3 environment (3 Cu-S bonds of 2.26 Å) and three additional Cu---Cu interactions (2.65, 2.71 and 2.8 Å for L^1). The EXAFS data are correctly interpreted by using atomic coordinates of model Cu_4S_6 clusters found in the literature.⁵ Besides, the amount of the two species could be measured by using linear combination of the edge spectra in Athena software and are in total accordance with thermodynamic constants previously measured by UV for L^1 (Fig. 2).⁶ For L^2 and L^5 these data could be used to measure the unknown equilibrium constants between the two Cu(I) complexes.

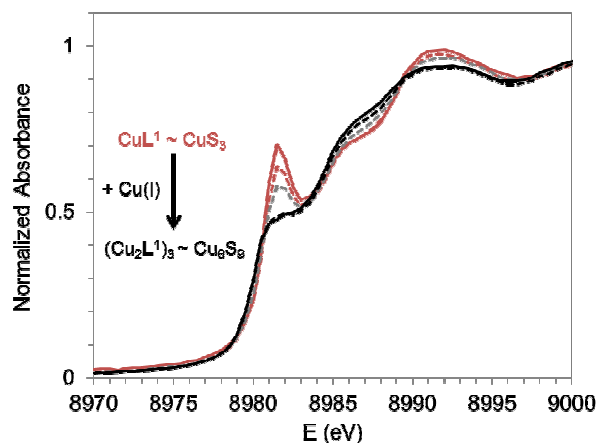


Fig. 1. Normalized Cu edge spectra obtained for ligand L^1 with increasing amounts of Cu (I).

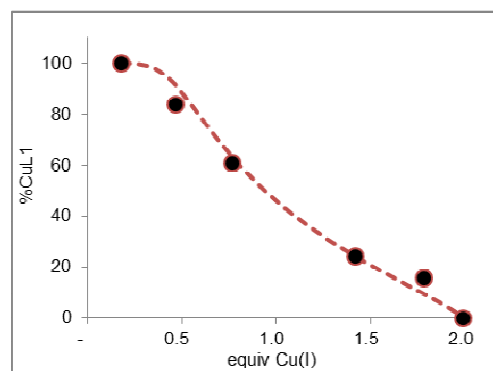


Fig. 2. Comparison between the proportions of mononuclear CuL^1 complex obtained after linear combinations of the edge spectra in Athena (black circles) and the proportion expected with the previously measured thermodynamic constants $\log\beta_{11} = 19.2$ and $\log K = 20.7$ (dotted red line)

Thioether derivatives T^{1-4} :

As expected with neutral ligands, the affinity of tripodes T^{1-4} for Cu(I) is significantly lower than the one measured with thiol ligands. The edge regions of the XAS spectra indicate a major CuS_3 environment in the complexes with an extra O/N coordination. The presence of this extra donor is consistent with the lower affinity of thioether's sulfur in comparison to thiolate's sulfurs.

These data are preliminary and will be refined during the following months.

Conclusions:

This experiment allowed us to obtain the final proof of Cu(I) coordination environments in Cu complexes of potential medical interest. Moreover we could measure new thermodynamic data about complex equilibrium in solution. Interestingly the coordination of Cu(I) is perfectly trigonal planar whereas the one determined previously with the analogous metal ion Hg(II)⁷ is highly dissymmetric. This demonstrates that the tripodal geometry of ligands derived from nitrilotriacetic acid is perfectly suited to coordinate the small Cu(I) ion with a large affinity. The results with thiolate ligands $L^{1,2,5}$ are fully interpreted and will be soon submitted in two publications. Results obtained with thioether ligands are still under refinement.

References:

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