Cu-ligand complexes as anticancer agents

Copper is an essential trace element in humans and therapeutic approaches based on the interaction of synthetic ligands with Cu attracted considerable medicinal interest. For instance, Cu-ligand complexes (Cu-L) are intensively investigated as anticancer agents. An often-implicated mechanism of cytotoxicity in cancer cells is the increased production of reactive oxygen species (ROS) catalysed by the Cu-L. This can occur in the presence of native reductants, such as ascorbate or glutathione (GSH), under aerobic conditions. Based on the literature and our recent results, the lysosome might be an important place of action for these Cu-L. Moreover, the GSH oxidation by Cu-phenanthroline complexes increased at acidic pH.

Within this proposal, we performed X-ray Absorption Spectroscopy (XAS) measurements at the BM30 beamline. The measured samples consided of Cu in complex with different ligands, such as phenanthroline (Phen), glutathione (GSH), and cysteine (Cys), in different Cu oxidation states and at different pH values. It is worth pointing out that XAS is very suited to study the Cu(I) state, which is not accessible by other common techniques (no d-d bands, no EPR, etc.), and especially to distinguish between N-donors and S-donors, like those coming from Cys or GSH molecules. The detailed and quantitative analysis of the collected data is still ongoing, however in this report we show preliminary results obtained from the comparison of XANES and EXAFS data.

By comparing the spectra of the complexes formed by Cu and Phen at pH 5 and 7.4, we observed that the changes in pH have an effect on changes on the Cu(I)-Phen coordination, but not on the Cu(II)-Phen binding mode.

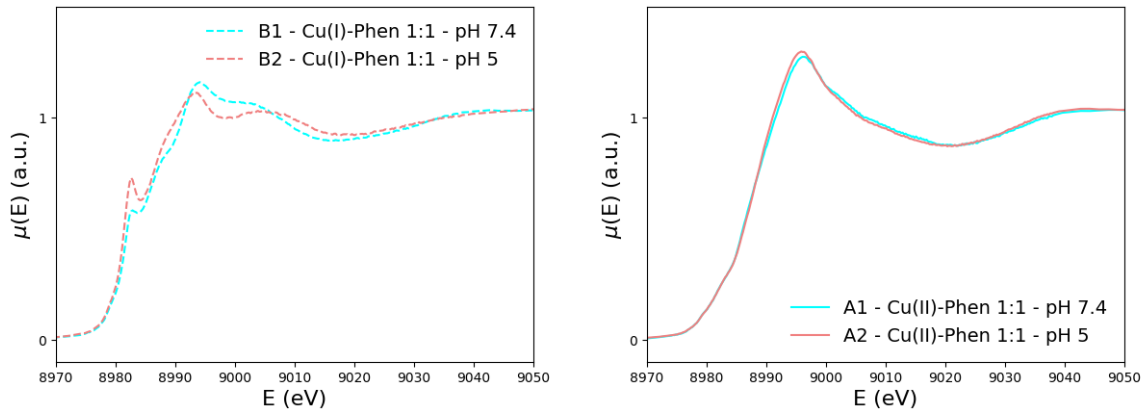

Figure 1 - XANES spectra of Cu(I) (dashed lines) and Cu(II) (solid lines) Phen complexs at pH=5 and pH=7.4 show that pH has an effect on.

We also compared XANES and EXAFS spectra of Cu-Cys and Cu-GSH, finding out that in these two complexes the Cu coordination mode is identical. Preliminary EXAFS fits show that there are S and Cu atoms located in the vicinity of the absorber, but a quantitative analysis of the XANES and more extensive fits of the EXAFS regions, which are still ongoing, are required in order to get detailed information on the number of S and Cu atoms located in the vicinity of the absorbing Cu.

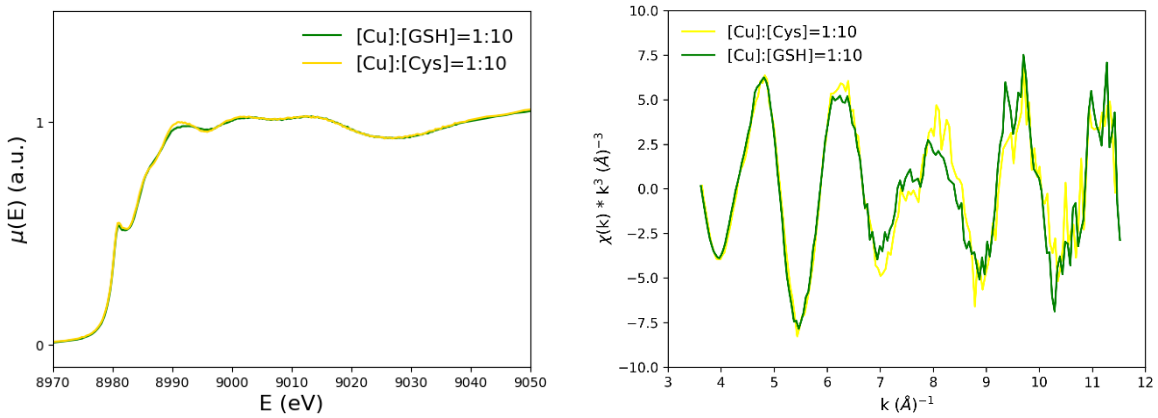

Figure 2 – XANES and EXAFS spectra of Cu-Cys and Cu-GSH samples.

This study has a twofold significance. From the fundamental chemical point of view, as it is well established that the reactivity of thiols as nucleophiles and reducing agents drops by lowering the pH, it sheds light on the mechanism that allows a higher activity at lower pH with Cu-Phen. Secondly, it has a major impact on the design of Cu-ligands for biomedical applications and the relevance of their lysosomal localization for biological activity.