THE GEOMETRY OF BIOACTIVE CU(II) COMPLEXES DETERMINED BY XAS AND UV-VIS SPECTROSCOPIES

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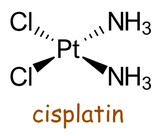
INTRODUCTION

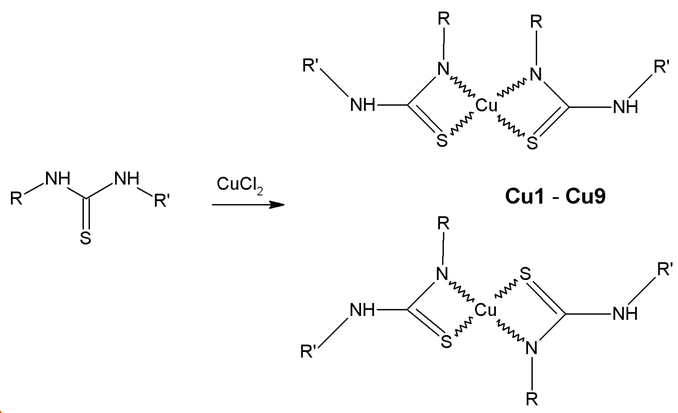
Cancer is the second leading cause of death in the world. According to WHO data, over 9 million people died from this disease in 2018. For about 20 years, much effort has been put into the development of connection with physiologically relevant, endogenous metals such as copper which are a promising alternative to highly effective but also very toxic platinum-based drugs such as cisplatin.



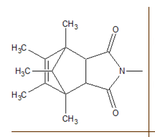
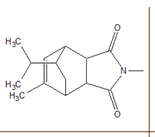
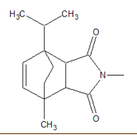
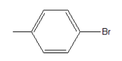
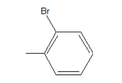
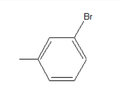
cisplatin

It has been shown that copper have the unique role in angiogenesis, which is a critical process for tumor growth and metastasis. Moreover, in numerous cancerous tissues, such us prostate, breast, brain and lung, the copper concentration exceeds the concentration of normal tissues. In this field, copper complexes are highly perspective in the metal-based anticancer drug discovery.

SYNTHESIS



Cu1 - Cu9

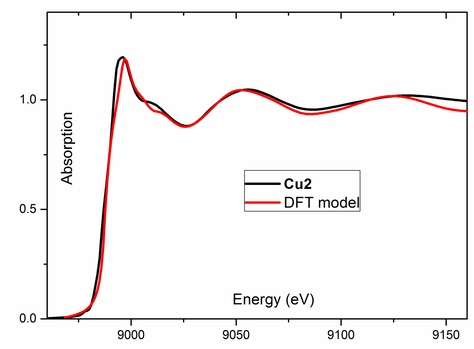
			R \ R'
Cu1	Cu2	Cu3	
Cu4	Cu5	Cu6	
Cu7	Cu8	Cu9	

MOLECULAR STRUCTURE IN SOLID STATE

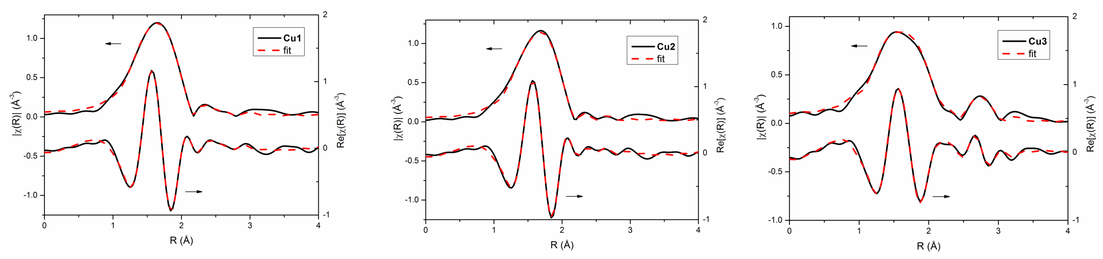
EXAFS fitting parameters of bioactive complexes

	Bond	R (Å)	N	σ^2 (Å^2)	R-factor	
Cu1	Cu-N	1.97(2)	2.0	0.003(1)		
	Cu-S	2.27(2)	2.0	0.005(1)	0.001	monomers
	Cu-C	2.58(2)	2.0	0.009(2)		
	Cu-N	2.95(2)	2.0	0.009(2)		
Cu2	Cu-N	1.98(2)	2.0	0.003(1)		
	Cu-S	2.27(2)	2.0	0.004(1)		
	Cu-C	2.62(2)	2.0	0.013(2)	0.002	
	Cu-N	3.09(2)	2.0	0.013(2)		
Cu3	Cu-N	1.93(1)	2.0	0.002(1)		
	Cu-S	2.25(1)	2.0	0.005(1)		dimer
	Cu-C	2.58(3)	2.0	0.002(2)		
	Cu-N	3.37(5)	2.0	0.002(2)	0.006	
	Cu-S	2.82(3)	1.0	0.005(1)		
	Cu-Cu	3.11(1)	1.0	0.005(2)		

Experimental and theoretical XANES spectra for monomer — complex Cu2

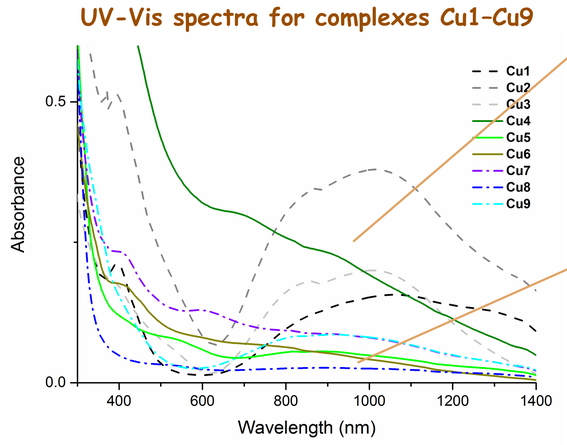


Moduli and a real part of the FT EXAFS oscillations for complexes Cu1–Cu3 with the best fit



1. A tetra-fold coordination, CuN_2S_2, is obtained by bidentate coordination of two ligands to the metallic center via S and deprotonated N atoms.
2. Another Cu and S atoms were identified in the second coordination sphere for complex **Cu3** indicating the formation of dimer composed of two CuN_2S_2 units.

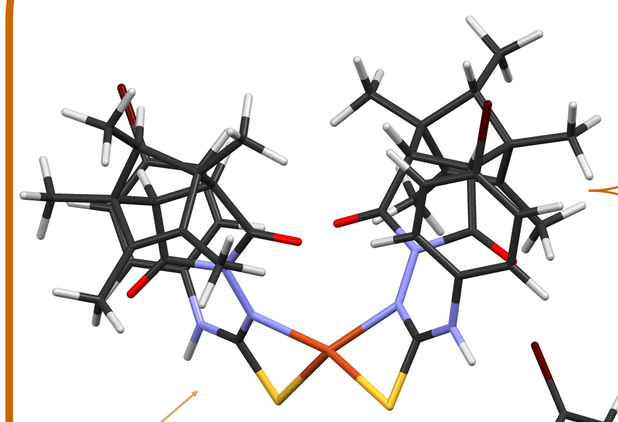
UV-Vis spectra for complexes Cu1–Cu9



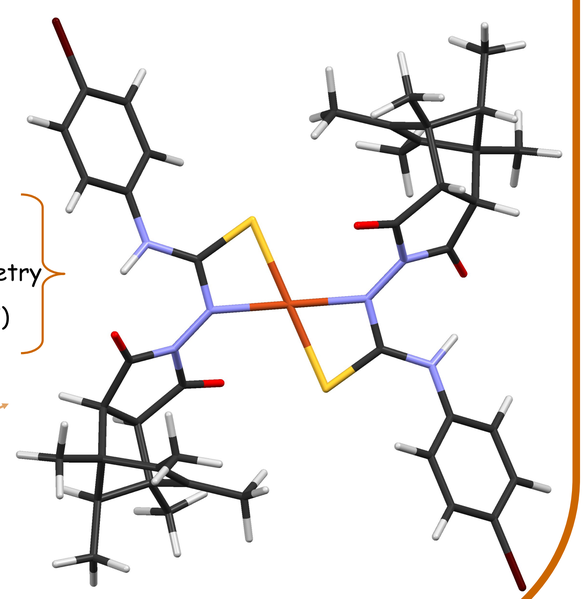
1. The low intensity of *d-d* band observed for complex **Cu8** suggests a nearly square planar geometry.
2. The high intensity of *d-d* band is observed for **Cu1–Cu3** — such feature is expected for a pseudo tetrahedral chromophores .
3. The spectra shape in the range of *d-d* transition of other complexes suggests the intermediate geometries between tetrahedral and square planar.

MOLECULAR STRUCTURE IN GAS PHASE

Structural models of Cu1, having C_2 and C_i symmetry, optimized at DFT/PBE level



- pseudo-tetrahedral structure
- noncentrosymmetric complex - C_2 symmetry
- *cis*-N_2S_2 arrangement around Cu(II)

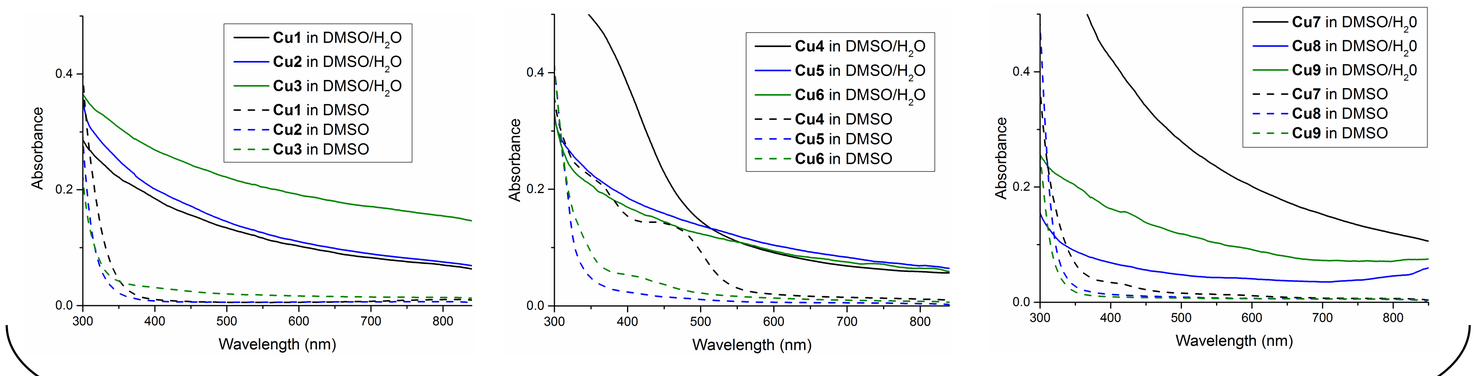


- distorted square planar geometry
- centrosymmetric complex — C_i symmetry
- *trans*-N_2S_2 arrangement around Cu(II)

CYTOTOXICITY ACTIVITY

1. The **Cu1** and **Cu3** are cytotoxic against SW480 (primary colon cancer) and PC3 (metastatic prostate cancer) cells: IC_{50} 4-19 μm, and non-cytotoxic against HaCaT cells: $IC_{50} \geq 84$ μm.
2. The complexes induced apoptosis in cancer cells, however, **Cu3** was estimated to be highly active inducer of late apoptosis in SW480 and PC3 cells at lower toxicity against normal cells.
3. The likely mechanism of action of compounds is correlated with decreasing release of IL-6 in cancer cell lines.

MOLECULAR STRUCTURE IN DMSO AND DMSO/H_2O SOLUTIONS



UV-Vis spectra of Cu1-Cu9 complexes in DMSO and DMSO/H_2O solutions with concentration of $6.25 \cdot 10^{-5}$ M

1. After dissolving **Cu1-Cu9** compounds in DMSO, they all adopt centrosymmetric coordination (either square planar or octahedral one, with DMSO molecules acting as axial ligand) which is manifested by the low intensity of the *d-d* bands in their electronic spectra.
2. Intensity of *d-d* bands increases again when the solution is diluted with H_2O (which takes place during the samples preparation for biological test), indicating the tetrahedral geometry of biologically characterized compounds.

CONCLUSION

1) Nine Cu(II) complexes were obtained by reacting 1,3-disubstituted thioureas with $CuCl_2$.
2) The molecular structure of each complex consists of two thiourea ligands chelated to the Cu(II) *via* the S and deprotonated N atoms.
3) In the solid state the coordination polyhedron of metal ion exhibits pseudo-tetrahedral or distorted square-planar geometries.
4) The complexes after dissolving in DMSO adopt a centrosymmetric coordination, while after diluting this solution with H_2O, the reorganization of atoms around the cation is observed, leading to the formation of the tetrahedral compounds.
5) Two thiourea complexes, **Cu1** and **Cu3**, with pseudo-tetrahedral geometry have shown significant activity to cancer cell lines SW480 and PC3, being more selective than doxorubicin and cisplatin used as references.

More details can be found in article:
A. Drzewiecka-Antonik, P. Rejmak, M.T. Klepka, A. Wolska, A. Chrzanowska, M. Struga, *J. Inorg. Biochemistry*
https://doi.org/10.1016/j.jinorgbio.2020.111234