2nd International Electronic Conference on Medicinal Chemistry

1-30 November 2016
chaired by Dr. Jean Jacques Vanden Eynde

sponsored by pharmaceuticals

Interaction of zinc(II) and copper(II) terpyridine complexes with biomolecules

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Abstract: Transition metal ions exhibit a unique role in diverse biological activities of proteins by acting as cofactors. In particular, zinc and copper ions modulate enzymes activities as well as many catalytic and oxidative/reductive processes. The kinetics and mechanism of the substitution reactions of dichloro [ZnCl2(terpy)] and [CuCl2(terpy)] (terpy = 2,2′:6′,2′′-terpyridine) with biologically relevant ligands have been studied as a function of nucleophile concentrations at pH 7.38, under pseudo-first-order condition by UV-Vis spectrophotometric techniques. The interactions of Cu(II) and Zn(II) complexes with tripeptide glutathione (GSH) were investigated under pseudo-first-order conditions with respect to the complex concentration. For the substitution process of Zn(II) complex with glutathione (GSH), pre-equilibrium and chelate formation have been noted. The [CuCl2(terpy)] is more reactive than [ZnCl2(terpy)] complex and the second-order rate constants for the first step follow the order of reactivity: GSH > DL-Asp > L -Met > 5′-GMP ~ 5′-IMP for Cu(II) complex, while for Zn(II) the order of reactivity is: DL-Asp > L -Met > GSH ~ 5′-GMP > 5′-IMP. The results are discussed in terms of mechanisms of interactions between metalloproteins and biomolecules.

Keywords: Zinc(II); Copper(II); Biomolecules

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Introduction

✓ Transition metal compounds play crucial roles as cofactors in metalloproteins [1]. Two essential metal ions, namely zinc and copper ions, modulate enzymes activities, catalytic and regulatory functions, oxidative-reductive processes, etc [1].

✓ Zinc(II) acts as an essential structural element in zinc-fingers, hydrolases, peptidases, anhydrases, and it is involved in gene regulation, etc [1].

✓ As a catalytic cofactor, Cu(II) is required in metalloproteins and influences biological oxidation-reduction reactions and electron transfers thanks to the couple Cu(II)/Cu(I) [1].

[1] I. Bertini, H.B. Gray, E.I. Stiefel, J.S. Valentine (Ed.), Biological Inorganic Chemistry. Structure and Reactivity, University Science Books: Sausalito, CA, 2007; R.M. Roat-Malone (Ed.), Bioinorganic Chemistry: A Short Course, John Wiley & Sons, Inc., Hoboken, NJ, 2002.
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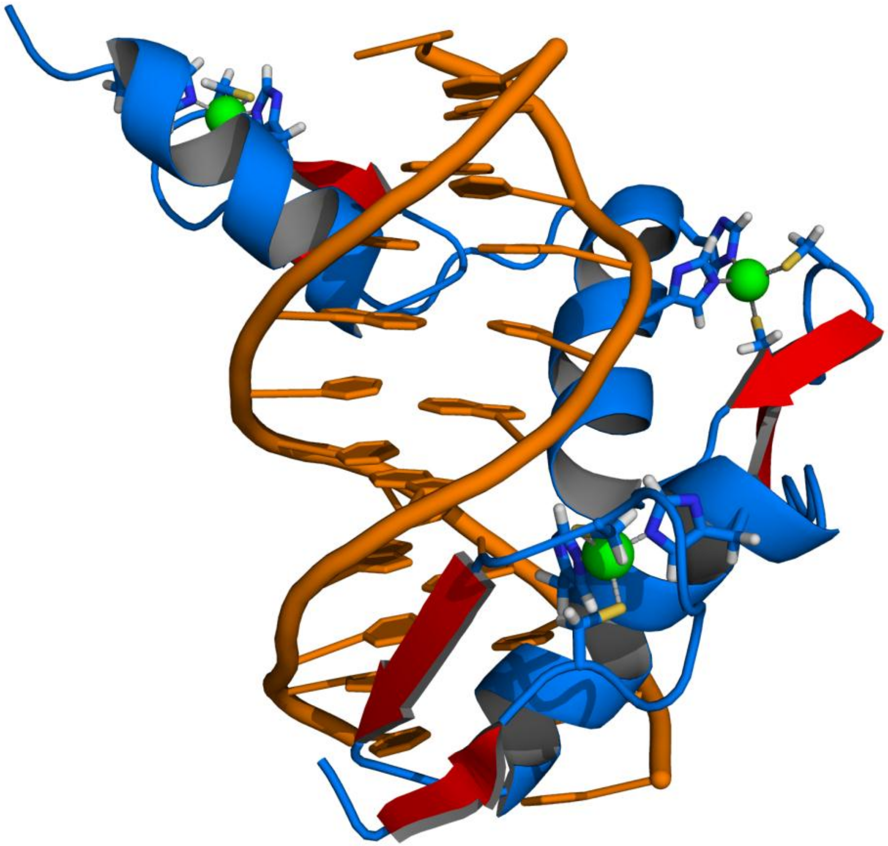
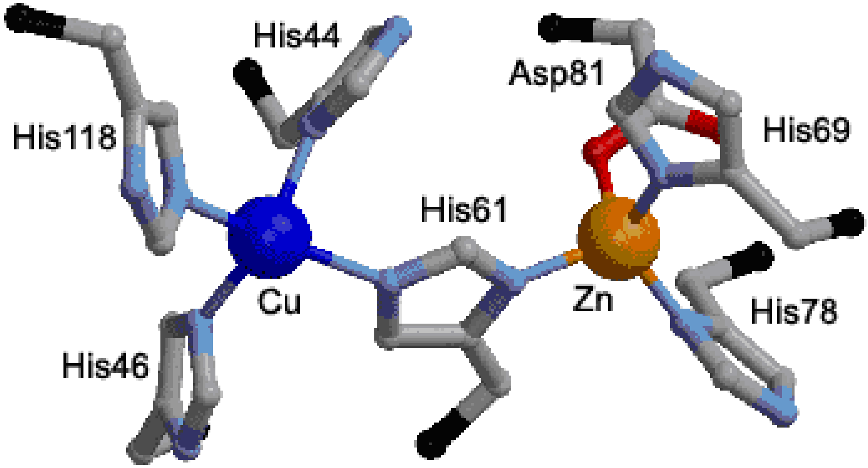


Zinc-finger_DNA_complex

✓ Zinc proteins are involved in control of nucleic acid replication, transcription and repair. They are implicated in many diseases and health complications so that they are recognized as medicinal targets [2].

✓ The anticancer drug cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, *cis*-DDP, releases Zn(II) from the zinc coordination domain of polymerase-α isolated from prostate cells (PA3) and inhibits the replication process [3]. The regulation of zinc-finger transcription factors has been shown by treatment of gene expression profiles of cells with cisplatin [4,5].

[3] T.J. Kelley, S. Moghaddas, R.N. Bose, S. Basu, Cancer Biochem. Biophys. 13 (1993) 135–146.
[4] H. Ishiguchi, H. Izumi, T. Torigoe, Y. Yoshida, H. Kubota, S. Tsuji, K. Kohno, Int. J. Cancer 111 (2004) 900–909.
[5] R. N. Bose, W.W. Yang, F. Evanics, Inorg. Chim. Acta 358 (2005) 2844–2854.



The active site of Cu/Zn-superoxide dismutase

- ✓ Cu(II) as active centre is present in Cu/Zn-superoxide dismutase (SOD1) located in cytoplasm and mitochondria. It exhibits an antioxidant defence function; it is known for its ability to detoxify free radicals [6].
- ✓ Copper controls cancer development. It serves as a limiting factor for multiple aspects of tumour progression, growth, angiogenesis and metastasis [6].
- ✓ Many studies are focused on the design of appropriated cofactors (e.g. Cu(II)-terpyridine complex) for G-quadruplex DNA metalloenzymes showing enantioselective catalytic effects [7,8].

[6] D. Denoyer, S. Masaldan, S. La Fontaine, M.A. Cater, Metallomics 7 (2015) 1459– 1476.
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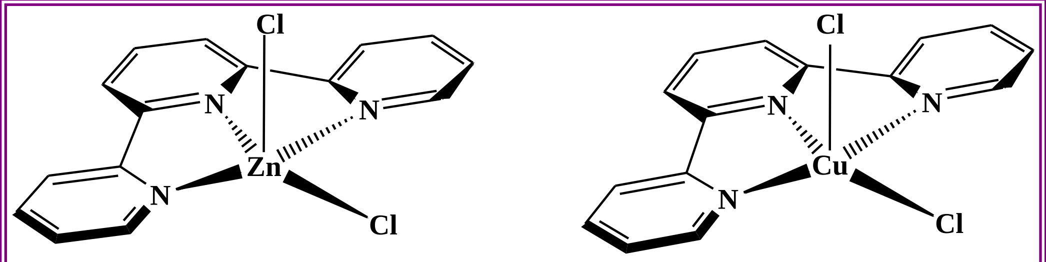
[8] Y. Li, M. Cheng, J. Hao, C. Wang, G. Jia, C. Li, Chem. Sci. 6 (2015) 5578–5585.

Results and discussion



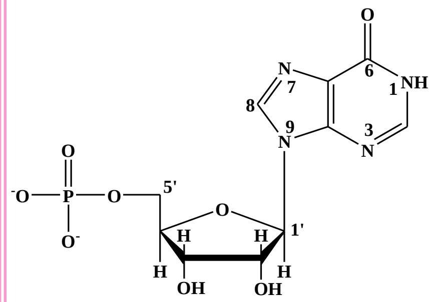
[$ZnCl_2$(terpy)] [$CuCl_2$(terpy)]

Structures of the investigated complex

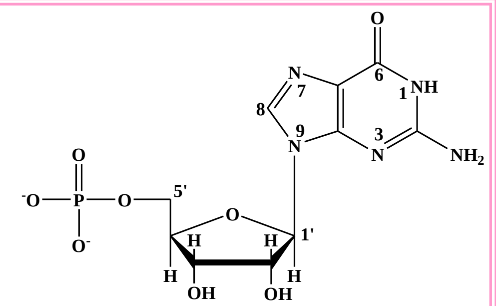
- ✓ Our aim of work is to investigate the mechanism of interaction between zinc(II) and copper(II) model complexes and biomolecules in proteins environment.
- ✓ The kinetics studies under physiological conditions were performed to provide more information for understanding structure-reactivity correlation between model cofactors pentacoordinated [$ZnCl_2$(terpy)] and [$CuCl_2$(terpy)] complexes and biological relevant nucleophiles.

Results and discussion

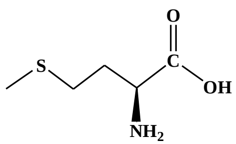
The substitution reactions include two steps both depending of the biomolecules concentration.



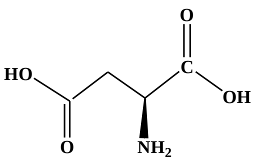
inosine-5'-monophosphate (5'-IMP)



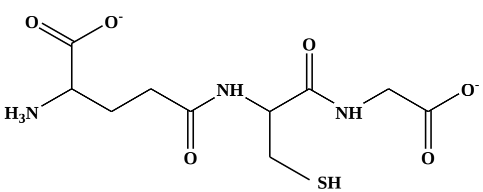
guanosine-5'-monophosphate (5-GMP)



L-methionine (L-Met)



DL-aspartic acid (DL-Asp)



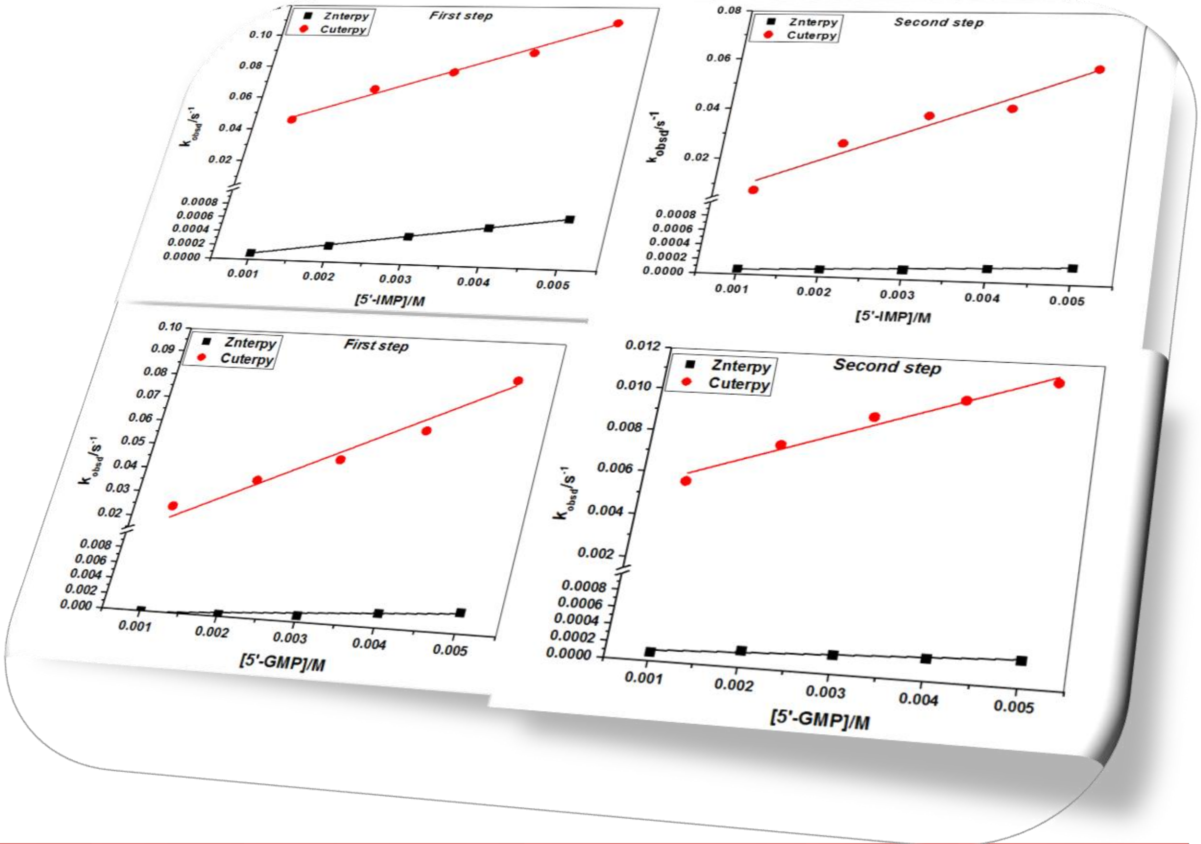
glutathione (GSH)

Structures of the investigated biomolecules

Results and discussion

✓ The so-obtained pseudo-first order rate constants, k_{obsd1} and k_{obsd2}, calculated from the kinetic traces (absorbance/time traces) were plotted versus the concentrations of the entering nucleophiles.

✓ A linear dependence on the biomolecule concentration was observed for the reactions with DNA constituent (5’-IMP and 5’-GMP) and amino-acids (L-Met and DL-Asp).



Pseudo-first order rate constants as a function of nucleophile concentration for the first and second substitution reactions with DNA constituent 5’-IMP and 5’-GMP at pH 7.38 .

Results and discussion

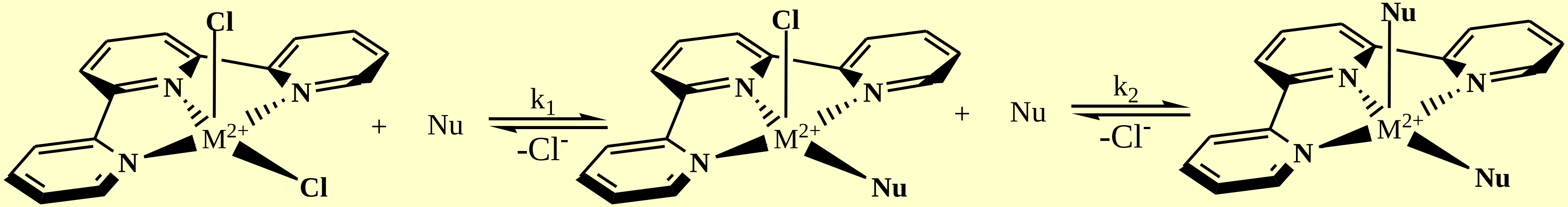
[$ZnCl_2$(terpy)]		
Nu	$10^2\ k_1 (M^{-1}s^{-1})$	$10^2\ k_2\ (M^{-1}s^{-1})$
5'-IMP	15.4 ± 0.1	4.1 ± 0.1
5'-GMP	67 ± 9	4.9 ± 0.1
L-Met	224 ± 31	73 ± 19
DL-Asp	7530 ± 449	685 ± 80

Tables 1 and 2
Second-order rate constants of the [$ZnCl_2$(terpy)] and [$CuCl_2$(terpy)] complexes with biomolecules: 5'-IMP, 5'-GMP, L-Met and DL-Asp at pH 7.38.

[$CuCl_2$(terpy)]				
Biomolecule	$10^2\ k_1 (M^{-1}s^{-1})$	$10^2\ k_{-1} [Cl^-](M^{-1}s^{-1})$	$10^2\ k_2\ (M^{-1}s^{-1})$	$10^2\ k_{-2} [Cl^-](M^{-1}s^{-1})$
5'-IMP	1517 ± 90	3.2 ± 0.2	1139 ± 141	-
5'-GMP	1543 ± 261	-	134 ± 11	0.47± 0.03
L-Met	2062 ± 202	-	359 ± 40	-
DL-Asp	8389 ± 1122	8.7 ± 0.4	4832 ± 393	3.5 ± 0.1

Results and discussion

Proposed mechanism of the substitution reactions:

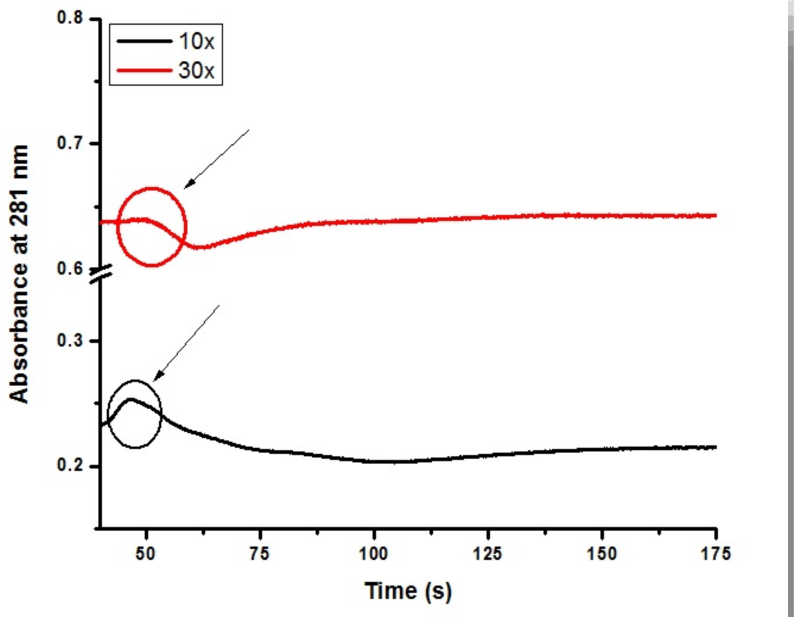


M= Zn, Cu
Nu= 5'-IMP, 5'-GMP, L-Met, DL-Asp

✓ **Coordination of DNA constituent to Cu(II) is occurring trough phosphate group while coordination to Zn(II) complexes takes via N7 atoms for the first reaction [9].**
✓ **The coordination of L-Met and DL-Asp takes place via *O*-carboxylate donor atoms, formation of chelate *O-N*-amine has not been observed [10].**

[9] F. Arjmand, S. Paraveen, RSC. Adv. 2 (2012) 6354-6362.
[10] C. Z. Gomez-Castro, A. Vela, L. Quintanar, R. Grande-Aztatzi, T. Mineva, A. Goursot, J. Phys. Chem. B 118 (34) (2014) 10052-10064.

Results and discussion



Time traces obtained for the reaction of 0.02 mM GSH and 10 and 30-fold excess of the concentration of $[ZnCl_2(terpy)]$ complexes at pH 7.38 (the arrows point to the rise and fall in absorbance).

- ✓ For the substitution reactions between $[ZnCl_2(terpy)]$ and glutathione, first-order linear dependence, k_{obsd1} on the complex concentration was observed at low concentration. At higher concentration, saturation kinetics was obtained.
- ✓ Fast pre-equilibrium formation of an intermediate pseudo-octahedral complex was observed, followed by rearrangement to the final complex whereas one chloride ion is substituted by GSH.
- ✓ For the reactions between $[CuCl_2(terpy)]$ and glutathione, linear dependence on the complex concentration was observed for both reaction steps.

Conclusions

- ✓ Higher reactivity of [$CuCl_2$(terpy)] then [$ZnCl_2$(terpy)] toward biologically relevant nucleophiles was obtained.

- ✓ The substitution reactions includes two reactions steps both mostly depend on biomolecules concentration.

- ✓ The second-order rate constants for the first reaction step follow the order of reactivity: GSH > DL-Asp > L -Met > 5'-GMP ~ 5'-IMP for the [$CuCl_2$(terpy)] complex, while for [$ZnCl_2$(terpy)] the order of reactivity is: DL-Asp > L -Met > GSH ~ 5'-GMP > 5'-IMP.

- ✓ The π-acceptor properties of the tridentate N-donor chelate (terpy) predominantly control the overall reaction pattern.

- ✓ The different mechanism of interactions of the pentacoordinate complexes with 5'-GMP, 5'-IMP and GSH have been obtained.

Acknowledgments

The authors gratefully acknowledge financial support from State University of Novi Pazar, Novi Pazar, Republic Serbia and T. Soldatović also gratefully acknowledges financial support from Ministry of Education, Science and Technological Development, Republic of Serbia (Project No. 172011).