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

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Abstract: The kinetics and mechanism of the substitution reactions of dichloro [$ZnCl_2$(terpy)] and [$CuCl_2$(terpy)] (terpy = 2,2′:6′,2′′-terpyridine) with biologically relevant ligands have been investigated 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 [$CuCl_2$(terpy)] is more reactive then [$ZnCl_2$(terpy)] complex. 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.

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

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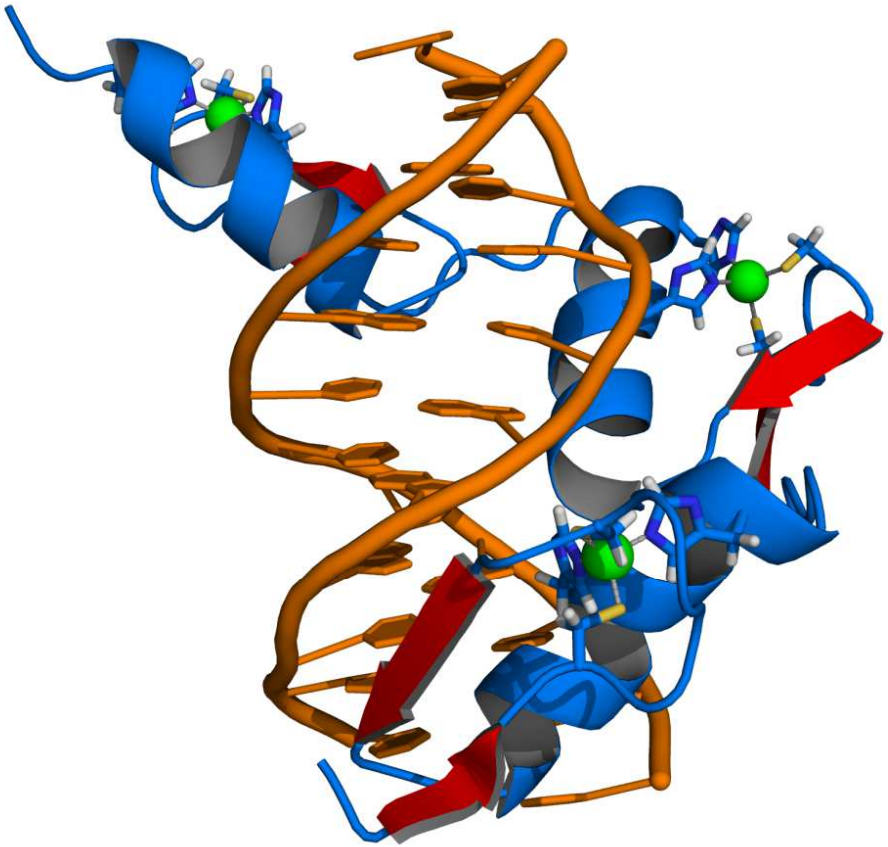
Introduction

✓ Transition metal compounds play crucial role as a cofactor in metalloproteins [1]. They have unique role in diverse biological activities. Two essential metal ions zinc and copper have important role in enzyme activity, catalytic, regulatory function, oxidative-reductive processes and etc [1].

✓ Biometal ions exist in single oxidation states such as zinc(II), which plays important role as a structural element in zinc-fingers, hydrolases, peptidases, anhydrases, in gene regulation, etc [1].

✓ As a catalytic cofactor Cu(II) is required in metalloproteins, plays important role in biological oxidation-reduction reactions, in electron transfer, because exists in multiple oxidation states 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.
[2] A.I. Anzellotti, N.P. Farrell, Chem. Soc. Rev. 37 (2008) 1629–1651.

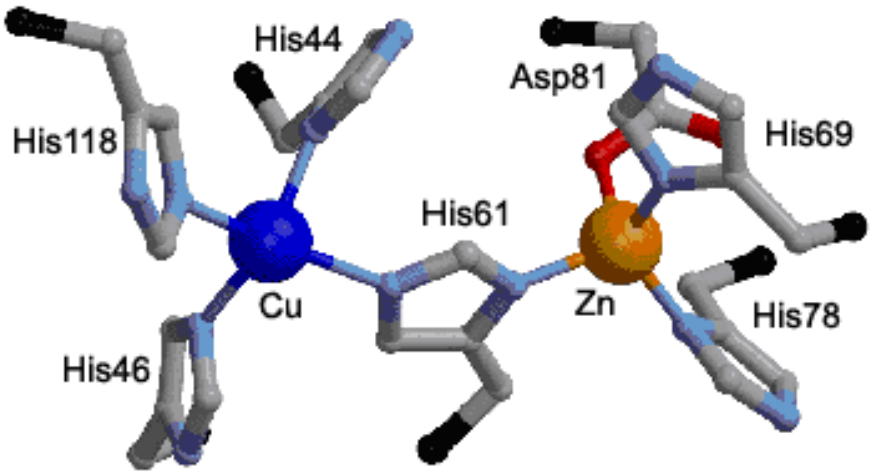


Zinc-finger-DNA complex

✓ Zinc proteins are involved in control of the nucleic acid replication, transcription and repair, are implicated in many diseases and health complications because of that are recognized as medicinal target [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 cell 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

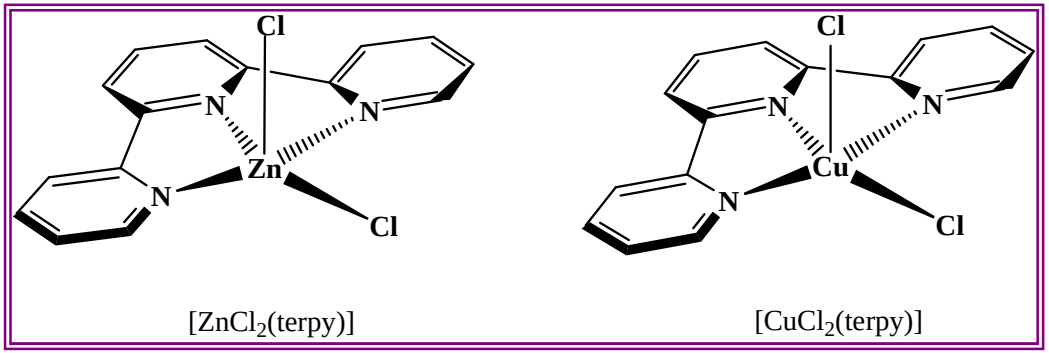
✓ Cu(II) as active centre is present in Cu/Zn-superoxide dismutase (SOD1) located in cytoplasm and mitochondria. SOD1 has antioxidant defence function, in regard to free radical detoxification [6].

✓ Copper, also, has importance in cancer development and progression and serves as a limiting factor for multiple aspects of tumour progression, growth, angiogenesis and metastasis [6].

✓ Many studies are focused to design appropriated cofactors (e.g. Cu(II)-terpyridine complex) for G-quadruplex DNA metalloenzymes for enantioselective catalysis [7,8].

[6] D. Denoyer, S. Masaldan, S. La Fontaine, M.A. Cater, Metallomics 7 (2015) 1459– 1476.
[7] J. Bos and G. Roelfes, Curr. Opin. Chem. Biol. 19 (2014) 135-143.
[8] Y. Li, M. Cheng, J. Hao, C. Wang, G. Jia, C. Li, Chem. Sci. 6 (2015) 5578–5585.

Results and discussion



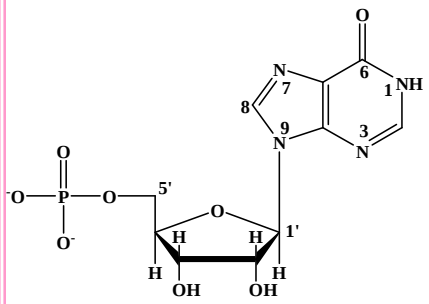
Structures of the investigated complex

✓ Our aim of work is to investigate the mechanism of interaction between zinc(II) and copper(II) complexes and biomolecules in proteins environmental.

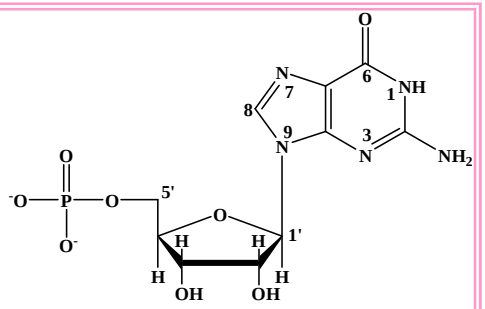
✓ The kinetics studies under physiological conditions were performed to provide more information for understanding structure-reactivity correlation between model cofactors pentacoordinated $[ZnCl_2(terpy)]$ and $[CuCl_2(terpy)]$ complexes and biological relevant nucleophiles.

Results and discussion

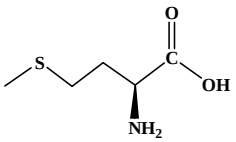
The substitution reactions include two steps. Both steps are depending of the biomolecules concentration.



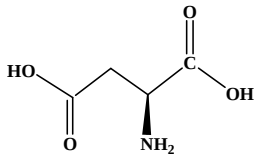
inosine-5'-monophosphate (5'-IMP)



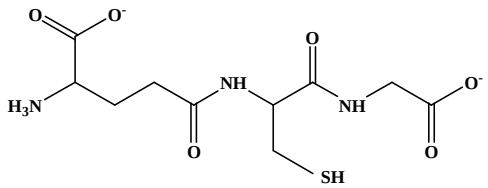
guanosine-5'-monophosphate (5-GMP)



L-methionine (L-Met)



DL-aspartic acid (DL-Asp)



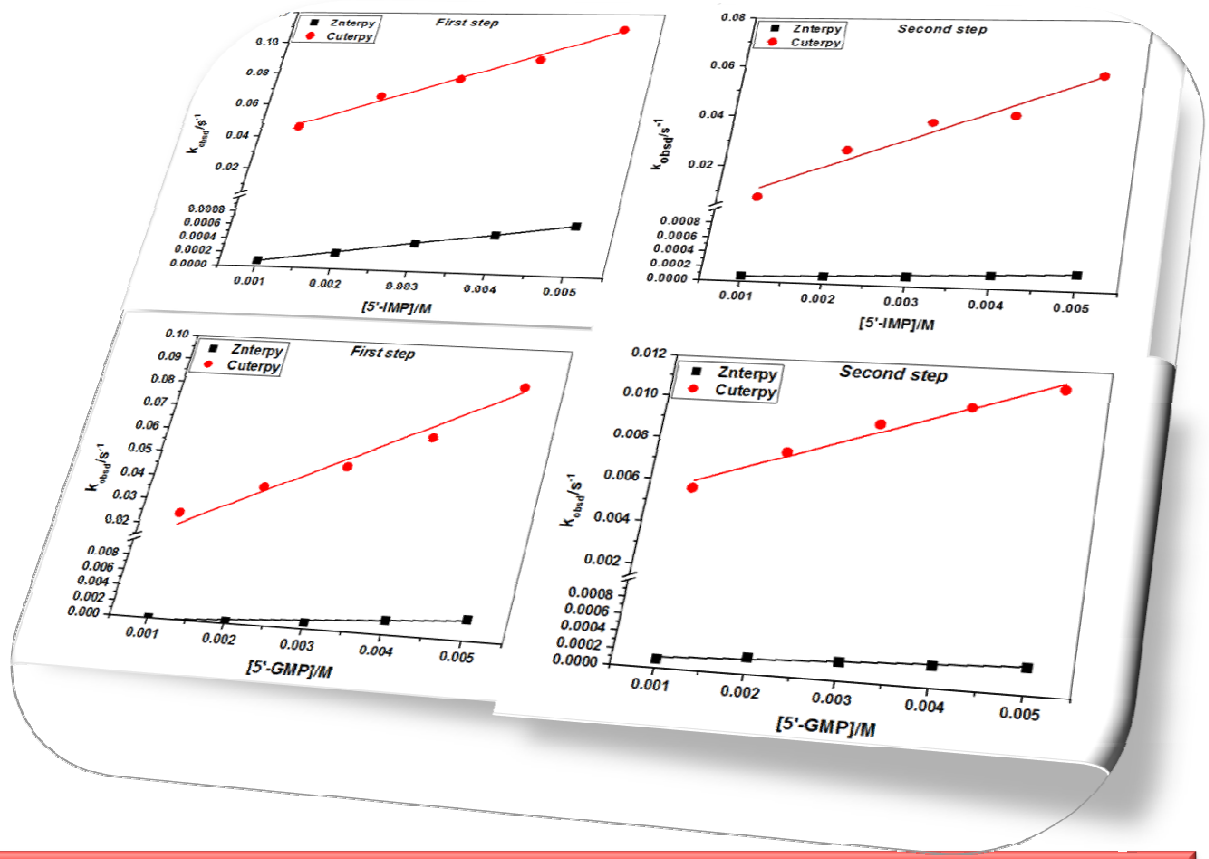
glutathione (GSH)

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

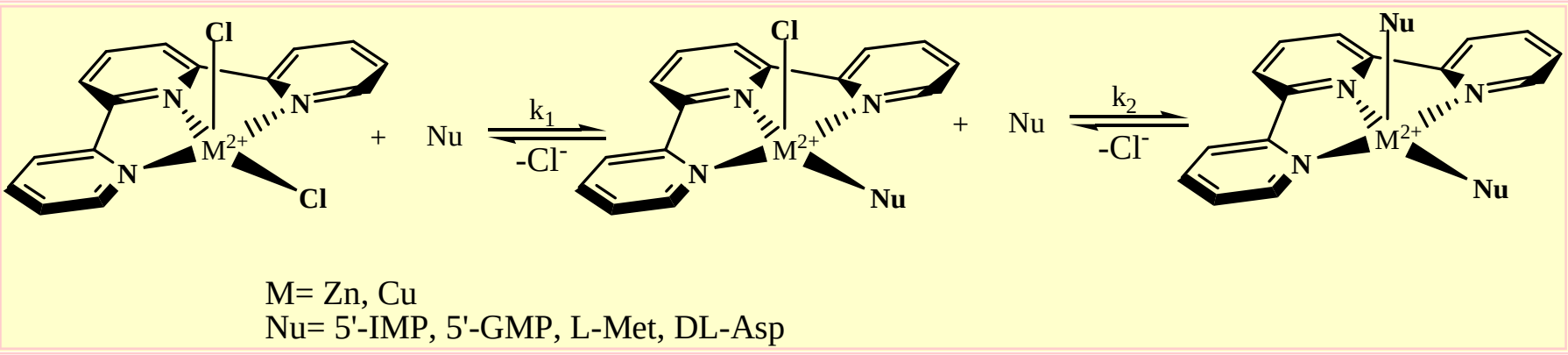
[$ZnCl_2$(terpy)]		
Biomolecule	$10^2 k_1 (M^{-1}s^{-1})$	$10^2 k_2 (M^{-1}s^{-1})$
5'-IMP	15.4 ± 0.1	4.1 ± 0.1
5'-GMP	67 ± 9	4.9 ± 0.1
L-Met	224 ± 31	73 ± 19
DL-Asp	7530 ± 449	685 ± 80

Tables 1 and 2
Second-order rate constants for the reactions of [$ZnCl_2$(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:



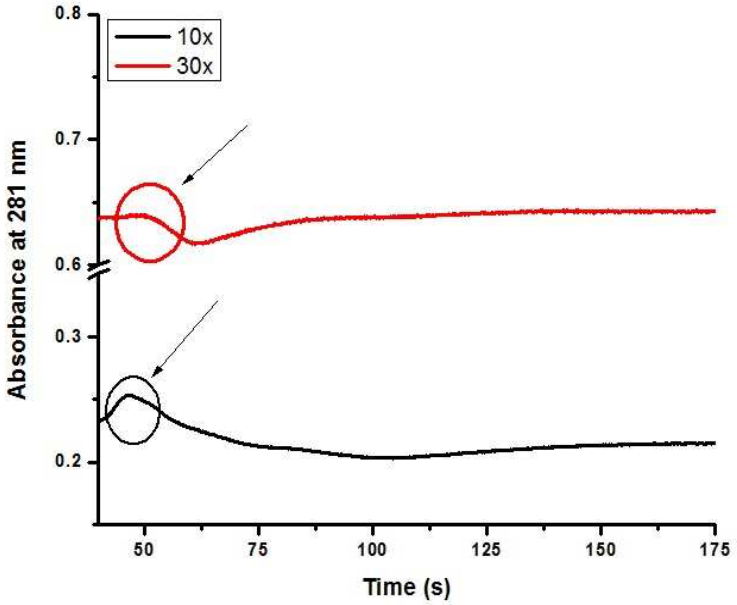
M= Zn, Cu
Nu= 5'-IMP, 5'-GMP, L-Met, DL-Asp

✓ **Coordination of DNA constituent to Cu(II) is occurring through 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*-ammine hasn't 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 with 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, at low concentration was observed. At higher concentration saturation kinetics was obtained.

✓ Fast pre-equilibrium formation of intermediate, pseudo-octahedral complex, was observed, followed by rearrangement to final complex whereas one chloride is substituted by GSH.

✓ For the reactions between [$CuCl_2$(terpy)] and glutathione linear dependence on the complex concentration was observed for the both reaction steps.

Conclusions

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

✓ The substitution reactions include 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 mechanisms of interactions of the pentacoordinate complexes with 5'-GMP, 5'-IMP and GSH have been obtained.

Acknowledgments

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