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Interaction of Zinc(II) Complexes with Relevant Nitrogen Nucleophiles under Physiological Conditions

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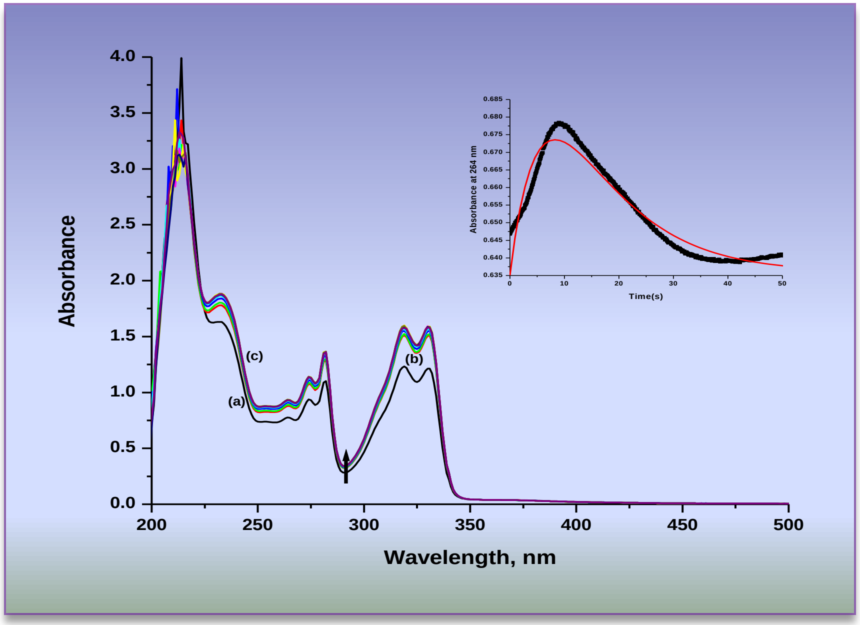
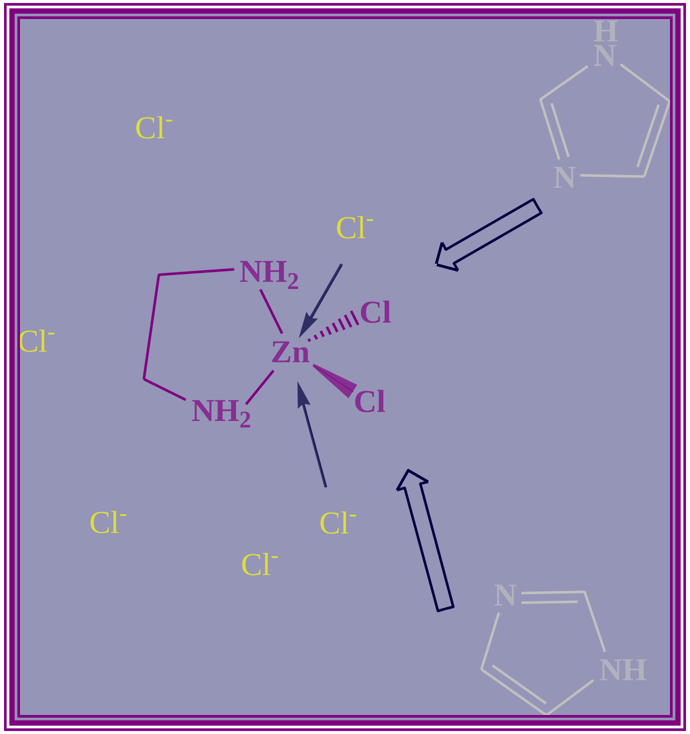




Abstract: The mole-ratio method was used for determining metal-ligand stoichiometry between $[ZnCl_2(en)]$ (where en= 1,2-diaminoethane or ethylenediamine) and imidazole at pH 7.2 in the presence of different chloride concentrations. The results indicated step-wise formation of 1:1 and 1:2 complexes in the presence of 0.010 M NaCl and 1:1 complexes in the presence of 0.001 M NaCl. Those results are correlated with additional coordination of chlorides in the first coordination sphere and with changes in coordination geometry. In the presence of 0.001 M NaCl, five-coordinate complex anion $[ZnCl_3(en)]^-$ is formed initially, and then substitution reaction with imidazole occurred. In the presence of 0.010 M NaCl the octahedral complex anion $[ZnCl_4(en)]^{2-}$ formed.

The kinetics of ligand substitution reactions between complex and relevant nitrogen nucleophiles such as imidazole, 1,2,3-triazole and L-histidine were investigated at pH 7.2 as a function of nucleophile concentration in the presence of 0.001 M and 0.010 M NaCl. The reactions were followed under *pseudo*-first-order conditions by UV-vis spectrophotometry. The substitution reactions included two steps of consecutive displacement of chlorido ligands and changes in coordination geometry of [ZnCl2(en)] complex. Results are discussed in terms of mechanisms of interactions between potential antitumor zinc-based drugs and biomolecules.

Keywords: Zinc; Imidazole; 1,2,3-Triazole; L-Histidine;

Introduction

✓ Zinc is implicated as an important cytotoxic/tumor suppressor agent in several cancers [1]

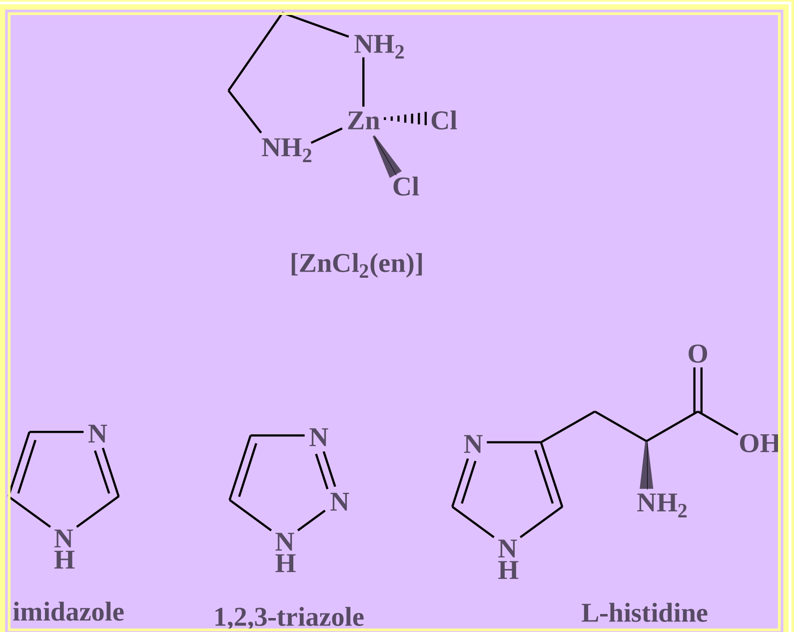
✓ Cellular zinc levels are markedly decreased in prostate cancer, because the concentration of zinc that exists in the normal prostate epithelial cells is cytotoxic in the malignant cells [2]

✓ Promising anticancer agents could be the zinc-based compounds

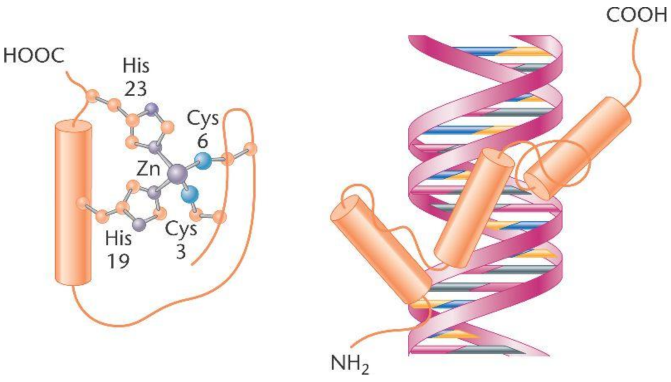
✓ The mechanism of potential anticancer activity of zinc(II) complexes could be connected to the peculiar properties of the coordination compounds of the zinc(II) ion, because of the potential formation of coordination compounds in which zinc(II) ion can readily accommodate four-, five-, or six molecules [3]

[1] Costello, L. C. and Franklin, R.B. (2012) *Expert Rev Anticancer Ther.*, **12(1)**, 121–128.
[2] Costello, L. C., and Franklin, R.B. (2006) *Mol. Cancer,* **5(17)**, 1-13.
[3] Bertini, I., Luchinat,C., Rosi, M., Sgamellotti, A. and Tarantelli F. (1990) *Inorg.. Chem.*, **29**, 1460-1463.

Results and discussion



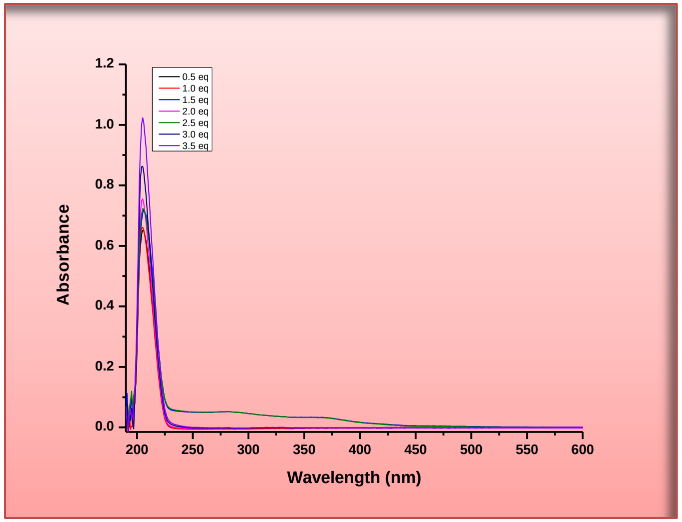
Structures of the investigated complex and nucleophiles

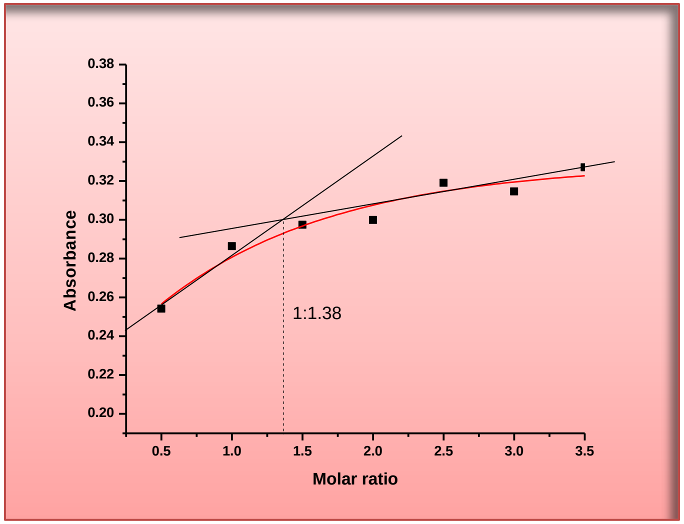


✓ The main goal of these studies was to determine metal-ligand stoichiometry between different zinc(II) complexes and imidazole, as well as, to investigate the kinetics and mechanism of ligand-substitution reactions between zinc(II) complexes and relevant nitrogen nucleophiles under physiological conditions

Results and discussion

Step-wise formation of 1:1 and 1:2 complexes in the presence of 0.010 M NaCl and 1:1 complexes in the presence of 0.001 M NaCl between $[ZnCl_2(en)]$ and Imidazole



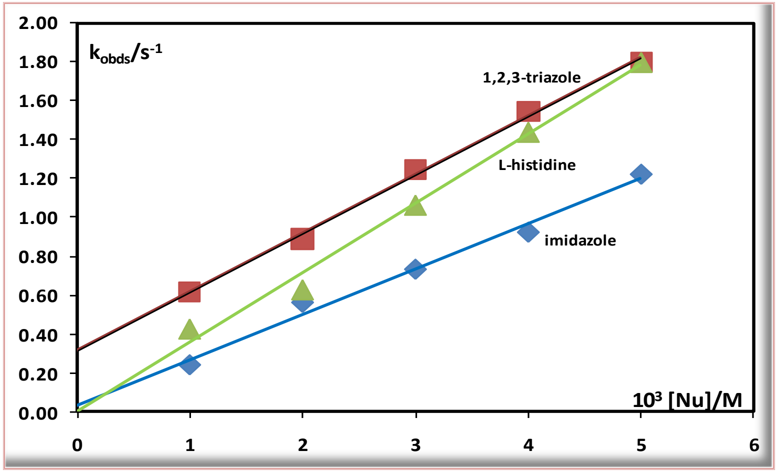


Titrations of $[ZnCl_2(en)]$ with imidiazole as monitored by UV-vis spectra. Left: $[ZnCl_2(en)]$- imidiazole, Right: Cross-section of UV-vis spectra at 200 nm in presence of 0.001 M NaCl

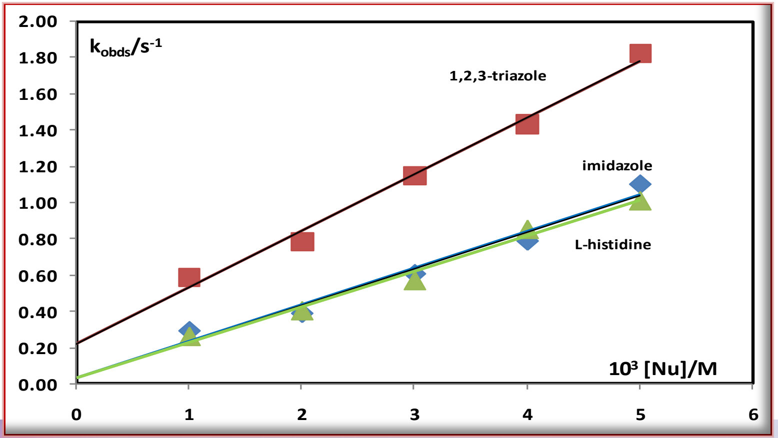
Results and discussion

0.001 M NaCl

The kinetics of ligand substitution reactions between complex and relevant nitrogen nucleophiles such as imidazole, 1,2,3-triazole and L-histidine were investigated at pH 7.2 as a function of nucleophile concentration in the presence of 0.001 M and 0.010 M NaCl



0.010 M NaCl



Results and discussion

Second-order rate constants for the first and second substitution reactions between zinc(II) complex and imidazole, 1,2,3-triazole, L-histidine at pH 7.2 (0.025 M Hepes buffer) in the addition of 0.001 and 0.010 M NaCl at 295 K

$[ZnCl_2(en)]$ 1mM	imidazole	1,2,3- triazole	L-histidine
$k_1^{295}/M^{-1}s^{-1}$	233 ± 15	301 ± 10	355 ± 20
$10^2\ k_{-1}^{295}[Cl^-]/M^{-1}s^{-1}$	-	0.31± 0.03	-
$k_2^{295}\ /M^{-1}s^{-1}$	82 ± 8	15.9 ± 0.3	49 ± 3
$10^2\ k_{-2}^{295}[Cl^-]/M^{-1}s^{-}$		0.20 ± 0.01	0.057 ± 0.009
$[ZnCl_2(en)]$ 10mM	imidazole	1,2,3- triazole	L-histidine
$k_1^{295}/M^{-1}s^{-1}$	202 ± 21	311 ± 18	195 ± 13
$10^2\ k_{-1}^{295}[Cl^-]/M^{-1}s^{-1}$	-	0.22 ± 0.06	-
$k_2^{295}\ /M^{-1}s^{-1}$	12 ± 1	7 ± 1	49 ± 5
$10^2\ k_{-2}^{295}[Cl^-]/M^{-1}s^{-}$	0.024 ± 0.004	0.033 ± 0.003	0.051 ± 0.014

Conclusions

✓The mole-ratio method was used for determining metal-ligand stoichiometry between $[ZnCl_2(en)]$ imidazole at pH 7.2 in the presence of different chloride concentration

✓The results indicated step-wise formation of 1:1 and 1:2 complexes with imidazole in the presence of 0.010 M NaCl and 1:1 complexes in the presence of 0.001 M NaCl. Those results are correlated with additional coordination of chlorides in the first coordination sphere and with changes in coordination geometry

✓ In the presence of 0.001 M NaCl five-coordinate complex anion $[ZnCl_3(en)]^-$ is formed initially, and then substitution reaction with imidazole occurred. In the presence of 0.010 M NaCl chloride the octahedral complex anion $[ZnCl_4(en)]^{2-}$ formed

✓The substitution reactions included two steps of consecutive displacement of chlorido ligands with changes in coordination geometry of $[ZnCl_2(en)]$ complex

✓The order of reactivity of the investigated nucleophiles for the first reaction step toward for $[ZnCl_2(en)]$ complex in the presence of 0.001 M NaCl is L-histidine > 1,2,3- triazole > imidazole, while in the presence of 0.010 M NaCl 1,2,3- triazole > imidazole > L-histidine

Acknowledgments

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