Current Chinese Science, 2021, *1*, 550-557

RESEARCH ARTICLE

Investigation of Substitution Reactions Between Zinc(II) Complexes with Different Geometries and N-Bonding Nucleophiles

Tanja Soldatović[1,*] and Enisa Selimović[1]

[1]*Department of Chemical-Technological Sciences, State University of Novi Pazar, Vuka Karadžića bb, Novi Pazar 36300, Serbia*

Abstract: ***Aims*:** The study aimed at investigating interactions between zinc(II) complexes with different geometrical structures and relevant nitrogen donor nucleophiles at physiological pH.

***Background*:** Lack of clear distinction between the therapeutic and toxic doses of platinum drugs is a major challenge for the design of novel non-platinum DNA and protein targeting metal-based anticancer agents. The non-platinum antitumor complexes could be alternatives to platinum-based drugs due to their better characteristics and different mechanisms of action.

***Objective*:** This study could provide more information regarding the design of future zinc-based anticancer drugs, providing a better understanding of the mechanism of interactions between Zn(II) complexes and nitrogen-donor nucleophiles (important from the medical point of view), and clarifying the changes in geometrical structures of zinc(II) that are referred to structure-reactivity correlations.

***Methods*:** Mole-ratio method and UV-V is spectroscopic kinetic method have been used.

***Results*:** The results indicated additional coordination of chlorides in the first coordination sphere with changes in coordination geometry and formation of the octahedral complex anion $[ZnCl_4(en)]^{2-}$ while the excess of chloride did not affect the square-pyramidal structure of $[ZnCl_2(terpy)]$. The substitutions of studied complexes and relevant nucleophiles proceeded in two consecutive reaction steps that depended on the nucleophile concentration. Octahedral complex anion $[ZnCl_4(en)]^{2-}$ forms rapidly and all substitution processes of this complex species should be considered. We assume that the first reaction step is accompanied by the dissociation of chloride ligands. Nucleophile 1,2,4-triazoles have shown the highest affinity toward $[ZnCl_2(en)]$, and rates of both steps were almost of the same value, indicating parallel reactions.

***Conclusion*:** The different order of reactivity of relevant N-donor ligands toward $[ZnCl_2(en)]$ and $[ZnCl_2(terpy)]$ complexes for the first reaction step occurred because of the influence of different geometrical structures of complexes, while low reaction rates for the second reactions of $[ZnCl_2(en)]$ complex with imidazole and pyrazine were a consequence of interconversion between octahedral and tetrahedral structure during substitution processes.

ARTICLE HISTORY

Received: January 11, 2021
Revised: April 17, 2021
Accepted: April 22, 2021

DOI:
10.2174/2210298101666210623114234

Keywords: Zinc(II), nitrogen relevant nucleophiles, structure-reactivity correlation, kinetics, cancer chemotherapy, platinum drugs.

1. INTRODUCTION

The use of platinum metal-based drugs in cancer chemotherapy was extensively studied after the discovery of the therapeutic properties of *cis*-diamminedichloroplatinum(II) (*cis*-$[Pt(NH_3)_2Cl_2]$, cisplatin) by Rosenberg *et al.* [1, 2]. However, the clinical efficiency of platinum-based drugs is limited by toxic side effects. Lack of clear distinction between the therapeutic and toxic doses of platinum drugs is a major challenge for the design of novel metal-based anticancer agents diverse from platinum(II). The non-platinum antitumor complexes have gained huge interest due to different characteristics which contribute to the different mechanisms of action [3].

The intermediate Lewis acid zinc(II) is redox inert and owns flexible coordination geometry; because of these facts, zinc(II) is a suitable cofactor in several proteins that perform essential biological functions [3]. Also, it has been discov-

*Address correspondence to this author at the Department of Chemical-Technological Sciences, State University of Novi Pazar, Vuka Karadžića bb, 36300 Novi Pazar, Serbia; Tel: +381-20-317-754; Fax: +381-20-337-669; E-mail: tsoldatovic@np.ac.rs

2210-2914/21 $65.00+.00

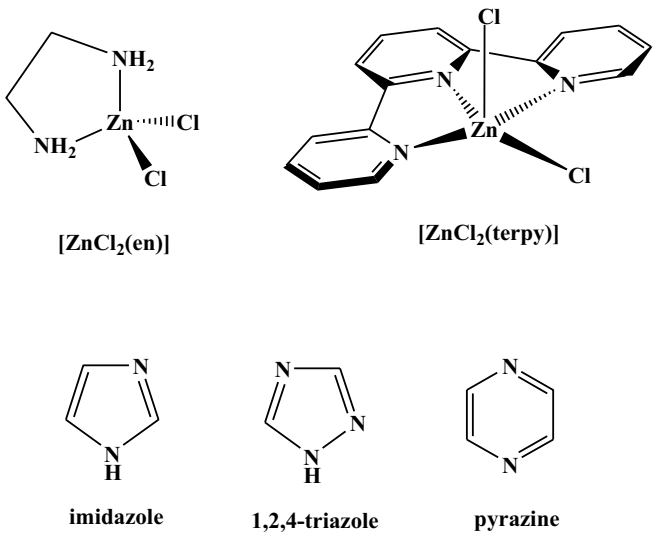

Fig. (1). Investigated complexes and nucleophiles along with the adopted abbreviation.

ered that zinc plays the role of a cytotoxic/tumor suppressor agent in several cancers [4]. Zinc(II) complexes could be potentially utilized as drugs with radioprotective and bioimaging [5], antibacterial or antimicrobial [6], antidiabetic, insulin-mimetic [7] and tumor photosensitizer [8] functions. The zinc(II) complexes are kinetically labile with the possibility of geometrical changes. The mechanism of antitumor effects of zinc(II) coordination compounds could be linked with the ability of changes in geometry (tetrahedral, five-coordinate, octahedral), which will have a diverse affinity toward donor site of biologically relevant nucleophiles [9, 10].

Investigation of the mechanism of interactions between zinc(II) complexes and bio-molecules provides valuable information regarding the synthesis of novel drugs. The study on substitution reactions between zinc(II) complexes under physiological conditions with nitrogen-donor ligands, such as imidazole, 1,2,4-triazole and pyrazine, is missing. Imidazole and triazoles have similar affinities over a large range of pH toward zinc enzymes and they are well-known inhibitors for enzymes [3].

Our previous results have indicated interconversion between tetrahedral $[ZnCl_2(en)]$ and octahedral $[ZnCl_4(en)]^{2-}$ complex in the presence of different chloride concentrations at pH 7.2 in 25 mM Hepes buffer [11, 12]. The coordination geometry of complex $[ZnCl_2(terpy)]$ was not changed due to the strong π-acceptor ability of the tridentate chelate 2,2′:6′,2”-terpyridine that stabilizes the square-pyramidal geometry [11]. In the presence of 1 mM NaCl according to metal-ligand stoichiometry between $[ZnCl_2(terpy)]$ and imidazole, the five-coordinate $[Zn(terpy)(imidazole)_2]$ complex was formed [11]. The investigation of the cytotoxic activity of zinc(II) complexes has shown the ability of complexes to reduce cell viabilities. The $[ZnCl_2(terpy)]$ complex was significantly cytotoxic on MDA-MB-231 cells (human breast cancer cell line) after 72 h and human colon cancer cell line, HCT-116, after 24 h without dose dependence, which can be linked with square-pyramidal geometry and absence of changes in the structure [13].

In order to complete our investigation of substitution reactions between zinc(II) complex and some biologically relevant nucleophiles, we investigated kinetics at pH 7.4 in 10 mM Tris-HCl buffer in the presence of 1 mM NaCl and metal-ligand stoichiometry between Zn(II) complexes and chloride by the mole-ratio method. The ligands, imidazole, 1,2,4-triazole and pyrazine, are chosen because of their medical applications (antifungal, antitumor, antibiotic, and diuretic applications).

The structures of the complexes and the selected nucleophiles are shown in Fig. (**1**).

2. MATERIAL AND METHODS

2.1. Experimental

All the reagents used in this study obtained from Sigma-Aldrich (*St. Louis, USA*) and Merck (*Darmstadt, Germany*) were of analytical grade or higher purity. Chemical analyses were performed on a Carlo Erba Elemental Analyser 1106. UV-Vis spectra were recorded on Uvikon XS and Shimadzu UV250 diode-array spectrophotometers equipped with thermostated 1.00 cm quartz Suprasil cells. The ^{1}H NMR spectra were acquired on a Varian Gemini-2000 spectrometer at 200 MHz. All chemical shifts have been referenced to TSP (trimethylsilylpropionic acid) in D_2O and downfield shifts were recorded as positive numbers. The pH meter Jenway 4330 with a combined Jenway glass microelectrode calibrated with standard buffer solutions of pH 4.0, 7.0, and 10.0 (Merck) was used for pH measurements. The KCl solution in the reference electrode was replaced with a 3 M NaCl electrolyte to prevent precipitation of $KClO_4$ during use [14, 15].

2.1.1. Synthesis of Complexes

The complexes $[ZnCl_2(en)]$ and $[ZnCl_2(terpy)]$ were synthesized according to procedures reported in the literature [16]. Calcd. for $C_2H_8Cl_2N_2Zn$ (%): N, 14.26; C, 12.23; H, 4.11. Found: N, 14.29; C, 12.19; H, 4.13. Characterization results for $[ZnCl_2(en)]$ complex were: ^{1}H NMR (D_2O, 295 K): d 4.71 (*t*, 2H), 5.81 (*s*, H) ppm; FT-IR (KBr): 3287 and

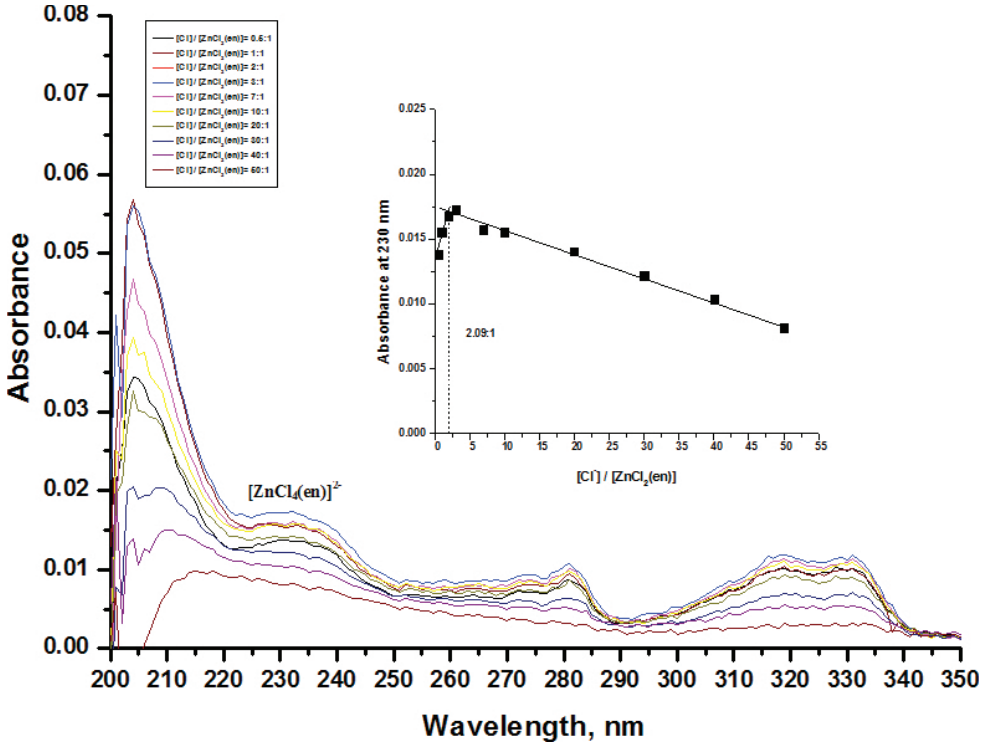

Fig. (2). Absorbance changes for the reactions between [$ZnCl_2$(en)] complex (0.1 mM) and chloride for different molar ratios at pH 7.4 (10 mM M Tris-HCl buffer) and 295 K. Inset: *Stoichiometry of chloride-[$ZnCl_2$(en)] complex by mole-ratio method.* (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3232 n(N-H, NH_2), 2953 n(C_{sp3}-H), 1138 n(C-N), 658 n(Zn-N) cm^{-1}. Calcd. for $C_{15}H_{11}Cl_2N_3Zn$ (%): N, 11.37; C, 48.75; H, 3.00. Found: N, 11.21; C, 48.31; H, 3.12 [13]. The complex [$ZnCl_2$(terpy)] was also characterized by the same techniques; the results were: ^{1}H NMR (D2O, 295 K): d 8.99 (*d*, 1H), d 8.69 (*m*, 2H), 8.44 (*t*, 2H), 7.85 (*t*, 2H) ppm; FT-IR (KBr): 3063 n(C-H), 1595 and 1454 n(aromatic ring), 1051 n(C-N) , 778 n(Zn-N) cm^{-1} [13]. The geometries of the complexes have been investigated and have been assigned as tetrahedral [17a] and square-pyramidal [17b].

2.1.2. Mole Ratio Method

10 mL solutions of [$ZnCl_2$(en)] or [$ZnCl_2$(terpy)] with constant (0.1 mM) concentrations were prepared while the concentration of chloride varied in different molar ratios ([Cl^-] / [$ZnCl_2$(en)] = 0.5, 1, 2, 3, 7, 10, 20, 30, 40, 50) [18, 19]. The pH 7.4 was adjusted by Tris-HCl buffer (10 mM). In the wavelength range of 200 to 450 nm, the absorbance of the solutions was recorded. The absorbance at 230 nm was plotted *vs*. the molar ratio of the reactants (Fig. **2**). The absorbance increased up to the combining ratio, where the formed complex absorbed more than the initial. At this point, further addition of chloride had no great impact and less increase in absorbance has been observed. At the mole ratio corresponding to the combining ratio of the chloride/complex, the slope fell down.

2.1.3. Kinetics Measurements

The kinetics of substitution reactions for imidazole, 1,2,4-triazole and pyrazine nucleophiles was studied under *pseud*o-first-order conditions with respect to the nucleophile concentration, *i.e.* at least 10-fold times higher at pH 7.4 (10 mM Tris-HCl buffer) and at 295 K in the presence of 1 mM NaCl. The substitutions started in thermostated UV-Vis spectrophotometric cell by mixing equal volumes of complex and ligand solutions and were followed for at least eight half-lives at a suitable wavelength (Fig. (**3**), Electronic supplementary material Tables **S1-S6**). The obtained k_{obsd} values are provided in Tables **S1-S6** (Electronic supplementary material), and were calculated as the average value from three to five independent kinetic runs. All kinetic traces were fitted as double exponential function by the Origin 2016 program.

3. RESULTS AND DISCUSSION

3.1. Mole-Ratio Method

In order to determine stoichiometry between Zn(II) complexes and chloride at pH 7.4 (10 mM Tris-HCl buffer), the molar concentration of Zn(II) was held constant, while the amount of chloride varied at 10 times higher compared to the initial complex concentration [18, 19]. The absorbance was monitored in a wavelength range from 200 to 450 nm for different molar ratios [Cl^-]/[$ZnCl_2$(en)] (Fig. **2**). The difference between the spectra was noticed in terms of the intensity of the absorbance, and the presence of mixed Cl-H_2O complexes was not confirmed. The equivalence point at 230 nm corresponds to the formation of 1:2 complex (Fig. **2**), which indicates that the presence of 1 mM NaCl affects the formation of $[ZnCl_4(en)]^{2-}$ species.

At the selected wavelength of 255 nm for [$ZnCl_2$(terpy)] complex, no equivalence point was observed (Fig. (S1), Electronic supplementary material), while the square-pyramidal geometry of complex remained unchanged. An

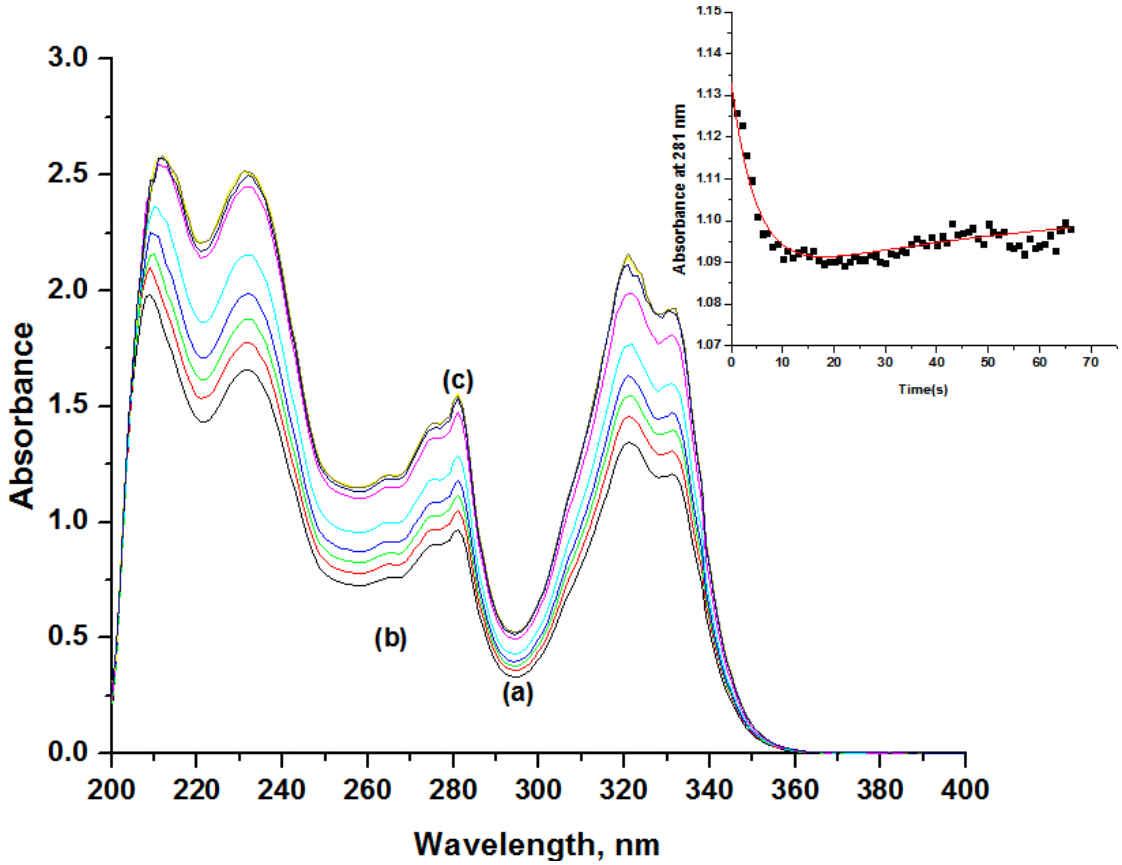

Fig. (3). Spectral changes of substitution reaction between [$ZnCl_2$(terpy)] complex (0.1 mM) and imidazole (4 mM) at pH 7.4 (10 mM Tris-HCl buffer) with the addition of 1 mM NaCl at 295 K. (**a**) Spectrum before the reaction; (**b**) spectrum obtained three seconds after mixing of the reactants; (**c**) spectrum obtained after 65 s. Inset: *time trace obtained for the reaction at 281 nm*. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

improved mole-ratio method for the identification of weak complexes in solution was used for the analysis of the obtained results [19] (Electronic supplementary material).

3.2. Kinetics Studies

Substitution reactions of investigated [$ZnCl_2$(en)] and [$ZnCl_2$(terpy)] complexes with N-bonding nucleophiles were monitored in the range of ca. 220-300 nm (Fig. (**3**). The results of mole-ratio studies confirmed the formation of $[ZnCl_4(en)]^{2-}$ anion in the presence of an excess of 1 mM chloride. The coordination number of Zn(II) changed from 4 to 6, and the geometry of the complex changed from tetrahedral to octahedral, as observed in our previous research [11]. The equilibrium between the tetrahedral and octahedral structures of Zn(II) complexes appeared in the solution [13]. The structure of [$ZnCl_2$(terpy)] complex remained square-pyramidal in the presence of an excess of chloride.

All kinetic traces were calculated as double exponential function (Fig. **3**). The *pseudo*-first-order rate constants, k_{obsd1} and k_{obsd2}, were calculated from the kinetic traces (absorbance/time traces) (Figs. (**4**, **5**) and Figs. (**S2-S3**), Electronic supplementary material).

Observed *pseudo*-first-order rate constants, k_{obsd1} and k_{obsd2}, were plotted versus the concentrations of investigated nucleophiles. A linear dependence on the nucleophile concentrations (Nu) for the first and second reactions was observed for all the reactions. According to Eqs. (1) and (2), from the slopes of the observed straight lines, the *second*-order rate constants, k_1 and k_2, were determined.

$$k_{obsd1} = k_1[Nu] + k_{-1} \quad (1)$$

$$k_{obsd2} = k_2[Nu] + k_{-2} \quad (2)$$

In the cases when linear fits passed through the origin, the possible parallel or backward reactions were insignificant or absent, *i.e.* k_{-1} and k_{-2} were negligible, and Eqs. (1) and (2) could be simplified to $k_{obsd1} = k_1[Nu]$ and $k_{obsd2} = k_2[Nu]$. The obtained rate constants are provided in Table **1**.

The ratio of k_{obsd1}/k_{obsd2} showed different manners of substitution reactions. The ratio around 2 to 6 indicates two parallel reaction paths, while when it is larger, 10-15 or even 20 to 60 (Tables **S1-S6**), the first reaction step is finished before the second one starts, which is typical for consecutive reactions. The observed small intercepts are associated with back-reaction with the excess chloride present in solution, in dichlorido [$ZnCl_2$(en)] complex with the formation of $[ZnCl_4(en)]^{2-}$ complex.

3.2.1. Substitution Reactions for [$ZnCl_2$(en)] Complex

According to the molar-ratio method, we assumed that the presence of 1 mM NaCl had an impact on the formation of octahedral complex anion $[ZnCl_4(en)]^{2-}$. All substitution reactions of this species could be considered. The additional

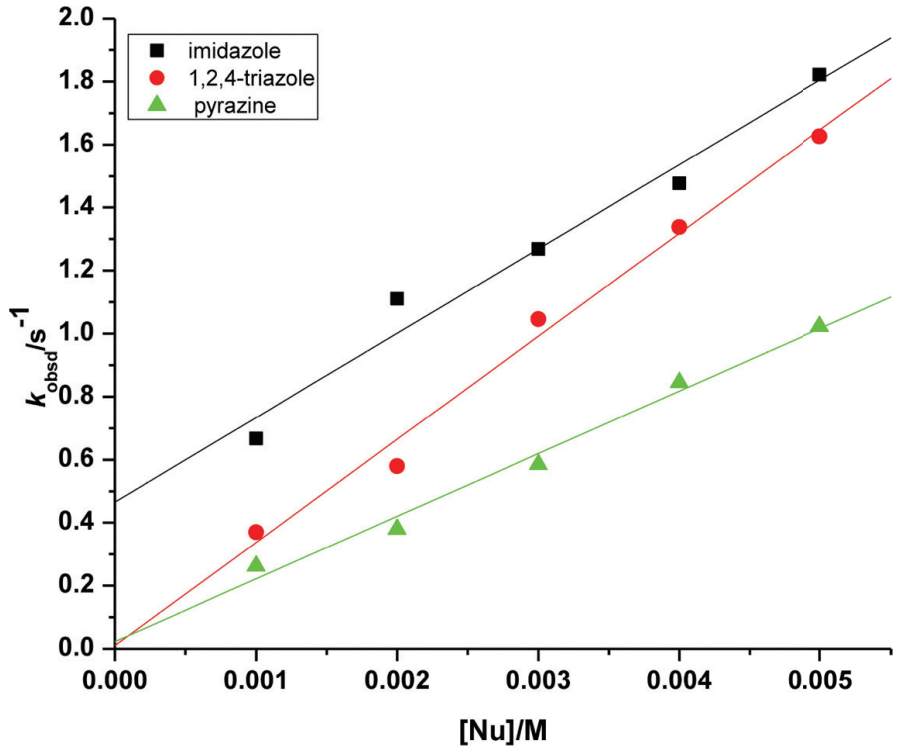

Fig. (4). *Pseudo*-first order rate constants plotted as a function of nucleophile concentration for the first reaction of the $[ZnCl_2(en)]$ complex by imidazole, 1,2,4-triazole and pyrazine at pH 7.4 (10 mM Tris-HCl buffer) with the addition of 1 mM NaCl at 295 K. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

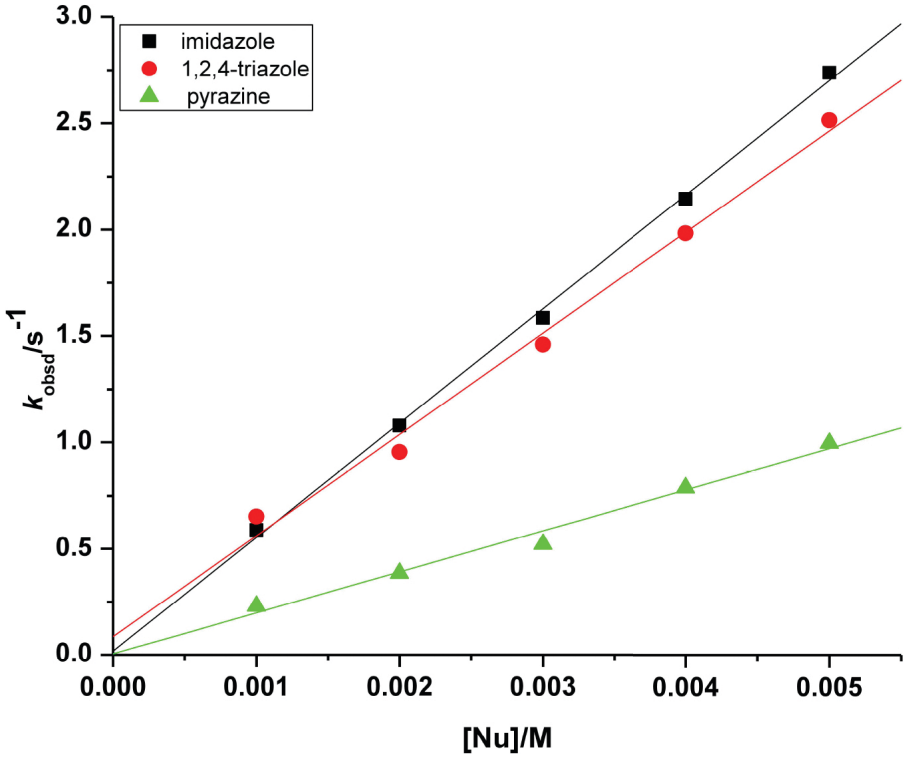

Fig. (5). *Pseudo*-first order rate constants plotted as a function of nucleophile concentration for the first reaction of the $[ZnCl_2(terpy)]$ complex by imidazole, 1,2,4-triazole and pyrazine at pH 7.4 (10 mM Tris-HCl buffer) with the addition of 1 mM NaCl at 295 K. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Second-order rate constants for the first and second substitution reactions between zinc(II) complexes and imidazole, 1,2,4-triazole and pyrazine at pH 7.4 (10 m M Tris-HCl buffer) with the addition of 1mM NaCl at 295 K.

$[ZnCl_2(en)]$	imidazole	1,2,4- triazole	pyrazine
$k_1^{295}/M^{-1}s^{-1}$	268 ± 26	327 ± 20	199 ± 13
$10^2\ k_{-1}^{295}[Cl^-]/M^{-1}s^{-1}$	47 ± 9	-	2.3 ± 0.4
$k_2^{295}/M^{-1}s^{-1}$	6.1 ± 0.3	172 ± 16	8.6 ± 0.5
$10^2\ k_{-2}^{295}[Cl^-]/M^{-1}s^{-1}$	0.58 ± 0.09	-	0.058 ± 0.001
$[ZnCl_2(terpy)]$	imidazole	1,2,4- triazole	pyrazine
$k_1^{295}/M^{-1}s^{-1}$	536 ± 12	475 ± 26	193 ± 14
$10^2\ k_{-1}^{295}[Cl^-]/M^{-1}s^{-1}$	-	-	-
$k_2^{295}/M^{-1}s^{-1}$	27 ± 2	60 ± 2	22 ± 1
$10^2\ k_{-2}^{295}[Cl^-]/M^{-1}s^{-1}$	14.7 ± 0.5	0.48 ± 0.01	10.4 ± 0.5

chloride ligands are kinetically labile and equal for parallel substitution routes (Scheme **1**), which is a consequence of large negative inductive effects of amino groups in ethylenediamine, *i.e.* the basicity of N-donors atoms increases and the interactions between Zn(II) and $-NH_2$ groups are stronger [11]. In Zn(II) complexes, there is no ligand field stabilization energy, and the coordination number is determined by a balance between bonding energies and repulsions among the ligands [3, 13]. Therefore, coordinated chloride ligands exchange rapidly because of their kinetic lability.

$$[Zn(L)Cl_4]^{2-} + Nu \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Zn(L)Cl(Nu)]^- + 3Cl^-$$

$$[Zn(L)Cl(Nu)]^- + Nu \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} [Zn(L)(Nu)_2] + Cl^-$$

L= ethylenediamine (en)

Nu= imidazole, 1,2,4-triazole and pyrazine

Scheme (1). Substitution reactions of formed $[ZnCl_4(en)]^{2-}$ complex with the nucleophiles, imidazole, 1,2,4-triazole and pyrazine, in the presence of 1 mM NaCl at pH= 7.4 (10 mM Tris-HCl buffer).

The first step of the substitution reactions could be interpreted as substitution of the axial chlorido ligand by the nucleophiles followed by dissociation of the two chlorido ligands, whereas the second step is the substitution of the last chlorido ligand [12]. The order of reactivity of the investigated nucleophiles for the first reaction step is 1,2,4-triazole > imidazole > pyrazine, while for the second reaction step, it is 1,2,4-triazole > pyrazine > imidazole. The second-order rate constants for 1,2,4-triazole in both reaction steps are similar in the order of magnitude (Table **1**), which indicates a parallel route of substitution and high affinity toward Zn(II).

It is well known that zinc is usually tetrahedrally coordinated in enzymes; also, it possesses five coordinates in some catalytic binding sites, but very rarely six coordinates [20, 21]. The lack of preference for a given coordinate number leads to the rapid exchange of coordinated ligands [3]. The free energies between six- and four-coordinate structures as a consequence of ligand addition/elimination have shown that the lowest-energy ground-state coordinate number of zinc is likely 4 in biological systems [22].

3.2.2. Substitution Reactions for [$ZnCl_2$(terpy)] Complex

The substitution reactions between $[ZnCl_2(terpy)]$ complex and nitrogen relevant nucleophiles occurred in two reactions. The presence of chloride in solution did not affect the geometrical structure; it remained square-pyramidal (Scheme **2**).

$$[Zn(L)Cl_2] + Nu \xrightarrow{k_1} [Zn(L)(Cl)(Nu)]$$

$$[Zn(L)(Cl)(Nu)] + Nu \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Zn(L)(Nu)_2]$$

L= 2,2′:6′,2″-terpyridine (terpy)

Nu= imidazole, 1,2,4-triazole and pyrazine

Scheme (2). Substitution reactions $[ZnCl_2(terpy)]$ complex with the nucleophiles: imidazole, 1,2,4-triazole and pyrazine in the presence of 1 mM NaCl at pH= 7.4 (10 mM Tris-HCl buffer).

The direct nucleophile substitution reaction is a major reaction pathway and the possible parallel or backward reactions are insignificant or absent. The observed intercepts for the second step could be ascribed to backward reactions with an excess of chloride present in the solution. The strong π-acceptor ability of the tridentate chelate 2,2′:6′,2″-terpyridine has an influence on the rates [23]. The order of reactivity of nitrogen relevant nucleophiles toward $[ZnCl_2(terpy)]$ complex for the first step is imidazole > 1,2,4-triazole > pyrazine, while for the second, it is 1,2,4-triazole > imidazole > pyrazine. If we compare obtained results in the present investigation with our previous results obtained from the aqueous solution [13, 23], we can conclude that the presence of chloride has a great influence on reaction rates [11, 13, 23]. The presence of chloride prevents the hydrolysis of $[ZnCl_2(terpy)]$ complex [11, 13, 23]. Hence in the presence of chloride, the substitution reaction is faster; this is associated with the absence of different hydrolytic species and parallel reactions that involve them.

The different order of reactivity of relevant nitrogen-donor ligands toward $[ZnCl_2(en)]$ and $[ZnCl_2(terpy)]$ complexes for the first reaction step could be explained by the influence of different geometrical structures of complexes (octahedral in the case of the excess of chloride and square-pyramidal). In the first step, we obtained the same order of magnitude for k_2, especially for pyrazine. The low reaction rates for the second reactions of $[ZnCl_2(en)]$ complex with imidazole and pyrazine could be the consequence of interconversion between octahedral and tetrahedral structures during substitution processes.

The obtained results indicate that the nature of inert ligand is very important for the design and synthesis of novel zinc(II) complexes with potential medical utilization. Intermolecular interactions such as π-π stacking interactions between zinc(II) and aromatic inert ligand could contribute to the stable geometrical structures of novel zinc(II) complexes and reaction rates. The molecule undergoes an arrangement of organic ligands and different supramolecular interactions, π···π interaction and H-bonding [24]. The novel direction in the design of antitumor agents is zinc-organic polymer/semiconductor nanoparticles [24, 25]. Specific properties of nanoparticles, such as their cytotoxicity and their physiochemical properties, make them a promising candidate for biomedical applications [25].

CONCLUSION

Two zinc(II) complexes with different geometrical structures have been investigated in order to define the metal-ligand stoichiometry and complex-formation reactions with relevant N-bonding nucleophiles at pH 7.4 in the presence of 1 mM chlorides. The results indicated additional coordination of chlorides in the first coordination sphere with changes in coordination geometry and formation of the octahedral complex anion $[ZnCl_4(en)]^{2-}$ while an excess of chloride did not affect the square-pyramidal structure of $[ZnCl_2(terpy)]$. We assume that the first reaction step of octahedral complex anion $[ZnCl_4(en)]^{2-}$is accompanied by dissociation of chloride ligands. Nucleophile 1,2,4-triazoles have shown the highest affinity toward $[ZnCl_2(en)]$, and rates of both steps were almost of the same value, which indicates parallel reactions. The different order of reactivity of relevant N-donor ligands toward $[ZnCl_2(en)]$ and $[ZnCl_2(terpy)]$ complexes for the first reaction step was observed due to the influence of different geometrical structures of complexes, while low reaction rates for the second reactions of $[ZnCl_2(en)]$ complex with imidazole and pyrazine were a consequence of interconversion between octahedral and tetrahedral structures during the substitution processes. This study provides useful information for the future design of potential zinc-based anticancer drugs in combination with ligands that already have medical applications.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data obtained or analyzed during this study are included in this published article.

FUNDING

The work was financially supported by the State University of Novi Pazar, Novi Pazar, Republic Serbia and Ministry of Education, Science and Technological Development, Republic Serbia.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise. Dr. T. Soldatović is a member of the editorial board of the Journal.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge financial support from the State University of Novi Pazar, Novi Pazar, Republic Serbia, and T. Soldatović also gratefully acknowledges financial support from the Ministry of Education, Science and Technological Development.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website.

REFERENCES

[1] Rosenberg, B.; Vancamp, L.; Krigas, T. Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode. *Nature,* **1965**, *205*, 698-699. http://dx.doi.org/10.1038/205698a0 PMID: 14287410

[2] Rosenberg, B.; VanCamp, L.; Trosko, J.E.; Mansour, V.H. Platinum compounds: A new class of potent antitumour agents. *Nature,* **1969**, *222*(5191), 385-386. http://dx.doi.org/10.1038/222385a0 PMID: 5782119

[3] Bertini, I.; Gray, H.B.; Stiefel, E.I.; Valentine, J.S. *Biological inorganic chemistry. Structure and reactivity*; University Science Books: Sausalito, CA, **2007**.

[4] Costello, L.C.; Franklin, R.B. Cytotoxic/tumor suppressor role of zinc for the treatment of cancer: An enigma and an opportunity. *Exp. Rev. Anticancer Ther.,* **2012**, *12*(1), 121-128. http://dx.doi.org/10.1586/era.11.190 PMID: 22149438

[5] (a) Emami, S.; Hosseinimehr, S.J.; Taghdisi, S.M.; Akhlaghpoor, S. Kojic acid and its manganese and zinc complexes as potential radioprotective agents. *Bioorg. Med. Chem. Lett.,* **2007**, *17*(1), 45-48. http://dx.doi.org/10.1016/j.bmcl.2006.09.097 PMID: 17049858
(b) Kumar, N.; Roopa, ; Bhalla, V.; Kumar, M. Beyond zinc coordination: Bioimaging applications of Zn(II)-complexes. *Coord. Chem. Rev.,* **2021**, *427*, 213550-213564. http://dx.doi.org/10.1016/j.ccr.2020.213550

[6] (a) Chohan, Z.H.; Arif, M.; Sarfraz, M. Metal-based antibacterial and antifungal amino acid derived Schiff bases: Their synthesis, characterization and *in vitro* biological activity. *Appl. Organomet. Chem.,* **2007**, *21*, 294-302. http://dx.doi.org/10.1002/aoc.1200
(b) Singh, V.P.; Katiyar, A. Synthesis, structural studies and bioactivity of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes with p-amino acetophenone salicyloyl hydrazone. *J. Coord. Chem.,* **2008**, *61*, 3200-3212. http://dx.doi.org/10.1080/00958970701598944

[7] (a) Nakayama, A.; Hiromura, M.; Adachi, Y.; Sakurai, H. Molecular mechanism of antidiabetic zinc-allixin complexes: Regulations of glucose utilization and lipid metabolism. *J. Biol. Inorg. Chem.,* **2008**, *13*(5), 675-684. http://dx.doi.org/10.1007/s00775-008-0352-0 PMID: 18288506
(b) Sakurai, H.; Yoshikawa, Y.; Yasui, H. Current state for the development of metallopharmaceutics and anti-diabetic metal complexes. *Chem. Soc. Rev.,* **2008**, *37*(11), 2383-2392. http://dx.doi.org/10.1039/b710347f PMID: 18949111

[8] Huang, Q.; Pan, Z.; Wang, P.; Chen, Z.; Zhang, X.; Xu, H. Zinc(II) and copper(II) complexes of beta-substituted hydroxylporphyrins

as tumor photosensitizers. *Bioorg. Med. Chem. Lett.,* **2006**, *16*(11), 3030-3033.
http://dx.doi.org/10.1016/j.bmcl.2005.02.094 PMID: 16540316

[9] Bertini, I.; Luchinat, C.; Rosi, M.; Sgamellotti, A.; Tarantelli, F. p*K*a of zinc-bound water and nucleophilicity of hydroxo-containing species. *Ab Initio* calculations on models for zinc enzymes. *Inorg. Chem.,* **1990**, *29*, 1460-1463.
http://dx.doi.org/10.1021/ic00333a004

[10] (a) Williams, R.J.P. Bio-inorganic chemistry: Its conceptual evolution. *Coord. Chem. Rev.,* **1990**, *100*, 573-610.
http://dx.doi.org/10.1016/0010-8545(90)85020-S
(b) Psomas, G. Copper(II) and zinc(II) coordination compounds of non-steroidal anti-inflammatory drugs: Structural features and antioxidant activity. *Coord. Chem. Rev.,* **2020**, *412*, 213259-213272.
http://dx.doi.org/10.1016/j.ccr.2020.213259

[11] Selimović, E.; Soldatović, T. Impact of the chloride concentration on ligand substitution reactions of zinc(II) complexes with relevant nitrogen nucleophiles. *Prog. React. Kinet. Mech.,* **2018**, *43*(3-4), 244-253.
http://dx.doi.org/10.3184/146867818X15319903829164

[12] Soldatović, T.; Selimović, E. Kinetic studies of the reactions between dichlorido[1,2-diaminoethane]zinc(II) and biologically relevant nucleophiles in the presence of chloride. *Prog. React. Kinet. Mech.,* **2018**, *43*(1), 53-61.
http://dx.doi.org/10.3184/146867818X15066862094897

[13] Soldatović, T.; Selimović, E.; Šmit, B.; Ašanin, D.; Planojević, N.; Marković, S.; Puchta, R.; Alzoubi, B. Interactions of zinc(II) complexes with 5′-GMP and their cytotoxic activity. *J. Coord. Chem.,* **2019**, *72*(4), 690-706.
http://dx.doi.org/10.1080/00958972.2019.1569229

[14] Jaganyi, D.; Hofmann, A.; van Eldik, R. Controlling the lability of square-planar Pt(II) complexes through electronic communication between π -acceptor ligands. *Angew. Chem. Int. Ed. Engl.,* **2001**, *40*(9), 1680-1683.
http://dx.doi.org/10.1002/1521-3773(20010504)40:9<1680::AID-ANIE16800>3.0.CO;2-K PMID: 11353478

[15] Hofmann, A.; Jaganyi, D.; Munro, O.Q.; Liehr, G.; van Eldik, R. Electronic tuning of the lability of Pt(II) complexes through pi-acceptor effects. Correlations between thermodynamic, kinetic, and theoretical parameters. *Inorg. Chem.,* **2003**, *42*(5), 1688-1700.
http://dx.doi.org/10.1021/ic020605r PMID: 12611540

[16] (a) Krishnan, K.; Plane, R. Raman and infrared spectra of complexes of ethylenediamine with zinc(II), cadmium(II), and mercury(II). *Inorg. Chem.,* **1966**, *5*, 852-857.
http://dx.doi.org/10.1021/ic50039a031
(b) Morgan, G.; Burstall, F.H. Researches on residual affinity and coordination. Complex metallic salts containing 2:6-di-2′-pyridylpyridine (2:2′:2”-tripyridyl). *J. Chem. Soc.,* **1937**, 1649-1655.
http://dx.doi.org/10.1039/JR9370001649

[17] (a) Fujita, T.; Yamaguchi, T.; Ohtaki, H. An X-ray diffraction study on the structures of *bis*- and *tris*-(ethylenediamine)zinc(II) complexes in solution. *Bull. Chem. Soc. Jpn,* **1979**, *52*, 3539-3544.
(b) Kong, C.-C.; Zhou, J.-Z.; Yu, J.-H.; Li, S.-L. Crystal structure of dichlorido(2,2′:6′,2″-terpyridine-κ3N,N′,N″)zinc: A redetermination. *Acta Cryst. E.,* **2014**, *E70*, m382-m383.

[18] Yoe, J.H.; Jones, A.L. Colorimetric determination of iron with disodium-1,2-dihydroxybenzene-3,5-disulfonate. *Ind. Eng. Chem. Anal. Ed.,* **1944**, *16*(2), 111-115.
http://dx.doi.org/10.1021/i560126a015

[19] Chriswell, C.D.; Schilt, A.A. New and improved techniques for applying the mole ratio method to the identification of weak complexes in solution. *Anal. Chem.,* **1975**, *47*(9), 1623-1629.
http://dx.doi.org/10.1021/ac60359a021

[20] (a) Marcus, Y. Ionic radii in aqueous solutions. *Chem. Rev.,* **1988**, *88*, 1475-1498.
http://dx.doi.org/10.1021/cr00090a003
(b) Brand, U.; Burth, R.; Vahrenkamp, H. Design of trigonal-bipyramidal ZnN_3S_2 complexes. *Inorg. Chem.,* **1996**, *35*(4), 1083-1086.
http://dx.doi.org/10.1021/ic950731d PMID: 11666290
(c) Alzoubi, B.M.; Puchta, R.; van Eldik, R. Ligand exchange processes on solvated zinc cations–DFT analysis of hydrogen cyanide exchange on $[Zn(HCN)_6]^{2+}$. *Z. Anorg. Allg. Chem.,* **2009**, *635*, 1536-1540.
http://dx.doi.org/10.1002/zaac.200900160

[21] (a) Alberts, I.L.; Nadassy, K.; Wodak, S.J. Analysis of zinc binding sites in protein crystal structures. *Protein Sci.,* **1998**, *7*(8), 1700-1716.
http://dx.doi.org/10.1002/pro.5560070805 PMID: 10082367
(b) Shaban, S.Y.; Ibrahim, M.M.; Heinemann, F.W. A new sterically loaded pentadentate N_3S_2 ligand and its zinc complexes. *Inorg. Chim. Acta,* **2007**, *360*, 2929-2934.
http://dx.doi.org/10.1016/j.ica.2007.02.014
(c) Alzoubi, B.M.; Puchta, R.; van Eldik, R. Ligand exchange processes on the solvated zinc cation II. $[Zn(H_2O)_4L]^{2+}\cdot 2H_2O$ with L = NH_3, $NH_2(CH_3)$, $NH(CH_3)_2$, and $N(CH_3)_3$. *Aust. J. Chem.,* **2010**, *63*, 236-244.
http://dx.doi.org/10.1071/CH09370
(d) Alzoubi, B.M.; Puchta, R.; van Eldik, R. Ligand-exchange processes on solvated zinc cations: Water exchange on [Zn(H2O)4(L)]2+.2H2O (L=heterocyclic ligand). *Chemistry,* **2010**, *16*(24), 7300-7308.
http://dx.doi.org/10.1002/chem.200902264 PMID: 20468026

[22] Dudev, T.; Lim, C. Tetrahedral *vs* octahedral zinc complexes with ligands of biological interest: A DFT/CDM study. *J. Am. Chem. Soc.,* **2000**, *122*, 11146-11153.
http://dx.doi.org/10.1021/ja0010296

[23] Selimović, E.; Soldatović, T. Study on the reactions between dichlorido[2,2′:6′,2″-terpyridine]zinc(II) and relevant nucleophiles in aqueous solution. *Prog. React. Kinet. Mech.,* **2019**, *44*(2), 105-113.
http://dx.doi.org/10.1177/1468678319825724

[24] (a) He, Z.; Chen, J.; Keumc, J.K.; Szulczewski, G.; Li, D. Improving performance of TIPS pentacene-based organic thin film transistors with small-molecule additives. *Org. Electron.,* **2014**, *15*, 150-155.
http://dx.doi.org/10.1016/j.orgel.2013.11.004
(b) He, Z.; Chen, J.; Li, D. Polymer additive controlled morphology for high performance organic thin film transistors. *Soft Matter,* **2019**, *15*(29), 5790-5803.
http://dx.doi.org/10.1039/C9SM01053J PMID: 31290910
(c) He, Z.; Zhang, Z.; Bi, S.; Chen, J.; Li, D. Conjugated polymer controlled morphology and charge transport of small-molecule organic semiconductors. *Sci. Rep.,* **2020**, *10*(1), 4344.
http://dx.doi.org/10.1038/s41598-020-61282-x PMID: 32152385

[25] (a) Bisht, G.; Rayamajhi, S. ZnO nanoparticles: A promising anticancer agent. *Nanobiomedicine (Rij),* **2016**, *3*(9), 9.
http://dx.doi.org/10.5772/63437 PMID: 29942384
(b) Sun, F.; Chen, G.; Zhou, X.; Wu, C.; Sun, L.; Yan, Q.; Guo, T.; Zhang, Y. Effects of embedded SiO2 nanoparticles on the moisture barrier performance of inorganic/organic laminates. *J. Mater. Sci. Mater. Electron.,* **2019**, *30*, 20899-20913.
http://dx.doi.org/10.1007/s10854-019-02478-4