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Impact of chloride concentration on ligand substitution reactions of zinc(II) complexes with biologically relevant nitrogen nucleophiles

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ABSTRACT

The mole-ratio method was used to determine the metal–ligand stoichiometry between $[ZnCl_2(en)]$ and $[ZnCl_2(terpy)]$ (where en = 1,2-diaminoethane or ethylenediamine and terpy = 2,2′:6′,2″-terpyridine) 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 for the $[ZnCl_2(en)]$ complex. These 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 the five-coordinate complex anion $[ZnCl_3(en)]^-$ is formed initially and then a substitution reaction with imidazole occurs. In the presence of 0.010 M NaCl the octahedral complex anion $[ZnCl_4(en)]^{2-}$ is formed. Additional coordination of chloride in the $[ZnCl_2(terpy)]$ complex is not found and the metal–ligand stoichiometry is 1:2. The kinetics of ligand substitution reactions of zinc(II) complexes and biologically 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 with changes only in the coordination geometry of the $[ZnCl_2(en)]$ complex. The order of reactivity of the investigated nucleophiles for the first reaction step towards both complexes was L-histidine > 1,2,3-triazole > imidazole, while in the presence of 0.010 M NaCl the most reactive ligand was 1,2,3-triazole towards the $[ZnCl_2(en)]$ complex.

KEYWORDS: zinc(II) complexes, nitrogen nucleophiles, chloride substitution

1. INTRODUCTION

In recent years, the coordination complexes of various transition metals have received considerable attention for the design of anticancer agents. Metal-based complexes offer a rich environment to build upon a variety of distinct molecular structures that confer a wide spectrum of coordination numbers and geometries, as well as kinetic properties [1]. Some transition metal ions are essential cellular components selected by nature to function in several biochemical processes; they act mainly as Lewis acids and have unique characteristics that include redox activity, variable coordination modes and reactivity towards biologically relevant nucleophiles.

Zinc-based compounds could be promising anticancer agents, especially because zinc is implicated as an important cytotoxic/tumour suppressor agent in several cancers [2]. 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 [3].

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 the zinc(II) ion can readily accommodate four, five, or six molecules [4]. Zinc is a good Lewis acid, especially in complexes with lower coordination numbers; it lowers the pK_a of coordinated water, is kinetically labile and the interconversion among its four-, five- and six-coordinate states is fast [5]. The investigation of the free energies of isomerisation between six- and four-coordinate structures containing Zn^{2+} bound to water and ligands of biological interest has shown that the lowest-energy ground-state coordination number of zinc bound to one acidic or two or more neutral protein ligands is likely to be four [6].

Recently, we determined the metal–ligand stoichiometry between the $[ZnCl_2(en)]$ complex and chloride at pH 7.2. In the presence of an excess of chloride (0.010 M NaCl), the octahedral $[ZnCl_4(en)]^{2-}$ formed in solution at pH 7.2. The substitution reactions of this complex and biologically relevant nucleophiles proceeded in two consecutive reactions steps that both depended on the nucleophile concentration. The first reaction step is accompanied by dissociation of one chlorido ligand in the equatorial position to yield a five-coordinate complex. The second reaction step is interpreted as substitution of the remaining chlorido ligand [7].

The main goal of these studies was to determine the metal–ligand stoichiometry between the different zinc(II) complexes and imidazole, as well as to investigate the kinetics and mechanism of ligand-substitution reactions between the zinc(II) complexes and biologically relevant nitrogen nucleophiles under physiological conditions. A detailed mole-ratio study for determining the metal–ligand stoichiometry in the presence of 0.001 and 0.010 M NaCl was performed and kinetic studies at pH 7.2 were undertaken. It was envisaged that this study could throw more

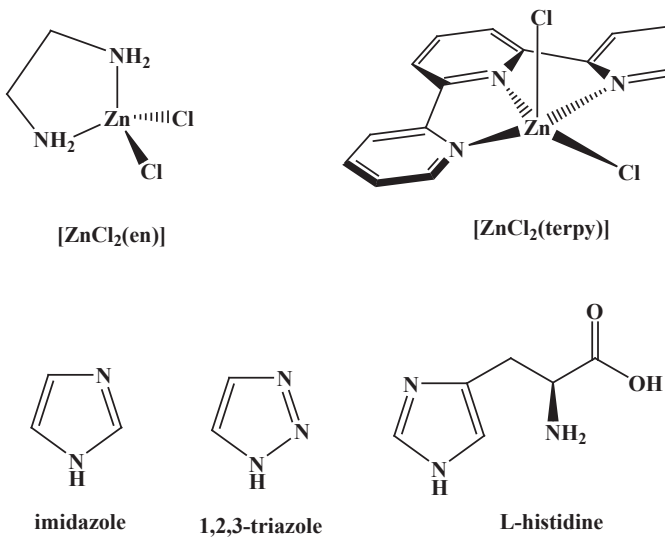

Figure 1 Structures of the investigated complexes and nucleophiles along with adopted abbreviations.

light on understanding the changes in geometrical structures of zinc(II) that relate to structure–reactivity correlation and also to provide more information for the design of potential zinc-based anticancer drugs. The structures of the complexes and the selected nucleophiles are shown in Figure 1.

2. EXPERIMENTAL

2.1 Chemicals

The nucleophiles imidazole, 1,2,3-triazole, L-histidine and the buffer 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (Hepes) were obtained from Sigma-Aldrich, Acros Organics and Fluka. Nucleophile stock solutions were prepared shortly before use by dissolving the chemicals in purified water. All other chemicals were of analytical reagent grade. Highly purified deionised water was used in the preparation of all solutions. To study the ligand substitution reactions at pH 7.2 a freshly prepared Hepes buffer (0.025 M) was used. NaCl was used to adjust the chloride concentration.

2.2 Synthesis of complexes

The complexes [$ZnCl_2$(en)] and [$ZnCl_2$(terpy)] were synthesised according to the literature method [8,9]. Chemical analysis was performed on a Carlo Erba 1106 elemental analyser: Anal. calcd for [$ZnCl_2$(en)]: N, 14.26; C, 12.23; H, 4.11; found: N, 14.29; C, 12.19; H, 4.13%. Anal. calcd for [$ZnCl_2$(terpy)]: N, 11.37; C, 48.75; H, 3.00; found: N, 11.21; C, 48.31; H, 3.12%. The geometry of the complex in solution was investigated and has been assigned as tetrahedral [10] and square-pyramidal [11].

2.3 Instrumentation

UV-Vis spectra were recorded on Uvikon XS and Shimadzu UV250 diode-array spectrophotometers in thermostated 1.00 cm quartz Suprasil cells. The temperature was controlled throughout all kinetic experiments to ±0.1 °C.

2.4 Mole-ratio method

In order to determine the metal–ligand stoichiometry, a series of solutions (10 mL) was prepared in which the concentration of [$ZnCl_2$(en)] and [$ZnCl_2$(terpy)] complexes was held constant (0.001 M) while the concentration of imidazole was varied in different molar ratios {[imidazole]/[Zn(II) complex] = 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0} [12,13]. Hepes (0.025 M) was used as a buffer at pH 7.2 in addition to 0.001 and 0.010 M NaCl. The absorbance of each solution was measured over the wavelength range 200 to 600 nm (see Figures 2–4). The chosen absorbances at 200, 205 and 350 nm respectively were plotted *versus* the molar ratio of the reactants (see Figures 2–4). Assuming the formed complex absorbs more than the initial reactants, this plot produces an increasing absorbance up to the combining ratio. At this point, further addition of imidazole will produce less increase in the absorbance. Thus a break in the slope of the curve occurs at the mole-ratio corresponding to the combining ratio of the imidazole/complex.

2.5 Kinetic measurements

Spectral changes resulting from mixing [$ZnCl_2$(en)] and [$ZnCl_2$(terpy)] and nucleophile solutions were recorded over the wavelength range 200–500 nm to establish a suitable wavelength at

which kinetic measurements could be performed [see Figure 5 and Electronic Supplementary Information (ESI) Tables S1–S12]. The ligand substitution reactions were studied for the nucleophiles imidazole, 1,2,3-triazole and L-histidine. Reactions were initiated by mixing equal volumes of thermostated solutions of the complex and ligand in the UV-Vis spectrophotometric cell and were followed for at least eight half-lives. All kinetic experiments were performed under pseudo first-order conditions with respect to the nucleophile concentration. The measured pseudo first-order rate constants (k_{obsd}) are summarised in Tables S1–S12 (see ESI). All kinetic runs could be fitted to a double exponential function. The k_{obsd} values were calculated as the average value from three to four independent kinetic runs. The reactions were studied at pH 7.2 (0.025 M Hepes buffer) at 295 K in the presence of 0.001 and 0.010 M chloride concentrations. The initial concentrations of [$ZnCl_2$(en)] and [$ZnCl_2$(terpy)] were 0.0001 M.

3. RESULTS AND DISCUSSION

An alternative to the method of continuous variations (Job's method) for determining the stoichiometry of metal–ligand complexes is the mole-ratio method in which the amount of one reactant, usually the molar concentration of metal, is held constant while the amount of the other reactant is varied [12,13]. In order to determine the metal–ligand stoichiometry between [$ZnCl_2$(en)] and [$ZnCl_2$(terpy)] complexes and imidazole at pH 7.2 in the presence of an excess of chloride, the absorbance changes over the wavelength range 200–600 nm for different molar ratios of [imidazole]/[Zn(II) complex] were recorded (see Figures 2–4). The differences between the spectra of the zinc(II) complexes and the spectra of solutions with various molar ratios {[imidazole]/[Zn(II) complex]} can only be detected in the intensity of the absorbance and the wavelength maximum being shifted due to coordination of the imidazole in [$ZnCl_2$(en)] from 208 nm to 220 nm. The presence of mixed Cl···H_2O complexes was not observed.
The absorbance was monitored at a wavelength where the metal–ligand complex absorbs.
Different stoichiometries of the zinc–imidazole complexes were observed in the presence of chloride for [$ZnCl_2$(en)]. According to our previous research, in the presence of chloride different complex species are formed [7]. The coordination number of Zn^{2+} is changed from 4 up to 6, according to the geometry of the complexes formed undergoing change [7].

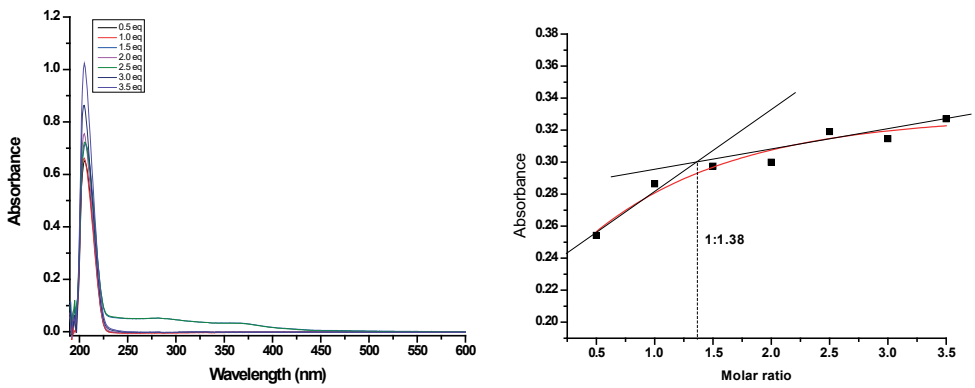

Figure 2 Titrations of [$ZnCl_2$(en)] with imidazole in the presence of 0.001 M NaCl as monitored by UV-Vis spectra. Left: [$ZnCl_2$(en)]–imidazole, Right: Cross-section of UV-Vis spectra at 200 nm.

In the presence of 0.001 M NaCl at the selected wavelength 200 nm, we observed one equivalence point, corresponding to formation of a 1:1 complexes species [$ZnCl_2$(en)(imidazole)] (see Figure 2). Otherwise, in the presence of 0.010 M NaCl at the selected wavelength 205 nm, we observed two equivalence points, corresponding to step-wise formation of 1:1 and 1:2 complexes and we assumed that the octahedral complex [$ZnCl_2$(en)$(imidazole)_2$] is formed rapidly (Figure 3).
For the complex [$ZnCl_2$(terpy)] we have not observed any additional coordination of chlorides (see Figure S1 in the ESI), so we assumed that the five-coordinate complex is very stable. In the presence of 0.001 M NaCl at the selected wavelength 350 nm, we observed one equivalence point. This result implied a 1:2.15 zinc:imidazole stoichiometry that probably corresponds to formation of the five-coordinate species [Zn(terpy)$(imidazole)_2$] in which chlorides are substituted by imidazole (Figure 4). In the presence of 0.010 M NaCl we did not obtain useful results. The reason could be competition for coordination between chloride and imidazole, with chloride suppressing the substitution.
As mentioned before, in the presence of chloride the coordination number of [$ZnCl_2$(en)] is changed and hence the geometry of the complexes formed undergo change [5–7]. Thus, in the presence of 0.001 M NaCl, we assumed complex species [$ZnCl_3$(en)]$^-$ is formed, while in the

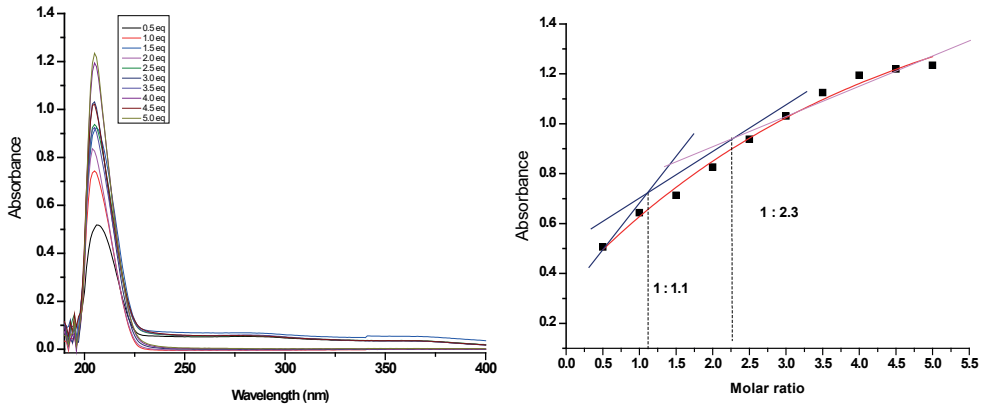

Figure 3 Titrations of [$ZnCl_2$(en)] with imidazole in the presence of 0.010 M NaCl as monitored by UV-Vis spectra. Left: [$ZnCl_2$(en)]–imidazole, Right: Cross-section of UV-Vis spectra at 205 nm.

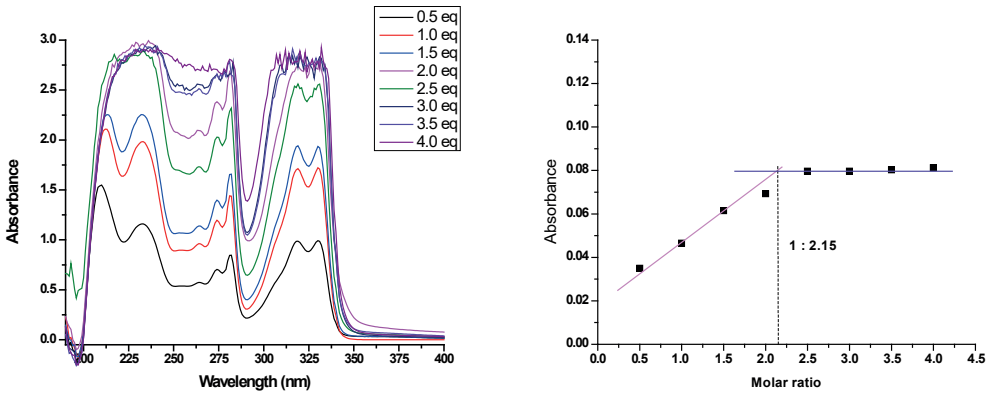

Figure 4 Titrations of [$ZnCl_2$(terpy)] with imidazole in the presence of 0.001 M NaCl as monitored by UV-Vis spectra. Left: [$ZnCl_2$(terpy)]–imidazole, Right: Cross-section of UV-Vis spectra at 350 nm.

presence of 0.010 M NaCl the octahedral complex anion $[ZnCl_4(en)]^{2-}$ is formed rapidly and all substitution processes of this complex species should be considered [7].

All kinetic experiments in this study were performed at physiological pH and 295 K, in the presence of chloride. An example of the UV-Vis spectra and time profile are shown in Figure 5. The substitution reactions between the complexes studied and biologically relevant nitrogen nucleophiles proceeded in two consecutive reaction steps that both depended on the nucleophile concentration. All kinetic traces gave an excellent fit to a double exponential function, typical for a two-step reaction. The so-obtained pseudo first-order rate constants, k_{obsd1} and k_{obsd2}, calculated from the kinetic traces were plotted against the concentration of the entering nucleophiles. A linear dependence on the nucleophile concentration for the first reactions was observed for all the complexes studied (see Figures 6 and 7). The linear dependence on the nucleophile concentration for the second reactions is shown in Figures S2 and S3 in the ESI.

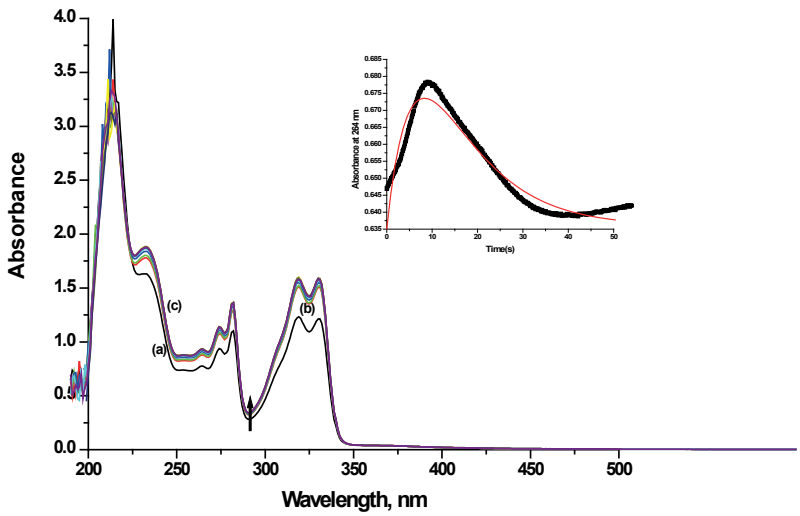

Figure 5 Rapid-scan spectra recorded for the reaction of the $[ZnCl_2(terpy)]$ complex (0.0001 M) with imidazole (0.005 M) at pH 7.2 (0.025 M Hepes buffer) in the presence of 0.001 M NaCl. at 295 K: (a) spectrum before reaction; (b) spectrum obtained several seconds after mixing of reactants and (c) spectrum obtained after 20 s. Inset: time trace obtained for reaction at 264 nm.

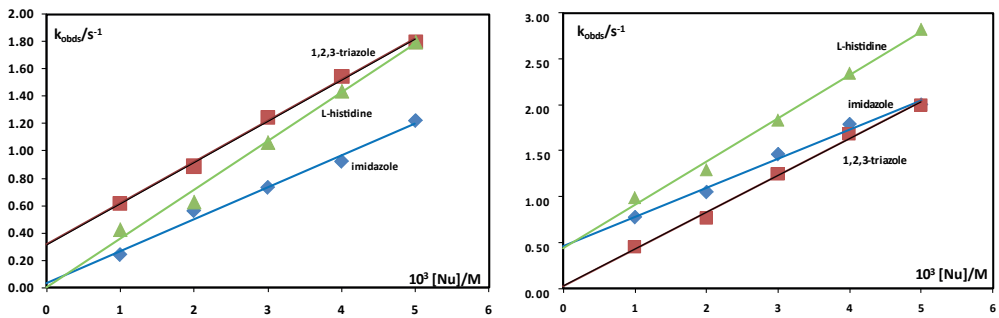

Figure 6 Pseudo first-order rate constants plotted as a function of nucleophile concentration for first reactions of the $[ZnCl_2(en)]$ (left side) and $[ZnCl_2(terpy)]$ (right side) complexes with imidazole, 1,2,3-triazole and L-histidine at pH 7.2 (0.025 M Hepes buffer) in the presence of 0.001 M NaCl at 295 K.

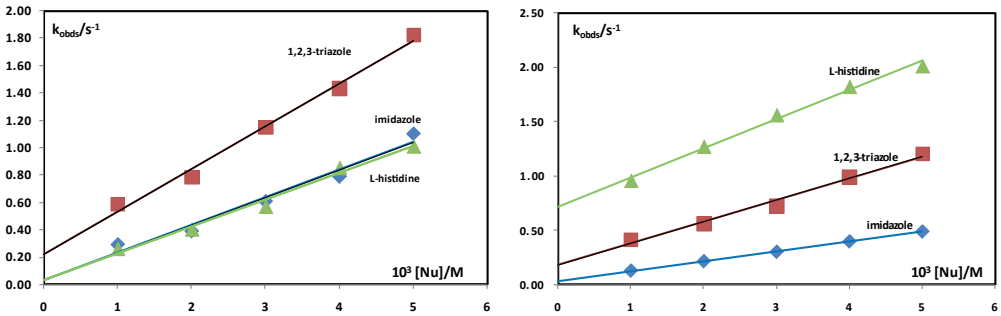

Figure 7 Pseudo first-order rate constants plotted as a function of nucleophile concentration for the first reactions of the [$ZnCl_2$(en)] (left side) and [$ZnCl_2$(terpy)] (right side) complexes with imidazole, 1,2,3-triazole and L-histidine at pH 7.2 (0.025 M Hepes buffer) in the presence of 0.010 M NaCl at 295 K.

Observed pseudo first-order rate constants k_{obsd1} and k_{obsd2} depend on the entering nucleophile concentration [Nu] as given in Eqns (1) and (2).

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

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

Linear fits pass through the origin for some reactions in the present study, indicating that possible parallel or reverse reactions are insignificant or absent, *i.e.* k_{-1} and k_{-2} are negligible and Eqns (1) and (2) simplify to $k_{obsd1} = k_1[Nu]$ and $k_{obsd2} = k_2[Nu]$. Thus, in the present systems, direct nucleophilic substitution is the major observed reaction pathway under the selected conditions. The observed intercepts are ascribed to the reverse reaction with excess chloride present in solution (see Figures 6 and 7 and Figures S2 and S3 in the ESI). The derived rate constants are summarised in Tables 1 and 2.

According to our previous research, in the presence of excess of chloride step-wise formation of 1:1 and 1:2 complex species is observed for the [$ZnCl_2$(en)] complex.

Thus, in the presence of 0.001 M NaCl we assumed the complex five-coordinate species $[ZnCl_3(en)]^-$ is formed, while in the presence of 0.010 M NaCl the octahedral complex anion $[ZnCl_4(en)]^{2-}$ is present and all substitution processes of these complex species should be considered. The first step could be interpreted as substitution of one chlorido ligand, while the

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

[$ZnCl_2$(en)] 0.0001 M	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^{-1})	–	0.20 ± 0.01	0.057 ± 0.009
[$ZnCl_2$(terpy)] 0.0001 M	Imidazole	1,2,3-Triazole	L-Histidine
k_1^{295} (M^{-1} s^{-1})	317 ± 18	401 ± 18	471 ± 23
10^2 k_{-1}^{295} [Cl^-] (M^{-1} s^{-1})	0.46 ± 0.06	–	0.441 ± 0.076
k_2^{295} (M^{-1} s^{-1})	84 ± 9	17 ± 1	118 ± 7
10^2 k_{-2}^{295} [Cl^-] (M^{-1} s^{-1})	–	0.039 ± 0.004	0.238 ± 0.020

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

$[ZnCl_2(en)]$ 0.0001 M	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^{-1})	0.024 ± 0.004	0.033 ± 0.003	0.051 ± 0.014
$[ZnCl_2(terpy)]$ 0.0001 M	Imidazole	1,2,3-Triazole	L-Histidine
k_1^{295} (M^{-1} s^{-1})	91 ± 1	199 ± 14	268 ±14
10^2 k_{-1}^{295} [Cl^-] (M^{-1} s^{-1})	–	0.18 ± 0.05	0.72 ± 0.05
k_2^{295} (M^{-1} s^{-1})	12 ± 2	20 ± 2	33 ± 3
10^2 k_{-2}^{295}[Cl^-] (M^{-1} s^{-1})	0.024 ± 0.006	0.028 ± 0.007	0.083 ± 0.009

second step is the substitution of another chlorido ligand in the position *cis* towards bidentate coordinated ethylenediamine. We assume that in the presence of 0.001 M NaCl the geometry of the five-coordinate complex species remains after substitution. The order of reactivity of the investigated nucleophiles for the first reaction step is L-histidine > 1,2,3-triazole > imidazole while for the second it is imidazole > L-histidine > 1,2,3-triazole.

In the presence of 0.010 M NaCl the octahedral complex anion $[ZnCl_4(en)]^{2-}$ is formed rapidly [7]. The first step of the substitution reactions could be interpreted as substitution of the axial chlorido ligands in the *cis* position towards bidentate coordinated ethylenediamine by the nucleophiles, whereas the second step is substitution of the equatorial chlorido ligand. Due to the large negative inductive effects of amino groups in ethylenediamine, the basicity of N-donor atoms increases and the interactions between Zn^{2+} and $–NH_2$ groups are stronger. According to this, both chlorido ligands in the axial position are kinetically labile and equal for parallel substitution routes. The first reaction step is accompanied by dissociation of one chlorido ligand in the equatorial position and the five-coordinate complex is obtained [7]. The dissociation of the ligand in the six-coordinate complex of zinc(II) and formation of a five-coordinate complex happens with little energy loss. On the other hand, four-coordinate complexes can add a fifth ligand with little energetic barrier [14,15]. The second reaction step could be interpreted as substitution of the last chlorido ligand. The order of reactivity of the investigated nucleophiles for the first reaction step is 1,2,3-triazole > imidazole > L-histidine, while for the second reaction step it is L-histidine > imidazole > 1,2,3-triazole.

The different orders of reactivity of the biologically relevant nitrogen nucleophiles could be a consequence of different geometrical structures of the $[ZnCl_2(en)]$ complex caused by different chloride concentration.

The structure of the $[ZnCl_2(terpy)]$ complex remains unchanged in the presence of chloride (see Figure S1 in the ESI), the substitution proceeds in two reaction steps and both chlorides are substituted by nucleophiles. The rates of nucleophilic substitution reactions are controlled by the strong π-acceptor ability of the tridentate chelate 2,2′:6′,2″-terpyridine and by the excess of chloride present in solution. Different chloride concentrations affect the rate of substitution. The substitution reactions in the presence of 0.001 M NaCl are approximately two or three times faster. The reason could be the competition between biologically relevant nitrogen nucleophiles and chloride. The order of investigated nucleophiles in the presence of different chloride

concentration is the same for the first step: L-histidine > 1,2,3-triazole > imidazole. The second order of reactivity in the presence of 0.001 M NaCl is L-histidine > imidazole > 1,2,3-triazole, while in 0.010 M NaCl the nucleophiles follow the order: L-histidine > 1,2,3-triazole > imidazole. We observed a similar order of magnitude for the second rate constants, for both substitution processes of the [$ZnCl_2$(terpy)] complex by L-histidine in the presence of 0.001 M NaCl. This suggests that there are two parallel reaction paths. The square-pyramidal structure of Zn^{2+} in biological systems prefers *O*-carboxylate, carbonyl and *N*-imidazole donor bioligands [16]. With the variable coordination geometries (tetrahedral, five-coordinate, octahedral) that zinc(II) is able to adopt, its balance in donor site preference (N, O) may account for the order of reactivity of biologically relevant nitrogen nucleophiles in the presence of excess chloride. Steric hindrance could also be the reason for the diverse reactivity of nucleophiles for the second reaction steps [17,18].

4. CONCLUSIONS

In this study, we tried to determine the metal–ligand stoichiometry between [$ZnCl_2$(en)] and [$ZnCl_2$(terpy)] complexes and imidazole at pH 7.2. 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 for the [$ZnCl_2$(en)] complex. In the presence of 0.001 M NaCl the result of the metal–ligand stoichiometry between the [$ZnCl_2$(terpy)] complex and imidazole implied formation of the five-coordinate species [Zn(terpy)$(imidazole)_2$]. The substitution reactions of the studied complexes and biologically relevant nucleophiles proceed in two consecutive reaction steps that both depend on the nucleophile concentration. The substitution reactions include two steps of consecutive displacement of chlorido ligands and changes in coordination geometry of [$ZnCl_2$(en)]. The order of reactivity of the investigated nucleophiles for the first reaction step towards both complexes is L-histidine > 1,2,3-triazole > imidazole; except in the presence of 0.010 M NaCl, the most reactive ligand is 1,2,3-triazole towards [$ZnCl_2$(en)]. The varying concentrations of chloride have a significant impact on the rate constants of the substitution processes of the [$ZnCl_2$(terpy)] complex by nucleophiles.

5. ACKNOWLEDGEMENTS

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6. ELECTRONIC SUPPLEMENTARY INFORMATION

The ESI (Tables S1–S12 and Figures S1–S3) is available through
http://ingentaconnect.com/content/stl/prk/2018/00000043/00000003

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