Kinetic studies of the Ru(II) polypyridyl complex with biologically relevant ligands

Milica Međedović[1], Dejan Lazić[2], Milan Vraneš[3], Ghodrat Mahmoudi[4], Biljana Petrović[1], Ana Rilak Simović[5*]

[1] University of Kragujevac, Faculty of Science, Department of Chemistry, 34000 Kragujevac, Serbia, Radoja Domanovića 12; e-mail: milica.medjedovic@pmf.kg.ac.rs, biljana.petrovic@pmf.kg.ac.rs
[2] University of Kragujevac, Faculty of Medical Sciences, Department of Surgery, 34000 Kragujevac, Serbia, Svetozara Markovića 69; e-mail: dlazic.kg@gmail.com
[3] University of Novi Sad, Faculty of Sciences, Department of Chemistry, Biochemistry and Environmental Protection, 21000 Novi Sad, Serbia, Trg Dositeja Obradovića 3; e-mail: milan.vranes@dh.uns.ac.rs
[4] University of Maragheh, Faculty of Science, Department of Chemistry, Maragheh, Iran, e-mail: ghodratmahmoudi@gmail.com
[5] University of Kragujevac, Institute for Information Technologies, Department of Natural Science, 34000 Kragujevac, Serbia, Jovana Cvijića bb; e-mail: anarilak@kg.ac.rs

* *Corresponding author*

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Abstract: In a group of transition metal complexes that scientists have synthesized to find a good replacement for cisplatin, ruthenium complexes, with various good properties, occupy a very important place. In this group, ruthenium polypyridyl complexes showed promising properties and became leading candidates for use as anticancer agents. In this study, we have synthesized a new ruthenium (II) polypyridyl complex of general formula [Ru(*L*)(*N-N*)Cl]Cl, where *L* is 2,2′:6′,2′′-terpyridine with the additional functional group in the 4′-position: 2-thienly and *N-N*= bpy (2,2′-bypiridine). The kinetics of the substitution reactions of the studied complex with important biomolecules, the nitrogen-containing ligand 5′-GMP and the S-containing ligand L-Cys, were monitored. The kinetic results showed a faster substitution of the labile aqua ligand with a nitrogen-containing ligand, than a sulfur-containing one.

Keywords: ruthenium(II), polypyridyl, kinetics, 5′-GMP, L-Cys

1. Introduction

Ruthenium complexes with a series of good properties, such as a range of oxidation states (Ru(II), Ru(III), and Ru(IV)), water solubility, slow ligand exchange rates, less toxicity, and anticancer activity, especially toward tumors resistant to cisplatin, became promising non-platinum compounds. A huge number of ruthenium polypyridyl complexes have been synthesized and studied to confirm their activity against cancer

cells. This research has provided confirmation that ruthenium complexes have multiple targets, and a combination of their actions contributes to their observed beneficial properties [1]. Recently, we reported the synthesis of a series of Ru(II) terpyridine compounds, with the general formula *mer*-[Ru(L_3)(N–N)(X)][Y]n, in which L3 is either 2,2′:6′,2″-terpyridine (tpy), 4′-chloro-2,2′:6′,2″-terpyridine (Cl-tpy) or 4′-(4-chlorophenyl)-2,2′:6′,2″-terpyridine (Cl-Ph-tpy); N–N is a bidentate chelating ligand (1,2-diaminoethane (en), 1,2-diaminocyclohexane (dach), 2,2′-bipyridine (bpy)); X is a monodentate ligand (Cl or dmso-S). These compounds, after the hydrolysis of the Cl ligand, form monofunctional adducts with N7 of guanine derivatives (i.e., 9-methylguanine (9MeG) or guanosine-5′-monophosphate (5′-GMP)) with rates and extents that depended strongly on the nature of the chelating ligand [2].

Here, we described the kinetics of the substitution reactions of the complex [Ru(thienyl-tpy)(bpy)Cl]Cl with biologically relevant molecules, such as 5′-GMP or amino acid L-Cys. This research confirmed the influence of the nature of entering nucleophiles on the substitution reactions and higher reactivity of the studied Ru(II) complex toward nitrogen-containing nucleophile, 5′-GMP.

2. Kinetic studies of Ru(II) complex with small biomolecules

The substitution kinetics of coordinated water with 5′-GMP and L-Cys in Ru(II) complex were investigated UV–Vis spectrophotometrically. The working wavelengths were previously determined by recording the reaction mixture at the wavelength range of 200 to 800 nm. All kinetic experiments were performed under *pseudo*-first-order conditions (i.e., the concentration of the nucleophile was at least 10-fold that of the complex). The reaction was initiated by mixing a solution of the studied complex (0.3 mL, 1.00 mM) with 2.7 mL of the thermally equilibrated nucleophile solution (5.56 mM) in the UV-Vis cuvette, and the reactions were followed for at least 5 hours. The substitution reactions were monitored in double distilled water as a medium. The observed *pseudo*-first-order rate constants, k_{obsd}, represent an average value of two or three independent kinetic runs for each experimental condition. Reactions were studied with small biomolecules, such as 5′-GMP and L-Cys, at 298 K. The first-order rate constants, k_2, for the substitution reactions with the studied nucleophiles, were obtained directly from the slopes of k_{obs} plots versus the concentration of the nucleophile. All kinetic data were computer-fitted to the appropriate equation using the programs Microsoft Excel 2016 and Origin 8.

The substitution process of the complex with 5′-GMP and L-Cys was represented by equation (1):

$$[\text{Ru(thienyl-tpy)(bpy)(H}_2\text{O)}]^{2+} + \text{Nu} \xrightarrow{k} [\text{Ru(thienyl-tpy)(bpy)(Nu)}]^{n} + \text{H}_2\text{O} \quad (1)$$

where n depends on the nature of the entering nucleophile Nu, 5′-GMP or L-Cys.

The rate constants for the substitution reaction were determined under *pseudo*-first-order conditions from the plot of the linear dependence of k_{obsd} versus nucleophile according to equation (2):

$$k_{obsd} = k\,[Nu] \qquad (2)$$

where Nu = 5′-GMP or L-Cys.

The direct nucleophilic attack is characterized by the rate constants k. The first-order rate constant, k, characterizing the formation of the product, can be calculated from a plot of k_{obs} *vs.* the concentration of entering nucleophiles. A linear dependence on the nucleophile concentration was observed for both nucleophiles, with zero intercepts demonstrating the irreversibility of the reactions (Figure 1).

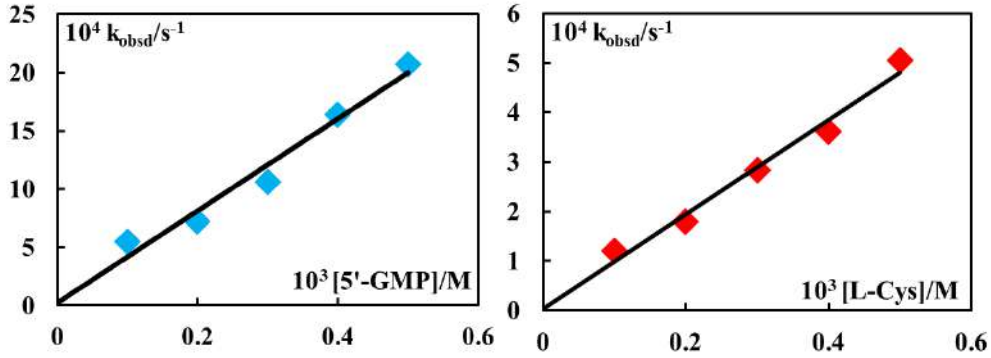

Figure 1. *Pseudo*-first order rate constants, k_{obsd}, as a function of the nucleophile concentration for the substitution reactions of Ru(II) complex with 5′-GMP and L-Cys.

The obtained values of the first-order rate constants for the substitution reactions with 5′-GMP and L-Cys, k = 4.0 ± 0.4 and 0.95 ± 0.08 M^{-1} s^{-1}, respectively, confirm the fact that the rate of the substitution reactions of the ruthenium(II) complex depends on the nature of the entering nucleophile. The Ru-thienyl-tpy complex reacts four times faster with 5′-GMP than with the amino acid L-Cys. Based on the borderline hard–soft acidic properties of ruthenium, it was expected for the ruthenium complex to show a higher affinity for nitrogen-bonding nucleophiles, which also possess borderline hard–soft properties. For comparison, Ru(II) polypyridyl complexes with the general formula *mer*-[RuL_3(N–N)Cl]Cl, where L is 2,2′:6′,2′′-terpyridine (tpy) or 4′-(4-chlorophenyl)-2,2′:6′,2′′-terpyridine (Cl-Ph-tpy) and N–N is o-benzoquinonediimine (o-bqdi), 2,3-naphthoquinonediimine (nqdi), 4,4′-dimethyl-2,2′-bipyridine (dmbpy), or 2,2′-bipyridine-4,4′-dicarboxylic acid (dcbpy), showed the same trend of reactivity with 5′-GMP and L-Cys [3].

3. Conclusions

The study of the kinetics of the substitution reactions of the selected complex with nitrogen- (5′-GMP) and sulfur-donor nucleophiles (L-Cys) showed higher reactivity of

Ru compound with 5′-GMP. The kinetic data for the reactions of Ru compound with 5′-GMP and L-Cys clearly showed that the rate of the reaction depends on the nature of the entering nucleophile: complex react ca. 4 times faster with 5′-GMP than with L-Cys. The results of the present work represent a further improvement in the structure–pharmacological relationship needed for the design of new antitumor ruthenium drugs and chemotherapeutic strategies.

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