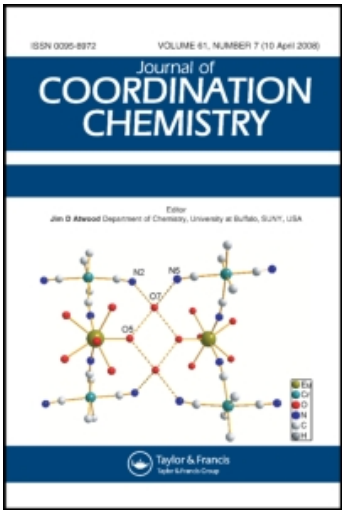

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

UV-Vis, HPLC, and ^{1}H-NMR studies of the substitution reactions of some Pt(IV) complexes with 5'-GMP and L-histidine

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First published on: 02 June 2010

To cite this Article Jovanović, Snežana , Petrović, Biljana and Bugarčić, Živadin D.(2010) 'UV-Vis, HPLC, and ^{1}H-NMR studies of the substitution reactions of some Pt(IV) complexes with 5'-GMP and L-histidine', Journal of Coordination Chemistry, 63: 14, 2419 — 2430, First published on: 02 June 2010 (iFirst)
To link to this Article: DOI: 10.1080/00958972.2010.490296
URL: http://dx.doi.org/10.1080/00958972.2010.490296

Journal of Coordination Chemistry
Vol. 63, Nos. 14–16, 20 July–20 August 2010, 2419–2430

UV-Vis, HPLC, and ^{1}H-NMR studies of the substitution reactions of some Pt(IV) complexes with 5′-GMP and L-histidine

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(*Received 31 January 2010; in final form 2 March 2010*)

Substitution reactions of [$PtCl_4$(en)] and [$PtCl_4$(dach)] with guanosine-5′-monophosphate (5′-GMP) and L-histidine were studied by different experimental methods. By UV-Vis spectrophotometry, these reactions were investigated under pseudo-first-order conditions at 310 K in 25 mmol Hepes buffer (pH = 7.2) and 10 mmol NaCl to prevent the hydrolysis of the complexes. [$PtCl_4$(en)] reacts slightly faster than the [$PtCl_4$(dach)]. Also, L-histidine is a better nucleophile than 5′-GMP. Final ^{1}H-HMR spectra of the substitution of Pt(IV) were in a good agreement with the spectra of Pt(II) complexes with the same nucleophiles, confirming the assumption of the reduction of Pt(IV) complexes during substitution. The same reactions were studied by high-performance liquid chromatography comparing the chromatograms during the reaction. The changes in the intensity of signals and their retention time show that at the end of substitution, there is only one dominant product in the system. We conclude that substitution of these Pt(IV) complexes is followed by rapid reductive elimination and final product is substituted Pt(II) complex.

Keywords: Pt(IV); Kinetics; Histidine; 5′-GMP

1. Introduction

Platinum complexes are recognized to be biologically very important since Rosenberg's discovery of the antitumor activity of *cis*-[$PtCl_2(NH_3)_2$] [1–3]. About 3000 platinum(II) complexes have been synthesized and investigated in an attempt to improve the antitumor activity, lower toxicity, and to design a drug that is able to overcome resistance [4–6]; only about 30 platinum complexes have entered into clinical trial. Interactions of different platinum complexes toward deoxyribonucleic acid (DNA) as well as interactions with other biomolecules were the major goal of research [7–11].

Platinum(IV) complexes have not been extensively studied because potential reactivity toward DNA was not expected for such inert molecules [12]. Pt(IV) complexes are stable in acidic conditions, so they could be applied orally as a drug. Now, there is growing interest in Pt(IV) complexes because of their anticancer activity,

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Journal of Coordination Chemistry
ISSN 0095-8972 print/ISSN 1029-0389 online © 2010 Taylor & Francis
DOI: 10.1080/00958972.2010.490296

especially since some of these complexes are toxic to tumors which are resistant to cisplatin [13]. Upon entering into the cell, there are two metabolic pathways for Pt(IV) complexes: reduction by agents present in the cell (glutathione, ascorbic acid) or direct interaction with DNA in the nucleus. The first pathway leads to well-known interactions of Pt(II) complexes, while the second proposes the formation of an adduct between Pt(IV) and DNA [14, 15].

Many papers describe that the reduction of platinum(IV) complexes is essential for their antitumor activity. The kinetic inertness of platinum(IV) complexes increase the opportunity for reaching the cell target. Different modification in their structures, especially changing the axial ligands, could affect the solubility and ability to enter into the cell before being reduced [13].

Published results for the substitution of different Pt(IV) complexes show that their reactivity depends on their reduction potential [13, 16]. For diammine complexes of platinum, the structure variation of diammine ligand has less effect on the rate of reduction, but the nature of axial ligands has higher influence on reduction potential [13, 17]. When axial ligands are chloride, reduction is very fast compared with carboxylate or hydroxide.

Reactivity of Pt(IV) complexes toward nucleotide guanosine-5′-monophosphate (5′-GMP) is frequently studied [16–20]. Nucleotide is coordinated to Pt(IV) *via* N7 of purine base as for Pt(II) complexes. Depending on reaction conditions, there is a possibility to substitute more than one chloride with 5′-GMP, but, usually reductive elimination occurs during substitution. Reduction could be catalyzed in the presence of Pt(II), however, Pt(II) does not need to be an analog to Pt(IV) to accelerate the substitution [17]. Using different methods of analysis confirmed that two electrons needed for the reduction come from the sugar portion of 5′-GMP [16–19].

We report here the study of the substitution between $[PtCl_4(en)]$ and $[PtCl_4(dach)]$ with 5′-GMP and L-histidine using UV-Vis spectrophotometry, ^{1}H-NMR spectroscopy, and high performance liquid chromatography (HPLC). It was envisaged that this study could throw light on the mechanism of the interactions of platinum(IV) complexes with nitrogen-bonding ligands and also provide a better understanding of the mechanism of platinum metabolism. Structures of studied complexes and ligands are shown in figure 1.

2. Experimental

2.1. *Chemicals*

Potassium-tetrachloroplatinate (K_2PtCl_4) was purchased from Strem Chemicals. The ligands, ethylenediamine (en) (Merck) and (1R, 2R)-1.2-diaminocyclohexane (dach) (Acros Organics), as well as nucleophiles, 5′-GMP sodium salt (Acros Organics) and L-histidine (His) (Merck), were used without purification. Hepes buffer (N-2-hydroxyethylpiperazine-N′-2-ethanesulfonic acid) obtained from Aldrich and D_2O (Deutero GmbH, 99.9%) were used as received. All other chemicals were of the highest purity that were available commercially. Ultrapure water was used for spectrophotometric measurements while for the liquid chromatography water with HPLC purity was used.

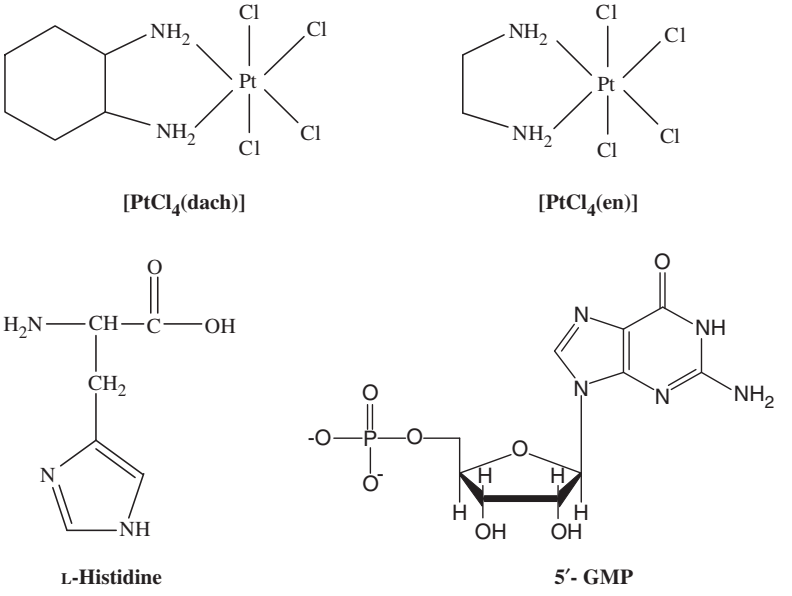


Figure 1. The structures of investigated complexes and ligands.

$[PtCl_4(en)]$ and $[PtCl_4(dach)]$ were prepared according to the published procedures by adding H_2O_2 to the solution of Pt(II) complexes in acidic water with the presence of NaCl to avoid the formation of hydroxo complexes [19, 21]. Chemical analysis, ^{1}H-NMR, and UV-Vis spectroscopic data were in good agreement with the previously obtained data. Anal. Calcd for $PtC_6N_2H_{14}Cl_4$: H, 3.10; C, 15.97; N, 6.21. Found: H, 2.82; C, 15.22; N, 5.94. Anal. Calcd for $PtC_2N_2H_8Cl_4$: H, 2.02; C, 6.04; N, 7.06. Found: H, 1.88; C, 6.82; N, 6.79.

2.2. *Instrumentation*

Chemical analyses were performed on a Carlo Erba Elemental Analyser 1106. UV-Vis spectra were recorded on Shimadzu UV 250 and Hewlett-Packard 8452A diode-array spectrophotometers. UV-Vis kinetic measurements were carried out on a Perkin Elmer Lamda 35 double-beam spectrophotometer equipped with thermostated 1.00 cm quartz Suprasil cells. The temperature was controlled throughout kinetic experiments to $\pm 0.1^{\circ}$C. HPLC results were obtained on a Shimadzu LC solution chromatograph with an SDP-M20A diode array detector. 250/4 NUCLEOSIL 100–5 C_{18} was used as a column CC. Nuclear magnetic resonance (NMR) spectra were acquired on a Varian Gemini-2000 spectrometer at 295 K with a commercial 5 mm Bruker broadband probe. All chemical shifts are referenced to trimethylsilylpropionic acid (TSP).

2.3. *Kinetics measurements*

Kinetics of the substitution reactions of $[PtCl_4(en)]$ and $[PtCl_4(dach)]$ with 5′-GMP and L-histidine were studied spectrophotometrically by following the change in absorbance

Table 1. Rate constants for substitution reactions of Pt(IV) complexes with L-histidine and 5′-GMP at 310 K in 25 mmol L^{-1} Hepes buffer (pH = 7.2) and 10 mmol L^{-1} NaCl.

	L-Histidine			5′-GMP		
	λ(nm)	$10^2\ k_2(M^{-1}s^{-1})$	$10^5\ k_1(s^{-1})$	λ(nm)	$10^2\ k_2(M^{-1}s^{-1})$	$10^5\ k_1(s^{-1})$
$[PtCl_4(en)]$	250	3.29 ± 0.05	0.11 ± 0.03	360	2.04 ± 0.04	0.070 ± 0.003
$[PtCl_4(dach)]$	360	3.04 ± 0.09	2.3 ± 0.6	360	1.93 ± 0.08	1.2 ± 0.5

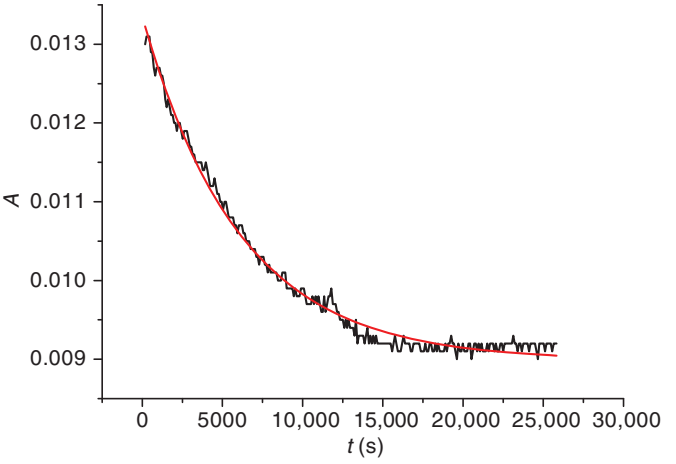
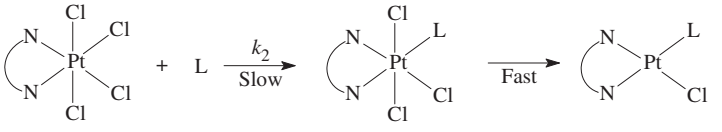


Figure 2. Kinetic traces for the reaction between $[PtCl_4(en)]$ (0.2 mmol L^{-1}) and 5′-GMP (10 mmol L^{-1}) at 310 K, λ = 360 nm, pH = 7.2, 25 mmol L^{-1} Hepes, 10 mmol L^{-1} NaCl.

at suitable wavelengths as a function of time at 310 K [22]. The working wavelength for each reaction system was determined by recording the spectra of reaction mixture over the wavelength range between 220 and 450 nm. These values are presented in the table 1. The reactions were initiated by mixing equal volumes of the complex and nucleophile solutions (1.5 mL) in the quartz cuvette. Concentration of ligand solution was always large enough (at least 10-fold) to provide pseudo-first-order conditions. The kinetic traces gave an excellent fit to a single exponential (an example is shown in figure 2). All reported pseudo-first-order rate constants, k_{obsd}, represent an average of two to four independent kinetic runs (data are given in Supplementary material, tables 1S and 2S).

2.4. *^{1}H-NMR measurements*

^{1}H-NMR measurements of reactions between complexes and nucleophiles were done with a freshly prepared sample of the reactants. A 5 mmol L^{-1} solution of the complex was prepared in 300 μL D_2O approximately 10 min prior to the start of the kinetic experiment. The solution with the same concentration of ligands (300 μL D_2O, 5 mmol L^{-1} ligand) was added to the solution of the complex to initiate the reaction. NMR spectra were recorded at 298 K over a period of several days until the completion



N–N = dach, en; L = 5′-GMP, L-Histidine

Scheme 1.

of the reaction. No buffer was used to prevent the increased activation of the complexes due to the coordination of phosphate [23] or interfering signals in the observed peak areas. The pH* (pD = pH + 0.4, [24]) changed slightly from 8.0 to 7.5 upon the completion of reaction.

The pH meter was calibrated with Fischer-certified buffer solutions of pH 4.00, 7.00, and 11.00. Meter readings were corrected for deuterium isotope effect by adding 0.4 units to the display readout. The pD was adjusted with 0.01–0.05 mol L^{-1} solutions of NaOD and DCl.

2.5. *HPLC measurements*

For HPLC determinations isocratic method was used with water as a mobile phase. Before measurement, the system was calibrated. The calibration was done with eluent which consists of acetonitrile and water, in different ratio, starting from $MeCN : H_2O = 100\% : 0\%$. The calibration is finished when only the water flows through the column. Then, the other parameters depending on reaction should be specified (pressure, flow rate, and working wavelength).

Reactions between studied Pt(IV) complexes with L-histidine were studied by this method. For each reaction the solutions of complex and ligand in 25 mmol L^{-1} Hepes per 10 mmol L^{-1} NaCl were mixed at the beginning and kept in thermo-blocker at 310 K during the reaction. At defined time intervals, a sample of reaction mixture (20 μL) was injected to the column and chromatograms recorded.

3. Results and discussion

Kinetic studies for substitution reactions of $[PtCl_4(en)]$ and $[PtCl_4(dach)]$ complexes with 5′-GMP and L-histidine were followed spectrophotometrically as pseudo-first-order reactions at 310 K in 25 mmol L^{-1} Hepes buffer (pH = 7.2) and 10 mmol L^{-1} NaCl to prevent the hydrolysis of complexes. Following the changes in absorbance at suitable wavelengths as a function of time, we calculated the values for pseudo-first-order rate constants, k_{obsd}, using Microsoft Excel and Origin 6.1.

Generally, the substitution of these Pt(IV) complexes can be described by scheme 1, where one of the chlorides from the coordination sphere of starting complex is substituted with entering ligand, characterized by rate constant k_2.

We obtained the graphs shown in figures 3 and 4 from the experimentally obtained values for k_{obsd} at different ligand concentrations, where linear dependence is confirmed.

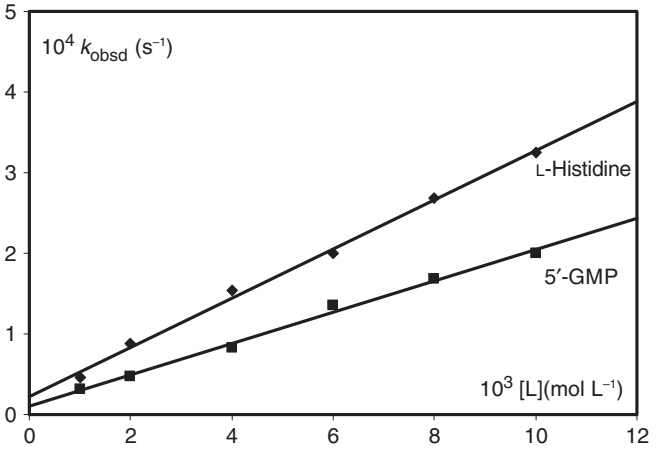


Figure 3. Pseudo-first-order rate constants, k_{obsd}, as a function of ligand concentration for substitution reactions of [$PtCl_4$(dach)] at 310 K, in 25 mmol L^{-1} Hepes buffer (pH = 7.02) with addition of 10 mmol L^{-1} NaCl.

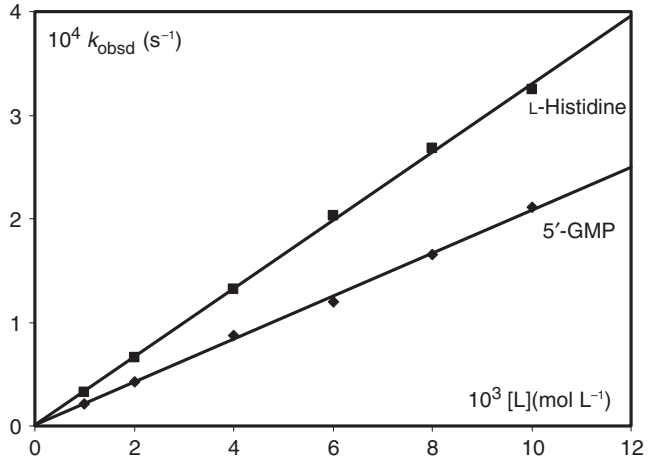
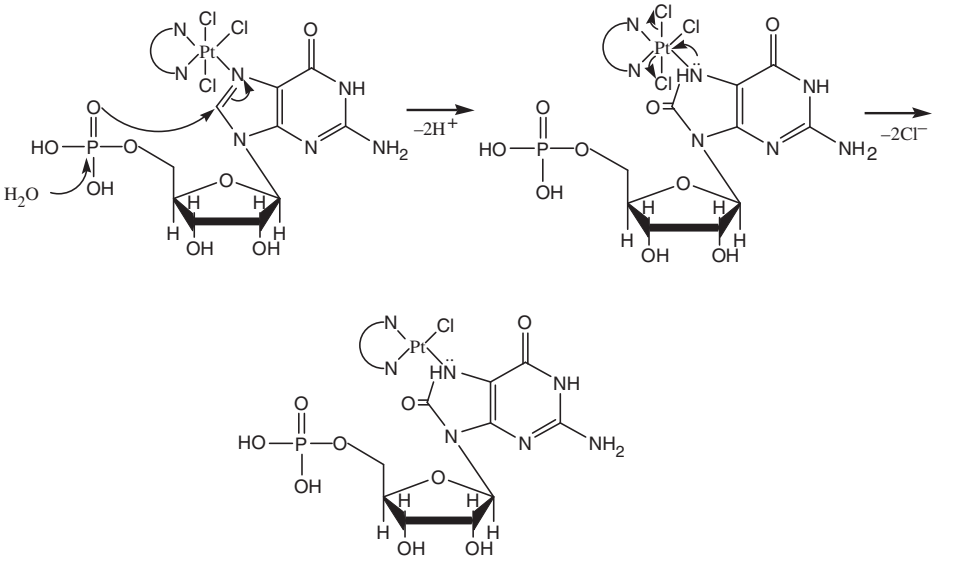


Figure 4. Pseudo-first-order rate constants, k_{obsd}, as a function of ligand concentration for substitution reactions of [$PtCl_4$(en)] at 310 K, in 25 mmol L^{-1} Hepes buffer (pH = 7.02) with addition of 10 mmol L^{-1} NaCl.

The value of k_2 could be calculated using equation (1), from the slope of the observed straight line. The rate constants of all studied reactions are summarized in table 1.

$$k_{obsd} = k_1 + k_2[L] \quad (1)$$

From the data, [$PtCl_4$(en)] reacts slightly faster than [$PtCl_4$(dach)] and L-histidine is better a nucleophile than 5′-GMP. These results could be easily explained by comparing the structures of en and dach, as well as the structures of the entering ligands. The reactivity of these complexes toward nucleotide was already explained by Choi *et al.* [17].



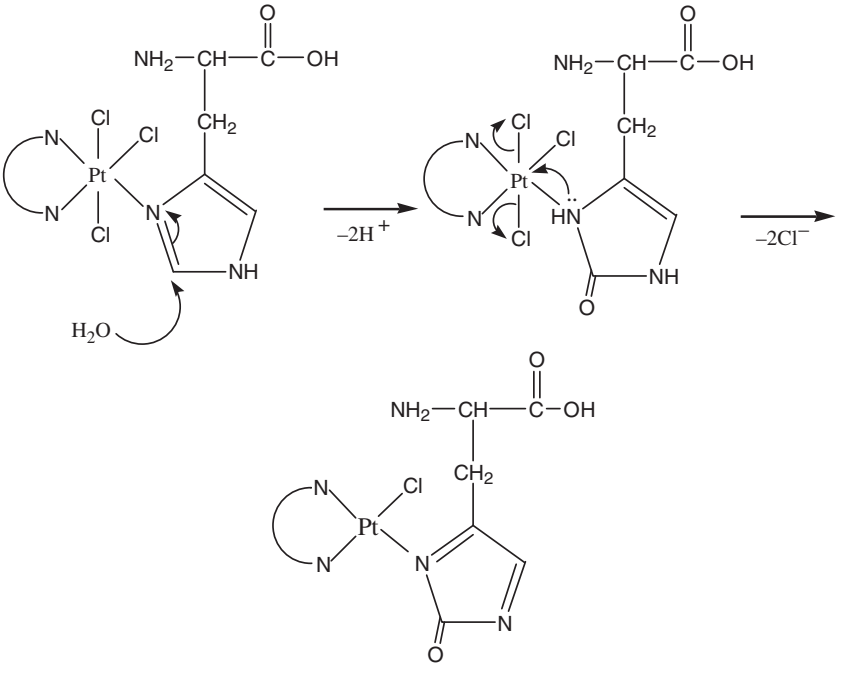
Scheme 2. Proposed mechanism for the reaction of Pt(IV) complexes with 5′-GMP.

Scheme 1 also describes that slow substitution of Pt(IV) complex is followed by very fast reduction to corresponding Pt(II) complex; the rate constants for reductive elimination are not determined. However, the proposed mechanism for the reduction of these Pt(IV) complexes in the presence of 5′-GMP is shown in scheme 2.

After coordination to platinum complex *via* N7 of 5′-GMP molecule, the attack of oxygen of phosphate on C8 position of purine base causes the transfer of electron pair of double bond to nitrogen. Further electron transfer leads to the reductive elimination and formation of square-planar Pt(II) complex substituted with 8-oxo-5′-GMP. This mechanism of substitution followed by reduction as well as the presence of final Pt(II) product were confirmed by NMR in solution [16–20].

The substitution and reduction of Pt(IV) complexes with L-histidine is shown in scheme 3. The inner-sphere transfer of electrons of double bond *via* coordinated nitrogen to platinum gives the final square-planar Pt(II) complex substituted with an imidazolone derivative of L-histidine, which is formed as a product of oxidation [25].

The same substitution reactions were studied by ^{1}H-NMR and the obtained spectra confirm the previous results. In the solution observed by mixing an equimolar concentration of [$PtCl_4$(en)] complex and L-histidine, after 24 h the signal between 7.2 and 7.9 ppm is dominant (figure 5). After 48 h, slight separation between the signals of coordinated and free ligand is monitored, while after 7 days these two signals are at 7.930 ppm for coordinated L-histidine and 7.878 ppm for free L-histidine. To confirm that the reduction of Pt(IV) occurs and that the final product is Pt(II) complex, we followed the same conditions as the reaction of [$PtCl_2$(en)] and L-histidine (time dependence is shown in figure 4S, Supplementary material). The spectrum of the reaction mixture after 7 days is the red-colored spectrum (figure 3). After 7 days, the two signals, for coordinated and free L-histidine, are at the same chemical shift for the [$PtCl_2$(en)] and [$PtCl_4$(en)] complexes (see figure 5S in "Supplementary material"),



Scheme 3. Proposed mechanism for the reaction of Pt(IV) complexes with L-His.

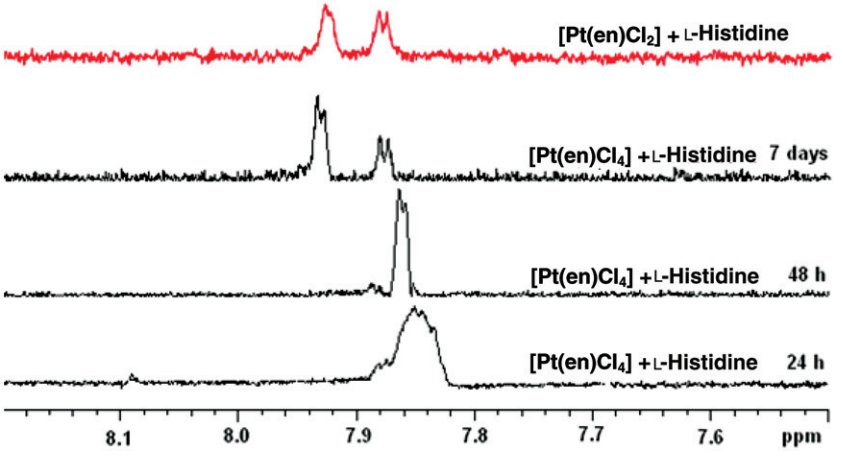


Figure 5. ^{1}H-NMR spectra of the reaction between [Pt(en)Cl$_4$] and L-histidine.

confirming that during the reactions the reduction of Pt(IV) to Pt(II) occurs in reactions with L-histidine.

In the reaction between [PtCl$_4$(en)] and 5′-GMP the signal of free ligand is at 8.225 ppm (figure 6). The signal of coordinated 5′-GMP, which intensity increase with the time, is at 8.768 ppm. The red colored spectra in figure 6 is the final spectrum obtained during the reaction of [PtCl$_2$(en)] with 5′-GMP (stepwise kinetics is shown in

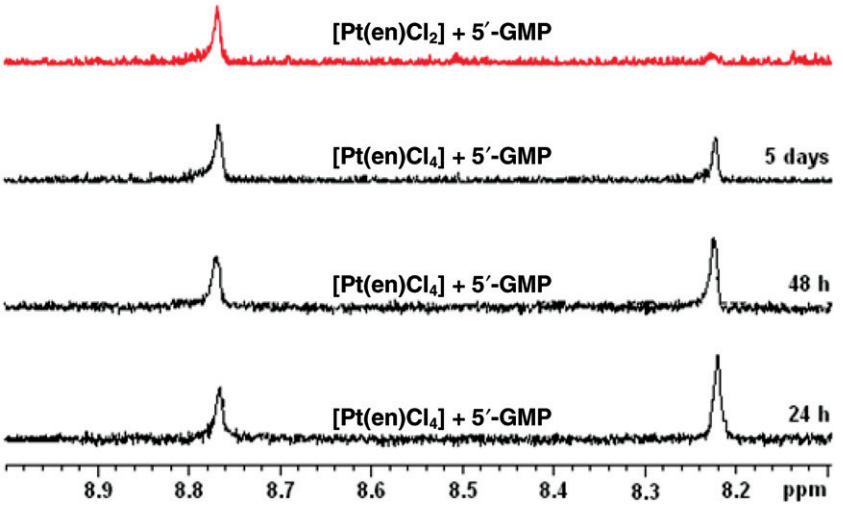


Figure 6. ^{1}H-NMR spectra of the reaction between [Pt(en)Cl_4] and 5′-GMP.

figure 3S, Supplementary material). The similarity between the final ^{1}H-NMR spectra provide the conclusion that the final product of the reaction between [$PtCl_4$(en)] and 5′-GMP is Pt(II) complex (in figure 6S in Supplementary material are compared just these two final spectra).

The reactions of [$PtCl_4$(dach)] with 5′-GMP and L-histidine were also studied by ^{1}H-NMR (figures 1S and 2S, Supplementary material). For the reaction with L-histidine, the signal of coordinated ligand is at 8.462 ppm and its intensity increases with time. In the reaction of [$PtCl_2$(dach)] with L-histidine, we again obtained the signal at 8.462 ppm (figure 7S, Supplementary material), indicating that in reactions of [$PtCl_4$(dach)] with L-histidine there is a reduction of Pt(IV) to Pt(II). However, in the spectra (1S Supplementary material) a downfield shift of the signals results from changes in pH.

For reaction with 5′-GMP, the free ligand is at 8.200 ppm. When the nucleotide reacts with the complex, a signal at 8.630 ppm appears with an increase in the intensity during the reaction (2S Supplementary material). After 24 h, this signal exists as a doublet because 5′-GMP is partially coordinated to Pt(IV) and the Pt(II) complex is reduced. But after few days, when the reduction is almost finished, signal at 8.630 ppm becomes a singlet [16].

Reactions of [$PtCl_4$(en)] and [$PtCl_4$(dach)] with L-histidine were monitored by HPLC as well. In the column the thermostated solution obtained by mixing appropriate complex and ligand solutions is injected. The chromatograms for the reaction between [$PtCl_4$(en)] and L-histidine at different time intervals are shown as figure 7. After mixing, a very small signal at 2.0 min appears while a very broad signal of free L-histidine is dominant. During the reaction, the signal at 2.0 min increases and after about 7 days the signals of product and free L-histidine have the same intensity. Also, a small peak at 3.0 min could be seen in the spectra, possibly a product of the first step. Its concentration is very small and appears in the spectra when the concentration of free L-histidine decreases. After about 10 days, only the final product and a small concentration of free ligand are observed in the solution.

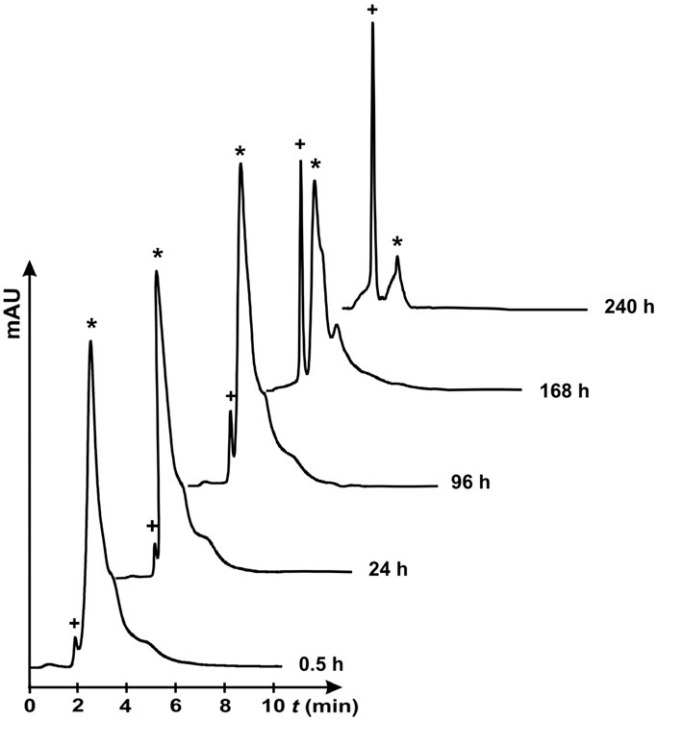


Figure 7. HPLC chromatograms for reaction between [$PtCl_4$(en)] and L-histidine at pH = 7.2, T = 310 K, λ = 250 nm; [*] – L-histidine (Retention time, RT = 2.5 min); (+) – product (RT = 2.0 min).

Figure 8 shows the results for the reaction between [$PtCl_4$(dach)] with L-histidine using HPLC method. There is a signal of free L-histidine at 2.5 min and a signal of the product of the reaction at 2.8 min. A signal at 6.9 min is already known as the free complex from the published results [16]. After about 10 days, only one product of the reaction and a small concentration of free ligand exist. Narrowing of the signal at the beginning of the reaction supports the fact that a substituted product of Pt(IV) complex could be present in the solution, but at the end we have only one reduced product.

4. Conclusion

The reactivity of Pt(IV) complexes depend on the structure of inert bidentate ligand as well as the structure of the entering nucleophiles, 5′-GMP and L-histidine. The substitution reactions of [$PtCl_4$(en)] are faster than those with [$PtCl_4$(dach)], while the smaller L-histidine nucleophile reacts faster than 5′-GMP. The substitution reactions were followed by fast reduction of Pt(IV) to Pt(II) complexes. Using different methods of analysis, the assumption that the final products in these reactions are Pt(II) complexes is confirmed. These results contribute to the understanding of the interactions of Pt(IV) complexes with some biologically important nucleophiles.

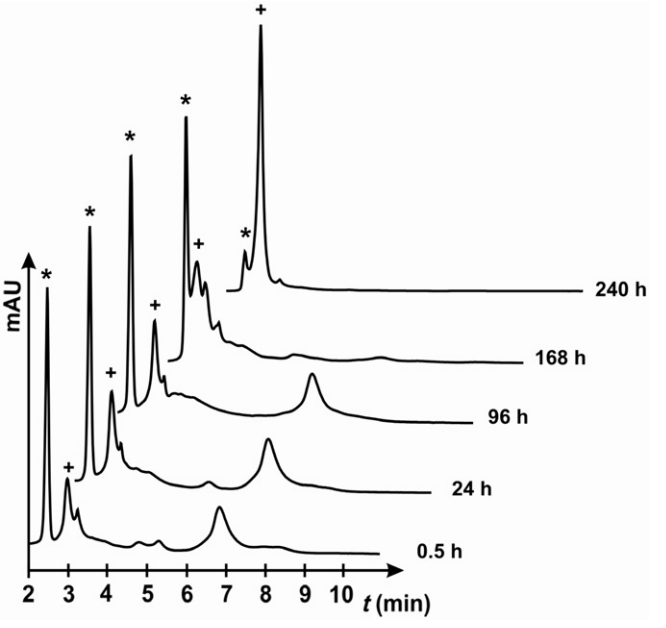


Figure 8. HPLC chromatograms for the reaction between $[PtCl_4(dach)]$ and L-histidine at pH = 7.2, $T = 310$ K, $\lambda = 360$ nm; [*] – L-histidine (RT = 2.5 min); (+) – product (RT = 2.8 min).

Acknowledgments

The authors are grateful to the Ministry of Science and Technology, Republic of Serbia, for providing financial support (Project no. 142008).

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