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Kinetic investigation of reactions of a 3-arylidene-2-thiohydantoin derivative with palladium(II) salts

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Abstract: ^{1}H-NMR spectroscopy was used to monitor the reactions of an arylidene 2-thiohydantoin derivative, 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**), with $PdCl_2$, *cis*-$[PdCl_2(dmso\text{-}S)_2]$ and $K_2[PdCl_4]$ in DMSO-d_6 in order to elucidate the reaction kinetics and mechanism. The 2-thiohydantoin derivative **3** formed *cis*-$[Pd(\mathbf{3}\text{-}N,S)(dmso\text{-}S)_2]^+$ complex (**5**) in reactions with $PdCl_2$ and *cis*-$[PdCl_2(dmso\text{-}S)_2]$, while no reaction with $K_2[PdCl_4]$ was observed. A two-step mechanism for the reactions of **3** with $PdCl_2$ and *cis*-$[PdCl_2(dmso\text{-}S)_2]$ is proposed, in which fast coordination to the side chain nitrogen occurs in the first step, while chelation and coordination to the sulfur atom in the 2-thiohydantoin ring is the second, slower, rate-determining step. The reaction rate constants were calculated and reactivities of the 2-thiohydantoin derivative **3** towards the palladium(II) salts were compared and discussed. Reaction of **3** with *cis*-$[PdCl_2(dmso\text{-}S)_2]$ was faster than with $PdCl_2$. The investigated palladium(II) salts also react with the solvent, DMSO-d_6, and the influence of these side reactions on the outcome and kinetics of the 2-thiohydantoin derivative complexation reaction is discussed in detail. The obtained results of this study can have an impact in explanation of the coordination behavior of antitumor active palladium(II) and platinum(II) complexes.

Keywords: ^{1}H-NMR spectroscopy; reaction mechanism; 2-thioxo-4-imidazolidinone; coordination; Pd(II) complexes.

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INTRODUCTION

Thiohydantoins are sulphur derivatives of hydantoin, in which one or both of the carbonyl groups in the cyclic ureide structure are replaced with a thiocarbonyl group.[1] Out of this class of compounds, 2-thiohydantoins are certainly the most prominent and extensively researched. 2-Thiohydantoins represent a valuable molecular scaffold, exhibiting various biological and pharmacological activities and they have found applications in both medicine and industry.[2,3] They display a wide range of biological activities, such as antibacterial and antifungal,[4] anti--HIV,[5] anticarcinogenic,[6,7] anti-ulcer and anti-inflammatory,[8] anticonvulsive,[9] antimutagenic[10] and antimelanogenic.[11] 2-Thiohydantoins found various applications in industry, such as C-terminal protein sequencing standards,[12] textile printing reagents[13] and polymerization and complexation catalysts.[14]

Coordination of active compounds with biologically relevant transition metal ions can, at times, increase their activities, especially in regards to anticarcinogenic activity.[15] A newer, hybrid approach, in discovering new potential antitumor agents is coordination of active compounds with metal ions in order to improve their activity and selectivity.[16,17] 2-Thiohydantoins have a great affinity for coordination with transition metal ions.[18,19] Even though it is a small molecule, 2-thiohydantoin has four derivatization points, making its derivatives very versatile ligands. In addition to the heteroatoms in the ring, 2-thiohydantoin derivatives most often contain heteroatoms in the side chains of its substituents. Many kinds of various 2-thiohydantoin complexes have been synthesized and reported so far.[20–26] In particular, transition metal complexes of arylidene 2-thiohydantoin derivatives have been researched extensively, largely due to the biological activities they exhibit, primarily antimicrobial and anticancer.[21,27,28]

The aim of this study was to investigate the kinetics and mechanism of the coordination reactions of 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone, an arylidene 2-thiohydantoin derivative, with some palladium(II) salts. As arylidene 2-thiohydantoin metal complexes, palladium(II) in particular,[28] show some promise as prospective antitumor agents, a better understanding of the mechanisms of their formation, coordination modes and kinetics might prove beneficial for the design and conceptualization of novel, more potent compounds.

EXPERIMENTAL

Materials and methods

All chemicals and reagents used in this investigation were commercially obtained (from either Sigma–Aldrich or Acros) and were high in purity. They were used as received, without additional purification. NMR spectra were recorded on a Varian Gemini-2000 spectrometer at 50 and 200 MHz. DMSO-d_6 was used as the solvent and all chemical shifts were referenced accordingly. Downfield shifts were recorded as positive numbers. Tetramethylsilane was used as the internal reference and all chemical shits were rounded to the nearest 0.01 ppm.

*Synthesis and characterization of 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**)*

3-((Phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**) was synthesized using a slight modification of the formerly published procedure.[28] Benzaldehyde (0.01 mol) and thiosemicarbazide (0.01 mol) in methanol (30 mL) were heated for 3 h under reflux and cooled thereafter. Ethyl chloroacetate (0.01 mol) and anhydrous sodium acetate (0.03 mol) were added *in situ* and the mixture was heated for another 6 h under reflux. Upon the completion of the reaction, the mixture was cooled at room temperature and then added to cold water, for the resulting product to precipitate. The product was filtered off, rinsed with hot water, dried and re-crystallized from hot methanol. Structure and purity of the compound was confirmed by NMR (^{1}H and ^{13}C) and IR spectroscopy. The corresponding IR and NMR (^{1}H and ^{13}C) spectra, as well as analytical and spectral data are provided in the Supplementary material to this paper.

^{1}H-NMR kinetic experiments

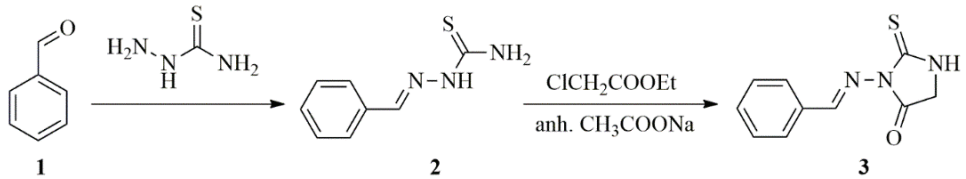
^{1}H-NMR kinetic measurements of the reactions of 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**) (0.021 mmol) with $PdCl_2$, *cis*-[$PdCl_2$(dmso-*S*)$_2$] and $K_2[PdCl_4]$ (0.021 mmol) in DMSO-d_6 (0.6 mL) were performed in standard 5 mm NMR tubes at room temperature in an overnight experiment. DMSO-d_6 solutions of the reactants (0.3 mL each) were freshly prepared right before the start of the experiment. After the mixing of the reactants, 29 spectra in total were recorded overnight for each of the experiments. The first six spectra were recorded with no delay, then the next three with a 5 min delay, then sets of three every 10, 15 and 30 min, and finally the last 11 spectra were recorded with an hour delay between them. The concentrations of the products at given experiment intervals were determined by integrating suitable proton signals in the ^{1}H-NMR spectra. The first-order rate constants were determined according to:

$$\ln c = -kt + \ln c_0 \quad (1)$$

where c is concentration, c_0 is starting concentration, k is the first-order rate constant and t is experiment time.

RESULTS AND DISCUSSION

3-((Phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**) was synthesized from benzaldehyde in a reaction with thiosemicarbazide (Scheme 1). Nucleophilic addition of thiosemicarbazide to benzaldehyde (**1**) yields thiosemicarbazone (**2**). Thiosemicarbazone (**2**) then undergoes a cyclocondenzation reaction with ethyl chloroacetate in the presence of anhydrous sodium acetate, forming the arylidene 2-thiohydantoin derivative, 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**).



1 **2** **3**

Scheme 1. Synthesis of 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**).

For the purpose of investigating the kinetics and mechanism of 3-arylidene--2-thiohydantoin coordination with Pd(II), a kinetic time-dependent experiment, monitoring the reactions of 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**) with $PdCl_2$, *cis*-[$PdCl_2$(dmso-*S*)$_2$] and $K_2[PdCl_4]$ in DMSO-d_6, was performed. DMSO-d_6 was used because it is suitable for dissolving both the 2-thiohydantoin derivative and the metal salts. Coordination of **3** to Pd(II) was tracked through the changes in specific signals in the spectra.

^{1}H-NMR spectra of the reaction of 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**) with *cis*-[$PdCl_2$(dmso-*S*)$_2$] in DMSO-d_6 are shown in Fig. 1. Signals of the coordinated 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**) can be observed, even from the first spectrum.

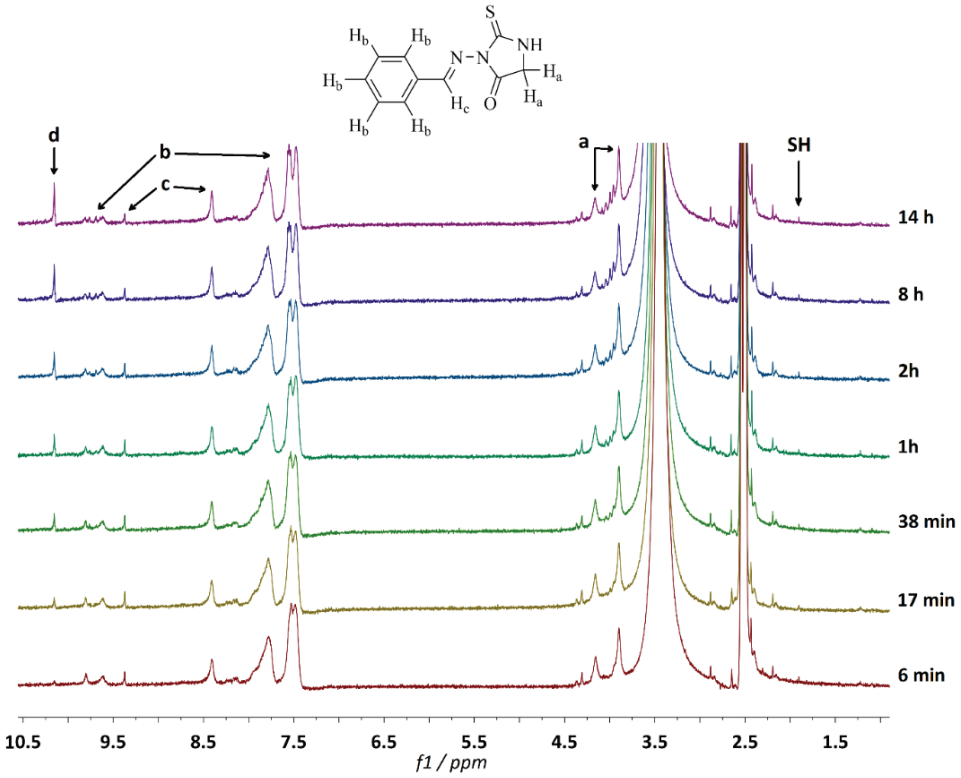
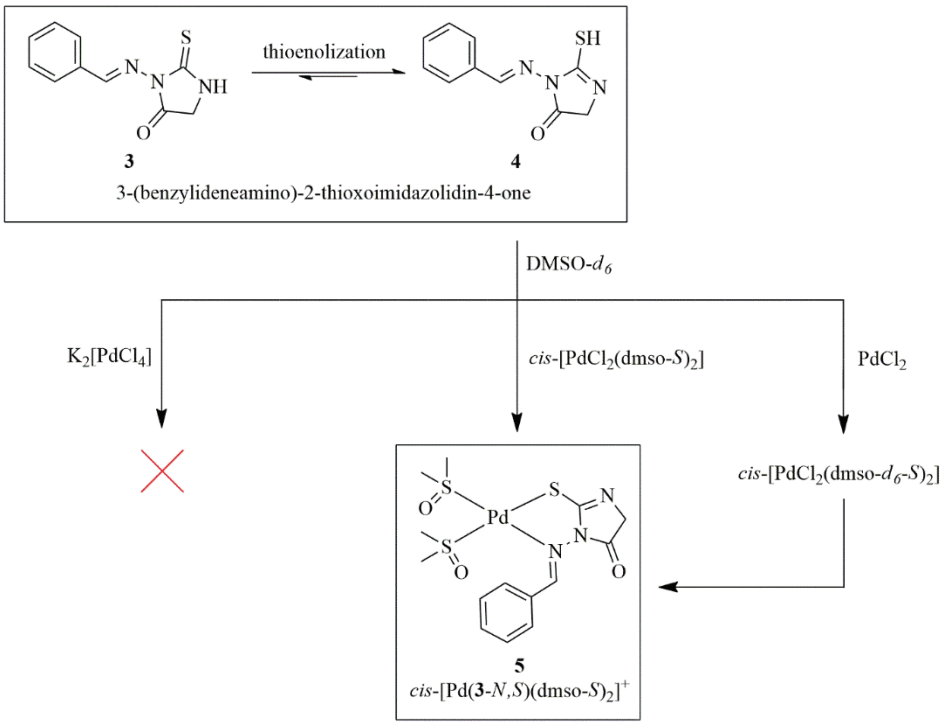


Fig. 1. Time-dependent ^{1}H-NMR spectra of the reaction of 3-((phenylmethylene)amino)-2--thioxo-4-imidazolidinone (**3**) and *cis*-[$PdCl_2$(dmso-*S*)$_2$] in DMSO-d_6.

As can be seen from Fig. 1, the singlet of the 2-thiohydantoin ring CH_2 group (a) is shifted downfield from 3.90 to 4.15 ppm. Multiplets of the aromatic benzene ring protons (b) moved downfield from 7.25–7.95 to 9.57–9.84 ppm, while the singlet of the double bond CH proton (c) is shifted downfield from 8.41

to 9.37 ppm. Signals of the coordinated 2-thiohydantoin derivative (a, b and c) can be observed from the first spectrum and their intensities do not change throughout the experiment. This, in fact, indicates fast initial coordination, too fast for the NMR time-scale.

One more thing that implies coordination is the absence of the broad singlet of the 2-thiohydantoion ring NH proton. 2-Thiohydantoins are known to exist in two tautomeric forms in equilibrium (Scheme 2).[29] It is proposed that the thio--enol tautomeric form (**4**) is responsible for coordination and furthermore, that this "keto-enol" equilibrium shifts to the thio-enol form during the reaction.[27] The SH protons of the thio-enol tautomer can be seen in the spectra as a singlet at 1.85 ppm (Fig. 1). Furthermore, a newly formed singlet at 10.15 ppm (d) can be observed increasing in intensity throughout the experiment. The new singlet at 10.15 ppm belongs to hydrochloric acid that forms from the deprotonation of the 2-thiohydantoin ring and the chloride anions that are substituted from *cis*--$[PdCl_2(dmso\text{-}S)_2]$.



Scheme 2. Reactions of 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**) with $PdCl_2$, *cis*-$[PdCl_2(dmso\text{-}S)_2]$ and $K_2[PdCl_4]$. No reaction of **3** was observed with $K_2[PdCl_4]$ during the course of the experiment (see Fig. S-4).

The reaction as a whole is proposed to proceed in two steps. In the first step (Eq.(2), initial coordination takes place through the nitrogen in the side chain. This is the faster reaction step, which is supported by the presence of the signals of the complex (a, b and c) in the first spectrum of the experiment, that then do not change in intensity during the experiment. The second, slower reaction step is diprotonation of the 2-thiohydantoin ring and coordination through the sulfur atom in the ring (Eq (3). The resulting complex (**5**) is a five-membered chelate with palladium(II) coordinated to the 2-thiohydantoin ring sulfur and the double bond nitrogen in the side chain:

$$cis\text{-}[PdCl_2(\text{dmso-}S)_2] + \mathbf{3} \rightarrow cis\text{-}[PdCl(\mathbf{3}\text{-}N)(\text{dmso-}S)_2]^+ + Cl^- \quad (2)$$

$$cis\text{-}[PdCl(\mathbf{3}\text{-}N)(\text{dmso-}S)_2]^+ + H_2O \rightarrow$$

$$cis\text{-}[Pd(\mathbf{3}\text{-}N,S)(\text{dmso-}S)_2]^+ (\mathbf{5}) + H_3O^+ + Cl^- \quad (3)$$

Even though the spectral data clearly shows a reaction between the 2-thiohydantoin derivative **3** and *cis*-$[PdCl_2(\text{dmso-}S)_2]$, it does not necessarily give a clear insight in the chemistry of reaction beyond modes of coordination. Concentrations of the formed complex **5** were calculated by integration of the suitable proton signal at 10.15 ppm (Fig. 2). As hydrochloric acid forms equimolarly with the complex **5**, according to Eq. (3), concentrations determined from that signal can be regarded as concentrations of complex **5**. The singlet at 10.15 ppm was integrated against the singlet of the uncoordinated 2-thiohydantoin derivative **3** at 8.40 ppm. The relative changes of the intensity of the singlet at 10.15 ppm is directly proportional to the change in concentration of complex **5**, and the concentrations were calculated from the relative integral values.

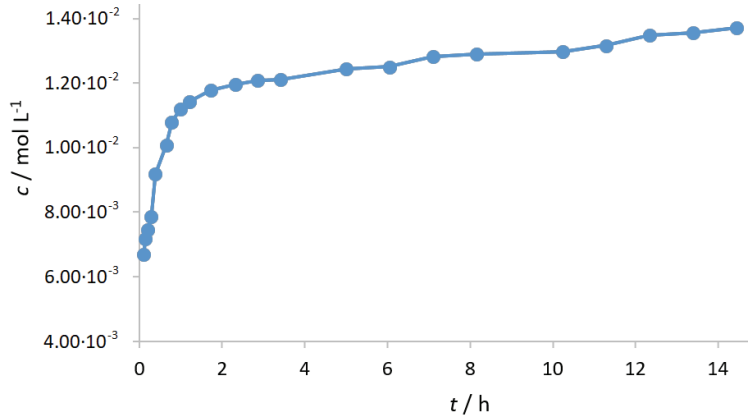


Fig. 2. Changes in product concentration, *cis*-$[Pd(\mathbf{3}\text{-}N,S)(\text{dmso-}S)_2]^+$, during the substitution reaction of *cis*-$[PdCl_2(\text{dmso-}S)_2]$ with 2-thiohydantoin derivative **3** in DMSO-d_6.

It can be seen in the plot that after about an hour into the experiment, complex formation slows down drastically. If we take into consideration the stoichio-

metry of the system, at the end of the experiment, more than half of the initial amount of the 2-thiohydantoin derivative **3** has not undergone any sort of reaction, implying that the reaction system is a bit more complex and that *cis*-[$PdCl_2$(dmso-*S*)$_2$] undergoes multiple competing reactions.

In order to gain a deeper insight into the details of the mechanism of the reaction, a plot of the logarithm of the product concentration *vs* experiment time was analyzed (Fig. 3). In the plot, it is clearly visible that this is not a linear first-order reaction, but instead, two linear slopes can be observed. This goes along with the conclusion that multiple processes are occurring, not just the reaction of *cis*-[$PdCl_2$(dmso-*S*)$_2$] with 2-thiohydantoin derivative **3**. For the first hour, the reaction direction can be described with the equation $y = (1.63\pm0.17)\times10^{-4}x$ – – 5.01. After about an hour, the reaction kinetics change course and the new direction can be described with the equation $y = (3.36\pm0.20)\times10^{-6}x - 4.46$. The first phase of the reaction is significantly faster, with the slope coefficient k_1 = = 1.63×10^{-4} s^{-1}, than the second phase with the coefficient $k_2 = 3.36\times10^{-6}$ s^{-1}. A change in the system occurred and a chemical species emerged, the concentration of which has only become significant after an hour into the experiment.

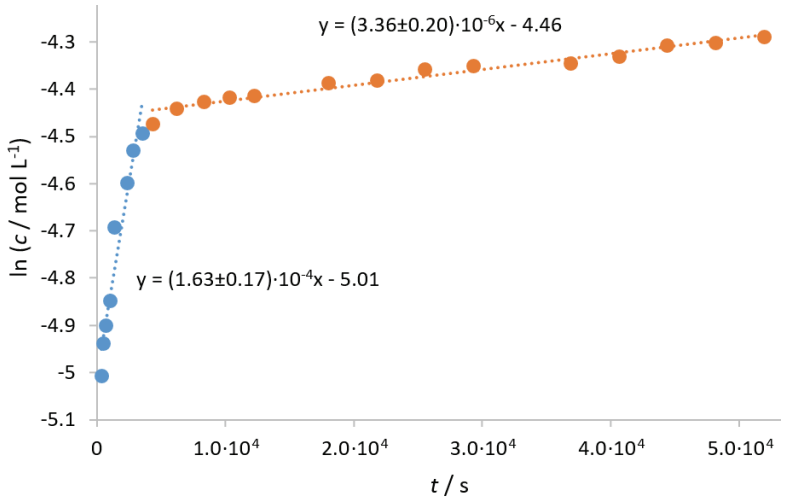


Fig. 3. First-order plot for the substitution reaction of *cis*-[$PdCl_2$(dmso-*S*)$_2$] with 2-thiohydantoin derivative **3** in DMSO-d_6.

cis-[$PdCl_2$(dmso-*S*)$_2$] most likely engages in a parallel reaction with the solvent, as it is known that *cis*-[$PdCl_2$(dmso-*S*)$_2$] can react with DMSO, yielding *cis*-[Pd(dmso-*O*)$_2$(dmso-*S*)$_2$]$^{2+}$.[30,31] *cis*-[$PdCl_2$(dmso-*S*)$_2$] has two molecules of DMSO in *cis*-configuration bonded through sulfur atoms. DMSO molecules coordinated through the sulfur atoms exhibit a very strong *trans* effect on the neighbouring chlorido ligands, which in turn weakens their bonds with palla-

dium(II). With this in mind, *cis*-[$PdCl_2$(dmso-*S*)$_2$], apart from reaction with the 2-thiohydantoin derivative **3**, reacts with DMSO, forming tetrakis(dimethyl sulphoxide)palladium(II), *cis*-[Pd(dmso-*O*)$_2$(dmso-*S*)$_2$]$^{2+}$, with the other two DMSO molecules bonded through the oxygen. There is a slight deviation from the ideal square-planar structure in *cis*-[Pd(dmso-*O*)$_2$(dmso-*S*)$_2$]$^{2+}$, the biggest of which being the angle between the two sulfur bonded DMSO molecules, due to steric repulsions between the methyl groups of one DMSO and the sulfoxy group of the other. These steric repulsions prohibit the *S*-bonding of the other DMSO molecules, which is believed to be the main reason for coordination through oxygen.[30]

Two parallel reactions of *cis*-[$PdCl_2$(dmso-*S*)$_2$] take place during the experiment. The first is with the 2-thiohydantoin derivative **3** (Eq. (4)) and the other is with the solvent, DMSO, Eq. (5):

$$\textit{cis}\text{-}[PdCl_2(\text{dmso-}S)_2] + \mathbf{3} + H_2O \rightarrow \textit{cis}\text{-}[Pd(\mathbf{3}\text{-}N,S)(\text{dmso-}S)_2]^+ + H_3O^+ + 2Cl^- \quad (4)$$

$$\textit{cis}\text{-}[PdCl_2(\text{dmso-}S)_2] + 2\text{DMSO} \rightarrow \textit{cis}\text{-}[Pd(\text{dmso-}O)_2(\text{dmso-}S)_2]^{2+} + 2Cl^- \quad (5)$$

The reaction is faster in the first phase, during the first hour of the experiment ($k_1 = 1.63\times10^{-4}$ s^{-1}), up until a dynamic equilibrium is achieved and a significant amount of *cis*-[Pd(dmso-*O*)$_2$(dmso-*S*)$_2$]$^{2+}$ is formed, then the complex formation reaction (Eq (4)) slows down in the second phase ($k_2 = 3.36\times10^{-6}$ s^{-1}), because there is a significantly smaller amount of the reactant, *cis*-[$PdCl_2$(dmso-*S*)$_2$], in the system.

Coordination of 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**) in the reaction with $PdCl_2$ takes place in the same manner as with *cis*-[$PdCl_2$(dmso-*S*)$_2$]. All the same signals with identical chemical shifts can be observed in the spectra of the reaction (Fig. 4). Pairs of signals of the coordinated and uncoordinated **3**, among which are singlets of the 2-thiohydantoin ring CH_2 group protons (a), multiplets of the aromatic benzene ring protons (b) and singlets of the double bond CH proton (c), can be seen at the same chemical shift in the spectra. Thio-enol tautomer –SH proton is at 1.85 ppm, the broad singlet of the 2-thiohydantoin ring –NH proton is missing and the HCl singlet at 10.15 ppm increases throughout the experiment.

Upon calculating the concentrations of the formed *cis*-[Pd(**3**-*N,S*)(dmso-*S*)$_2$]$^+$ complex (**5**, Eq. (3)) from the spectral data, an obvious difference in reaction rates was observed and it was noticed that the reaction with $PdCl_2$ is slower than with *cis*-[$PdCl_2$(dmso-*S*)$_2$]. Changes in complex **5** concentrations over the course of the experiment are shown in Fig. 5. The difference in the kinetics of the systems are somewhat perplexing, as spectral data confirms that the same reaction product is formed in both cases.

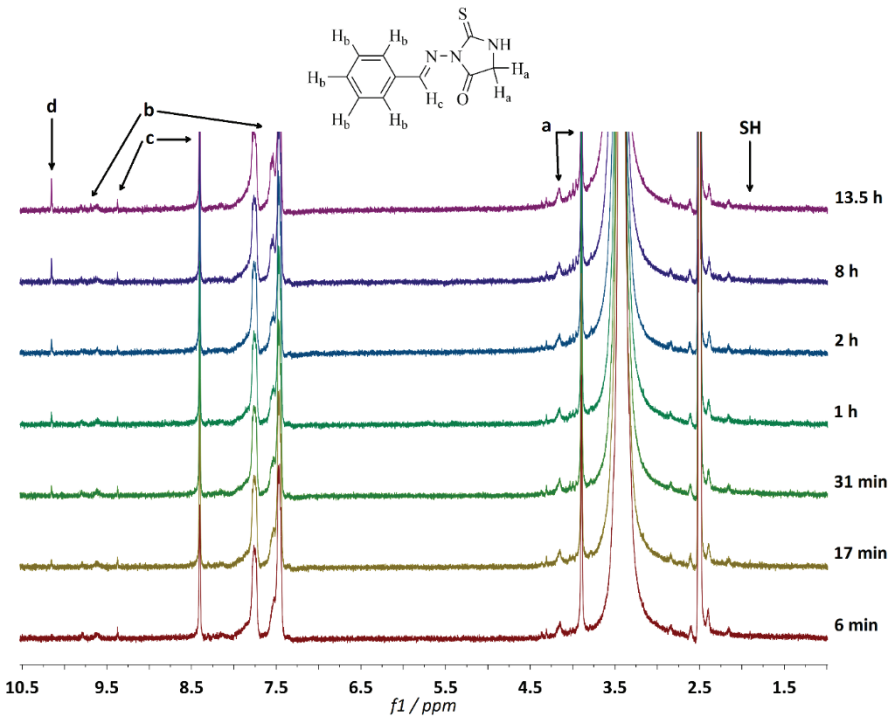


Fig. 4. Time-dependent ^{1}H-NMR spectra of the reaction of 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**) and $PdCl_2$ in DMSO-d_6.

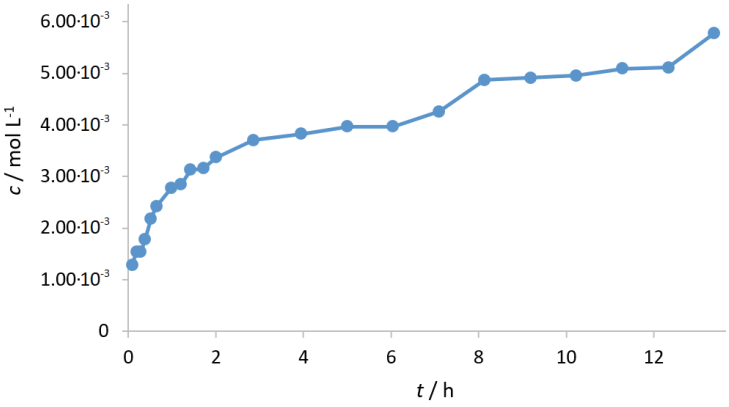


Fig. 5. Changes in *cis*-[Pd(**3**-*N*,*S*)(dmso-*S*)$_2$]$^+$ complex (**5**) concentration during the substitution reaction of $PdCl_2$ with 2-thiohydantoin derivative **3** in DMSO-d_6.

In order to get to the bottom of this, a plot of the logarithm of the product concentration *vs.* experiment time was analyzed (Fig. 6). As with *cis*-[$PdCl_2$(dmso-*S*)$_2$], in this case there are also two phases, with two linear slopes

that intercept after little over an hour. The first phase can be described with the equation $y = (1.80\pm0.22)\times10^{-4}x - 6.59$, while the second phase can be described with the equation $y = (1.25\pm0.09)\times10^{-5}x - 5.77$. The first phase, where most of the complex is formed, has a coefficient $k_1 = 1.80\times10^{-4}$ s^{-1}, which is very close to the slope coefficient of the first phase of the reaction of *cis*-[$PdCl_2$(dmso-*S*)$_2$] ($k_1 = 1.63\times10^{-4}$ s^{-1}). It is known that $PdCl_2$ has great affinity towards DMSO and reacts with it to form *cis*-[$PdCl_2$(dmso-*S*)$_2$],[32] according to:

$$PdCl_2 + 2DMSO \rightarrow \textit{cis}\text{-}[PdCl_2(\text{dmso-}S)_2] \quad (6)$$

It can be concluded that in both cases, basically the same reaction occurs (Eq. (4)), which is supported by the very close values of the reaction coefficients k_1. The reaction is slower with $PdCl_2$ because the salt itself does not react with the 2-thiohydantoin derivative **3**. Only when a sufficient amount of *cis*-[$PdCl_2$(dmso-*S*)$_2$] forms does the reaction take place. The lower rate of the reaction with $PdCl_2$ can be explained with the lower reactant concentration.

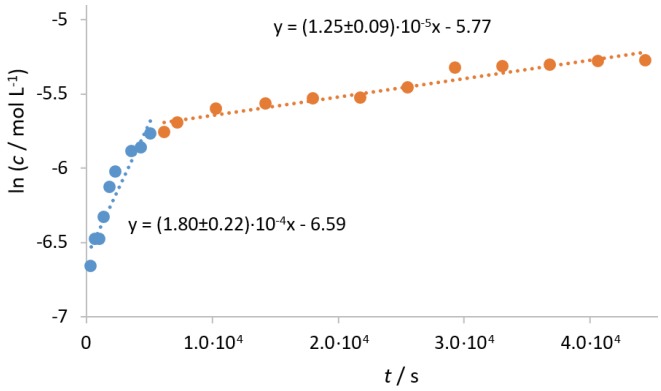


Fig. 6. First-order plot for the substitution reaction of $PdCl_2$ with 2-thiohydantoin derivative **3** in DMSO-d_6.

In the case of the third examined palladium(II) salt, $K_2[PdCl_4]$, there was no reaction with 3-((phenylmethylene)amino)-2-thioxo-4-imidazolidinone (**3**) during the course of the experiment. No signals of a newly formed 2-thiohydantoin complex species of any kind could be observed (Fig. S-4). The four chlorido ligands in $K_2[PdCl_4]$ are kinetically equivalent and a strong possibility is that all of them were substituted with DMSO, as tetrachloroplatinate(II) and also tetrachrloropalladate(II) can react with DMSO in this manner.[33] This would prohibit the reaction with the 2-thiohydantoin derivative **3**.

CONCLUSION

Reactions of an arylidene 2-thiohydantoin derivative, 3-((phenylmethylene)-amino)-2-thioxo-4-imidazolidinone (**3**) with $PdCl_2$, *cis*-[$PdCl_2$(dmso-*S*)$_2$] and

$K_2[PdCl_4]$ in DMSO-d_6 were monitored in a time-dependent kinetic ^{1}H-NMR experiment. In the cases of $PdCl_2$ and *cis*-[$PdCl_2$(dmso-*S*)$_2$], the complex *cis*-[Pd(**3**-*N,S*)(dmso-*S*)$_2$]$^+$ (**5**) was formed, with palladium(II) coordinated through the nitrogen in the side chain and the 2-thiohydantoin ring sulfur atom. The mechanism of complex **5** formation consists of two steps. The first step is fast monodentate coordination of **3** *via* its nitrogen atom in the side chain. This step is too fast for the NMR time-scale, but it is confirmed with the corresponding signals of the complex **5** that are unchanged during the course of the experiment. The second, rate determining step of the reaction is chelation of the intermediate *cis*-[PdCl(**3**-*N*)(dmso-*S*)$_2$]$^+$ complex through deprotonation of the 2-thiohydantoin ring of **3** and its coordination with the sulfur atom, finally yielding to the formation of complex **5**. Most of the complex **5** is formed during the first hour of the experiment. It is concluded that simultaneously, a competing reaction with the solvent occurs during which *cis*-[Pd(dmso-*O*)$_2$(dmso-*S*)$_2$]$^{2+}$ is formed, which ultimately halts the reaction. No reaction with $K_2[PdCl_4]$ was observed during the course of the experiment.

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SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12456, or from the corresponding author on request. CCDC 2269543-2269546.

ИЗВОД

КИНЕТИЧКО ИСПИТИВАЊЕ РЕАКЦИЈА 3-АРИЛИДЕНСКОГ ДЕРИВАТА 2-ТИОХИДАНТОИНА СА СОЛИМА ПАЛАДИЈУМА(II)

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Протонска НМР спектроскопија је употребљена за праћење реакције арилиденског деривата 2-тиохидантоина, 3-((фенилметилен)амино)-2-тиоксо-4-имидазолидинона (**3**), са $PdCl_2$, *cis*-[$PdCl_2$(dmso-*S*)$_2$] и $K_2[PdCl_4]$ у DMSO-d_6, да би се испитали кинетика и механизам реакције. Испитивани дериват 2-тиохидантоина **3** је наградио комплекс *cis*-[Pd(**3**-*N,S*)(dmso-*S*)$_2$]$^+$ (**5**) у реакцији са $PdCl_2$ и *cis*-[$PdCl_2$(dmso-*S*)$_2$], док са $K_2[PdCl_4]$ није уочена реакција. Претпостављен је двостепени механизам за реакције **3** са $PdCl_2$ и *cis*-[$PdCl_2$(dmso-*S*)$_2$], у коме се у првом кораку одиграва брза координација за азот из бочног низа, а хелатизација и координовање за тиохидантоински сумпор је други, спорији корак, који одређује брзину реакције. Израчунате су константе брзине реакције и реак-

тивности деривата 2-тиохидантоина **3** према солима паладијума(II) су упоређене и дискутоване. Реакција **3** са *cis*-[$PdCl_2$(dmso-S)$_2$] је била бржа од реакције са $PdCl_2$. Испитиване соли паладијума(II) су такође реаговале са растварачем (DMSO-d_6) и утицај ових реакција на исход и кинетику реакције комплексирања деривата 2-тиохидантоина је детаљно дискутован. Резултати добијени у оквиру овог истраживања могу имати утицај на појашњење координационог понашања антитуморски активних комплекса паладијума(II) и платине(II).

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