

## KINETICS OF THE REACTION OF AN ARYLIDENE 2-THIOHYDANTOIN DERIVATIVE WITH SOME Pd(II) COMPLEXES

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**Abstract:** Reactions of 3-(benzylideneamino)-2-thioxoimidazolidin-4-one with some palladium complexes (PdCl<sub>2</sub>, Pd(DMSO)<sub>2</sub>Cl<sub>2</sub> and K<sub>2</sub>PdCl<sub>4</sub>) were monitored with NMR spectroscopy, which is used as a convenient and practical tool for determining the kinetic parameters of the reactions. Rate constants of the reactions were determined and reactivity of the complexes towards the 2-thiohydantoin derivative was compared.

**Keywords:** kinetics, 2-thiohydantoin, NMR, complexes, Pd(II)

### Introduction

Thiohydantoins are sulphur analogues of hydantoin where at least one of the carbonyl groups is replaced with a thiocarbonyl group (Metwally and Abdel-Latif, 2012). The most recognizable and certainly the most researched compounds out of this group are 2-thiohydantoins. They are a valuable scaffold, with many biological, pharmacological and agricultural activities, with applications ranging from medicine and therapy to industry (Gawas et al., 2021). They possess a plethora of biological activities, such as antimicrobial (antibacterial and antifungal) (Marton et al., 1993), anti-HIV (Khodair et al., 1997), antimutagenic (Takahashi et al., 1996), anticancer (Al-Obaid et al., 1996), anticonvulsive (Habib et al., 2015), anti-ulcer and anti-inflammatory (Curran, 1976). Moreover, 2-thiohydantoins are used as reference standards for C-terminal protein sequencing (Mo et al., 1997), reagents for textile printing dye development (Nelson et al., 1997) and are used as well for metal complexation and polymerization catalysis (Kandil et al., 2004).

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2-Thiohydantoin possess a considerable coordination potential. Despite the small size of the 2-thiohydantoin molecule, it has four derivatization sites, which make its derivatives versatile ligands. Apart from the heteroatoms in the ring, the derivatives for the most part have heteroatoms in the side branches suitable for coordination and complexation. Many 2-thiohydantoin complexes have been synthesized so far. Particularly, arylidene 2-thiohydantoin complexes have been studied extensively, mostly because of their biological properties, such as antimicrobial and anticancer (Ismail et al., 2022).

In this study, for the purpose of examining the coordination potential of an arylidene 2-thiohydantoin derivative, 3-(benzylideneamino)-2-thioxoimidazolidin-4-one, towards palladium, the compound was subjected to  $^1\text{H}$  NMR monitoring of its reactions with some Pd(II) complexes,  $\text{PdCl}_2$ ,  $\text{Pd}(\text{DMSO})_2\text{Cl}_2$  and  $\text{K}_2\text{PdCl}_4$ . Studying the kinetics of the reaction will prove useful for the elucidation of mechanisms of 2-thiohydantoin coordination.

### Materials and methods

All chemicals and reagents used in this study were commercially available and of high purity and were used in their obtained state, without further purification. 3-(Benzylideneamino)-2-thioxoimidazolidin-4-one was synthesized according to a previously published protocol (Stanić et al., 2020).

$^1\text{H}$  NMR spectra were attained on a Varian Gemini-2000 spectrometer at 200 MHz. All chemical shifts were referenced to the solvent dimethylsulfoxide- $d_6$  ( $\text{DMSO}-d_6$ ) and downfield shifts were recorded as positive numbers.

$^1\text{H}$  kinetic experiments between 3-(benzylideneamino)-2-thioxoimidazolidin-4-one and the palladium complexes were performed on fresh samples of the reactants in  $\text{DMSO}-d_6$  at ambient temperature. The 300  $\mu\text{L}$  10 mM solutions of the thiohydantoin and complex were prepared right before the start of the experiment. After mixing the reactants, consecutive spectra were recorded with no delay, then every 5 minutes, and later on every 10 minutes, 30 minutes, 1 hour and to hours over the course of an overnight experiment.

### Results and discussion

Reactions of 3-(benzylideneamino)-2-thioxoimidazolidin-4-one with  $\text{PdCl}_2$ ,  $\text{Pd}(\text{DMSO})_2\text{Cl}_2$  and  $\text{K}_2\text{PdCl}_4$  were monitored using a time dependent kinetic  $^1\text{H}$  NMR experiment. The reactions were carried out in  $\text{DMSO}-d_6$ , because it is a suitable solvent, dissolving both the thiohydantoin and the metal complex. The

reactions were carried out in a 1:1 molar ratio, following second order kinetics. The second order reaction constants were calculated according to the equation:

$$k_2 t = \frac{x}{c_{a0}(c_{a0} - x)} \quad (1)$$

Concentrations used for calculating the rate constants were determined by integrating suitable signals in the spectra.  $^1\text{H}$  NMR spectra of the reaction of 3-(benzylideneamino)-2-thioxoimidazolidin-4-one and  $\text{PdCl}_2$  are shown in Figure 1.

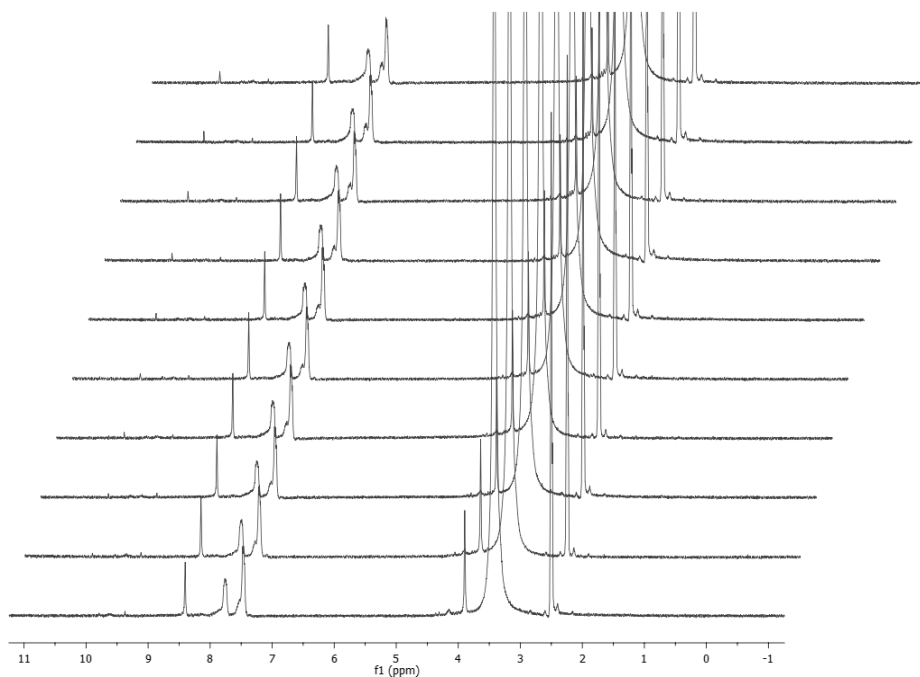


Figure 1.  $^1\text{H}$  NMR spectra of the reaction of 3-(benzylideneamino)-2-thioxoimidazolidin-4-one and  $\text{PdCl}_2$ .

In the spectra, we can observe the absence of NH proton broad singlets. It is known that 2-thiohydantoin exists in two tautomeric forms, and it is proposed that the tautomeric form in which the thiocarbonyl sulphur exists in its thiol form is responsible for coordination (Ismail et al., 2022). The proposed mode of coordination is presented in Scheme 1.

### Scheme 1. Coordination of 3-(benzylideneamino)-2-thioxoimidazolidin-4-one and PdCl<sub>2</sub>.

Along with the decreasing intensity of the signals of the reacting 2-thiohydantoin (which include the ring CH<sub>2</sub> singlet at 3.90 ppm, aromatic protons at 7.42-8.00 ppm and the singlet of the double bond CH proton at 8.40), we can also observe a singlet that increases with intensity at 10.15 ppm that belongs to the double bond CH proton of the coordinated 2-thiohydantoin in the newly formed complex. The newly formed singlet of the double bond CH proton of the coordinated 2-thiohydantoin indicates coordination to the adjacent double bond nitrogen. The result is a five-membered chelate complex, where Pd is coordinated to the thiolic sulphur and the double bond nitrogen. Coordination to the thiolic sulphur is too fast for the NMR time scale to quantify, but we can observe it through the lack of an NH proton signal. Coordination to the exocyclic double bond nitrogen is the slower, rate determining step of the reaction. The corresponding rate constants were determined by integrating the singlets of double bond CH protons of the free and coordinated ligand at 8.40 and 10.15 ppm respectively. The calculated rate constant for the reaction with PdCl<sub>2</sub> is  $6.83 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ , while for the reaction with Pd(DMSO)<sub>2</sub>Cl<sub>2</sub>, it is  $3.57 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ . There was no reaction with K<sub>2</sub>PdCl<sub>4</sub>. It seems that in DMSO, chloride ions are not exchangeable ligands for this reaction. Additionally, we can observe an NH signal at 12 ppm throughout the experiment with K<sub>2</sub>PdCl<sub>4</sub>, since 3-(benzylideneamino)-2-thioxoimidazolidin-4-one stayed in its non-reactive tautomeric form. The reaction with Pd(DMSO)<sub>2</sub>Cl<sub>2</sub> is faster than the reaction with PdCl<sub>2</sub> for a factor of 5. This is probably due to the labile DMSO ligands already in its structure, as PdCl<sub>2</sub> has to react with DMSO from the solvent first, forming Pd(DMSO-*d*<sub>6</sub>)<sub>2</sub>Cl<sub>2</sub>, and then react with the 2-thiohydantoin derivative.

### Conclusion

Reactions of an arylidene 2-thiohydantoin derivative, 3-(benzylideneamino)-2-thioxoimidazolidin-4-one with PdCl<sub>2</sub>, Pd(DMSO)<sub>2</sub>Cl<sub>2</sub> and K<sub>2</sub>PdCl<sub>4</sub> were monitored in a kinetic <sup>1</sup>H NMR experiment. Reaction rate constants were

determined for the reactions. The reaction with  $\text{Pd}(\text{DMSO})_2\text{Cl}_2$  was faster for a factor of 5 than with  $\text{PdCl}_2$ , probably because of the labile DMSO ligands, while there was no reaction with  $\text{K}_2\text{PdCl}_4$ . The resulting complexes were proposed to be five-membered chelates, bonded through the sulphur atom and the exocyclic double bond nitrogen. Bonding to the sulphur is a fast process, seen only indirectly through the absence of the NH proton of the 2-thiohydantoin, because it is too fast for the NMR time scale. The slower, rate determining step of the reaction is coordination to the exocyclic double bond nitrogen. The results of this study could prove beneficial for a better understanding of 2-thiohydantoin coordination chemistry.

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