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The influence of structural modification of Pd(II) pincer-type complexes on the kinetics of substitution reactions

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Abstract: This mini-review summarizes the kinetic data obtained for the substitution reactions of some palladium(II) complexes containing *bis*-pyrazolylpyridine derivatives as pincer-type ligands with biologically significant nitrogen- and sulfur-donor biomolecules as nucleophiles. Three structurally different palladium(II) complexes were selected: $[Pd(L1)Cl]^+$ (Pd1), $[Pd(L2)Cl]^+$ (Pd2) and $[Pd(L3)Cl]^+$ (Pd3) (where L1 = bis(2-(1H-pyrazol-1-yl)ethyl)amine, L2 = 2,6-bis(5-(tert-butyl)-1H-pyrazol-3-yl)pyridine, and L3 = 2,6-bis(5-(tert-butyl)-1-methyl-1H-pyrazol-3-yl)pyridine, while for the entering nucleophiles thiourea (Tu), L-methionine (L-met), and guanosine-5′-monophosphate (5′-GMP) were used. Kinetic measurements were carried out for all systems as *pseudo*-first order reactions (at least 10 times the ligand in excess relative to the complex) under physiological conditions using a stopped-flow UV-Vis spectrophotometer. By comparing the published results for the second-order rate constant, the relationship between the structural properties of the complexes and their reactivity towards selected nucleophiles was established. This overview shows that by tuning the lability of the inert ligands through steric and electronic (σ-donor and π-acceptor) effects, the biological behavior of the complexes can be significantly changed.

Keywords: Pd(II), structural modification, kinetics

1. Introduction

The application of transition metal ion complexes in chemotherapy is widely known [1]. Over the past decades, numerous Pt complexes have been designed and tested as potential antineoplastic agents [2]. Among them, cisplatin, carboplatin, and oxaliplatin entered the clinical trial, and today they are successfully used in the treatment of various types of cancers, such as testicular, ovarian, bladder, colon, head, neck, and small-cell

lung cancers [3]. However, serious side effects such as emesis, nephrotoxicity, neurotoxicity, ototoxicity, and drug resistance may occur during the application of these drugs as chemotherapeutics. These limitations have stimulated investigations for the improvement of existing platinum antitumor drugs and the development of new derivatives that display better therapeutic properties.

Special attention is directed towards palladium(II) complexes, which show higher kinetic reactivity and better solubility than platinum(II) compounds [4]. It is believed that palladium(II) complexes may possess an enhanced curative effect on cancers relative to platinum analogs. Thus, a huge number of structurally different palladium(II) complexes were synthesized and their influence on the tumor cells was examined, while the results indicated a better antitumor effect compared to analogous platinum compounds [5].

Mostly, the antitumor activity of some metallodrugs is based on their interactions with DNA molecules, while interactions with sulfur-containing biomolecules are responsible for the occurrence of toxic effects [6]. By studying the behavior of Pd-complexes in the presence of small biomolecules under physiological conditions, we can obtain key information that improves our understanding of the biochemical processes which occur in the body during the application of metal complexes as antitumor drugs.

2. Substitution reactions of complexes Pd1-Pd3 with different biomolecules

This mini review includes the results of testing the rate of substitution reactions of complexes Pd1-Pd3 (Figure 1) with nucleophiles, such as Tu, L-met and 5'-GMP by stopped-flow method [7, 8]. All kinetic measurements were carried out under the *pseudo*-first order conditions by monitoring the change in absorbance as a function of nucleophile concentration with time. The experiments were performed under physiological conditions at pH 7.2 and 25 ^{0}C in the presence of 50 mM NaCl to suppress the hydrolysis of complexes. The same reaction mechanism was reported for all systems, in which the labile chloride ligand from the inner coordination sphere of the starting complex was replaced by a nucleophile. This reaction is characterized by a second-order reaction rate constant, k_2. Calculated values for k_2 are given in Table 1 [7, 8].

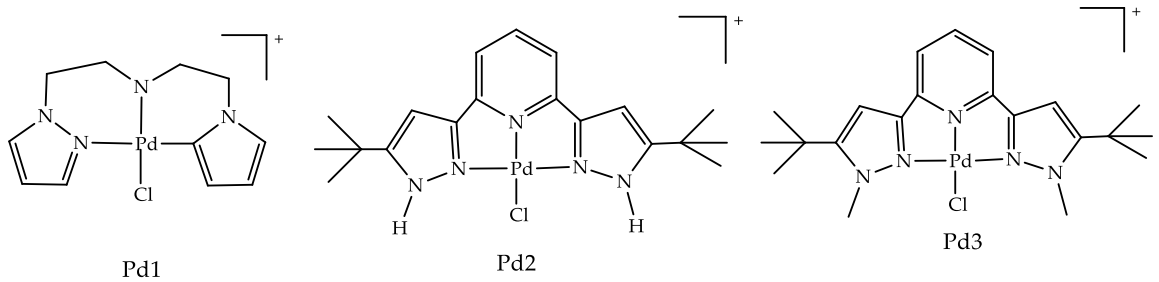

Figure 1. The structures of complexes.

Table 1. Second-order rate constants for the substitution reactions of Pd1-Pd3 complexes with selected nucleophiles.

Complex	Ligand	k_2 [M^{-1} s^{-1}]	
Pd1	Tu	432 ± 4	Ref [7]
	L-met	186 ± 4	
	5′-GMP	30 ± 1	
Pd2	Tu	23100 ± 700	Ref [8]
	L-met	12200 ± 100	
	5′-GMP	760 ± 20	
Pd3	Tu	18400 ± 200	Ref [8]
	L-met	10100 ± 100	
	5′-GMP	650 ± 20	

The reactivity of complexes towards nucleophiles decreases in the order: Pd2 > Pd3 > Pd1 (Table 1). A significant greater reactivity of Pd2 and Pd3 than Pd1 is caused by the electronic effect, due to the π-acceptor ability of the pyridine moiety, by which the electron density on the palladium center is reduced. On the other hand, slightly higher reactivity of Pd2 compared to Pd3 was observed. The presence of additional methyl groups on nitrogen atoms in L3 causes steric hindrance, so the approach of the entering ligands to the metal ion is more difficult. Additionally, methyl group is a good σ-donor and donates electrons to the metal center, increasing the electron cloud on the palladium center leading to a slower substitution reaction. The entering nucleophiles Tu, L-met and 5′-GMP, were selected due to their varied electronic and steric demands, binding abilities and biorelevance [7, 8]. Nucleophiles Tu and L-met were used as models for suphur-containing molecules, which are plentiful in the blood plasma. The molecule 5′-GMP (nitrogen donor) was utilised as a representative for nucleobases binding. The reactivity of nucleophiles decreases in order: Tu > L-met > 5′-GMP. A much higher reactivity of sulfur-donor molecules (Tu, L-met) compared to 5′-GMP as nitrogen-donor was noticed. It can be attributed to the fact that soft acid such as Pd(II) ion prefers to coordinate with sulfur atom. Thiourea has the highest reactivity since it combines the ligand properties of thiolates as π-donors, and thioethers as σ-donors and π-acceptors. In addition, thiourea is the least sterically demanding molecule from used ligands. The least reactivity of 5′-GMP can also be accounted for by its steric bulkiness in comparison to the other two nucleophiles. Overall, the selected ligands represent good entering nucleophiles for the studied substitution reactions, while the Pd1-Pd3 complexes exhibit a very high affinity towards chosen small biomolecules.

3. Conclusions

We have shown that the rate of the substitution reactions of metallocomplexes with biologically important molecules can be controlled by the suitable choice of inert chelating ligand. Thus, the chemical nature of inert tridentate ligands that combine

electronic and sterne effects has a very important role in the prediction of the kinetic behavior of some transition metal ion complexes. The information presented here can provide deeper insights into the possible use of kinetic studies as tools for the development of new metallodrugs.

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