Palladium and platinum derived diacetylmonoxime thiosemicarbazone complexes of medicinal interest

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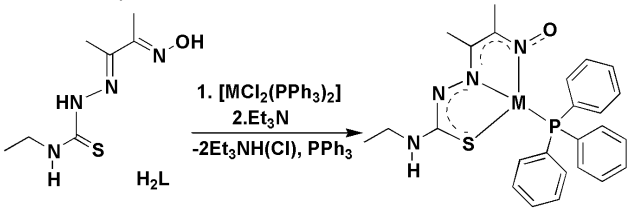
Introduction

Thiosemicarbazones (TSCs) and their transition metal complexes possess remarkable pharmacological properties including anti-neoplastic activity.[1] On the other hand, oximes are well known due their use in the preparation of brain perfusion imaging agents like ^{99m}Tc-HMPAO (Ceretec).[2] The combination of TSCs and oximes may lead to compounds with interesting biological properties.

Pt^{II} complexes, mainly cisplatin derivatives, are widely used in the treatment of a large number of cancer types. However, the efficacy of cisplatin is limited. In order to overcome these limitations, the development of platinum complexes that are structurally different to the classical cisplatin analogues is required. In addition, the chemical similarities of Pd^{II} (isoelectronic and isosteric) place this metal as first candidate to substitute Pt^{II} anticancer metallodrugs. In the present work we devote our interest to the coordination chemistry of an oxime TSC ligand system with Pt^{II} and Pd^{II}, aiming to obtain new anticancer agents.

Results and Discussion

The oxime thiosemicarbazone ligand (H_2otsc) was synthesized by refluxing diacetylmoxoime with one equivalent of ethylthiosemicarbazide. Reactions of $[MCl_2(PPh_3)_2]$ (M = Pt or Pd) with H_2otsc under reflux in acetonitrile with base addition afford the analog complexes $[M(PPh_3)(otsc)]\cdot H_2O$ (**1** for M = Pd and **2** for M = Pt).



Scheme 1. Synthesis of the complexes **1** and **2**.

The complexes have been characterized by CHNS analysis, conductimetry, UV-Vis, FTIR, NMR (^{1}H and ^{31}P) and by X-ray diffraction on single crystals.

The FTIR spectra of the complexes indicate the coordination of the ligand upon double deprotonation. The ^{1}H-NMR spectra of both complexes are very similar and present all the expected signals. The $^{31}P\{^1H\}$ NMR spectrum of **1** consists of a sharp singlet signal at δ 27.64 ppm, while the spectrum of **2** shows a resonance at δ 17.02 ppm, with a $J^1(^{195}Pt–^{31}P)$ coupling of around 3700 Hz.

X-ray structure analyses confirm the spectroscopic data. **Fig. 1** presents the molecular structure of the Pt^{II} complex, which is isostructural with the Pd^{II} one, crystalizing in the trigonal crystal system, space group $R\bar{3}$. The $otsc^{2-}$ ligand binds the M^{II} centers as *N,N,S*-chelate with double deprotonation. A considerable delocalization of π-electron density is evidenced in the five membered rings and is extended to the oxygen atom from the oxime moiety.

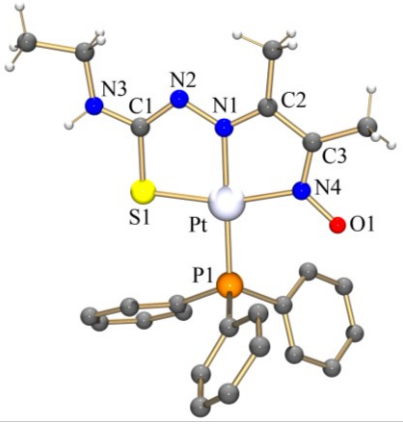


Figure 1. Crystal and Molecular Structure of $[Pt(PPh_3)(otsc)]\cdot H_2O$ (**2**). The H atoms of the PPh_3 ligand and the H_2O molecule were omitted for clarity.

Conclusions

New Pt^{II} and Pd^{II} complexes containing an oxime thiosemicarbazone ligand have been prepared and fully characterized. The biologic potential of these complexes is of high interest and *in vitro* cytotoxic studies against tumor cells are now underway.

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