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Synthesis, crystal structure, DNA-binding and cytotoxicity in vitro of novel *cis*-Pt(II) and *trans*-Pd(II) pyridine carboxamide complexes

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ABSTRACT

In an attempt to establish fundamental structure–activity relationships (SAR) of Pt/Pd-based anti-tumour compounds, we have recently designed monodentate pyridyl amide ligand containing central amide units which possess external metal co-ordinating pyridyl group and internal amide functionality. It was prepared in one step from commercially available compounds in moderate to good yield. Surprisingly, treatment of $K_2[MCl_4]$ [M = Pt(II), Pd(II)] with ligand *N*-(4-chlorophenyl)-3-pyridinecarboxamide (L) in the same reaction condition affords two different hydrogen-bonded polymers: *cis*-$[PtL_2Cl_2]\cdot CH_3OH\cdot DMF$ (**1**) and *trans*-$[PdL_2Cl_2]\cdot 2DMF$ (**2**). Fluorescence analysis indicates that the two complexes can bind to fish sperm DNA (FS-DNA) and gel electrophoresis assay demonstrates the ability of the complexes to cleave the pBR322 plasmid DNA. The two complexes exhibit cytotoxic specificity and significant cancer cell inhibitory rate. Furthermore, cytotoxicity values are higher in the case of *cis*-Pt(II) complex than *trans*-Pd(II) complex in four different cancer cell lines.

The carboxamide linkage, [–C(O)NH–], is an essential building unit in the primary structure of proteins, which has attracted much attention because it can provide models from the standpoint of bioinorganic chemistry.[1–3] Consequently, the behaviour of pyridinecarboxamide, containing this linkage, towards biologically relevant metals has been widely investigated.[4–11] This is because pyridine carboxamide ligand contains lipophilic group of aromatic ring and hydrophilic group of carboxamide. The lipophilic group can make drugs more capable of penetrating through cell membrane to bind to the target DNA, and the hydrophilic group can reduce toxicity from the drugs. Especially, the search for platinum(II) complexes with anti-tumour properties has been going on through the efforts of chemists from the medicinal chemistry field since the discovery of the anti-proliferation activity of cisplatin in the 1960s.[12] To an attempt to reduce toxicity and improve the original bioactivity of cisplatin, thousands of cisplatin analogues have been prepared and tested by varying the nature of the labile ligands (also called the leaving groups) and non-labile ligands (also called the carrier ligands). Meanwhile, for decades it is believed that *trans* platinum compounds are non-active as anti-tumour agents because transplatinum is biologically inactive although it binds to DNA. However, since the 1990s many *trans* platinum complexes have been discovered with significant anti-tumour activity against different tumour cells including these resistant to cisplatin.[13–16] Owing to the similar co-ordination modes of the cation Pd(II) and Pt(II) (d^8-electron configuration) there has also been renewed interest in attempts to obtain activity for *cis* and *trans* palladium(II) complexes.[17–21]

The aim of the studies was to broaden our knowledge on the antiproliferative activity of Pt(II)/Pd(II) complexes and understand the structure–activity relationships (SARs) of these new chemical compounds. Recently, we obtained two novel *cis*-dichloroplatinum(II) and *trans*-dichloropalladium(II) complexes containing non-chelation-controlled 3-pyridinecarboxamide derivatives as carrier groups (Scheme 1). A specific attention has been focused on the effect induced by solvent molecule on the nature of the resulting self-assembly under identical conditions. In the present Letter we describe the synthesis and characterisation of the self-assembled products, *cis*-$[PtL_2Cl_2]\cdot CH_3OH\cdot DMF$ (**1**) and *trans*-$[PdL_2Cl_2]\cdot 2DMF$ (**2**), (L = *N*-(4-chlorophenyl)-3-pyridinecarboxamide), as well as the DNA-binding abilities of them with FS-DNA via fluorescence spectroscopy. Their cleavage behaviour toward pBR322 DNA and the in vitro cytotoxicity against the human cervix epitheloid carcinoma (Hela), human hepatocellular carcinoma (Hep-G2), human oral epithelial carcinoma (KB) and human lung carcinoma (AGZY-83a) are also investigated.

According to our previous work,[22] the ligand was prepared by the reaction of nicotinoyl chloride hydrochloride with 4-chloroaniline in dry THF in presence of triethylamine under N_2 8 h (Scheme 1). The solid-state complex was obtained by mixing 2:1 molar ratio of the appropriate ligand and K_2PtCl_4 (or K_2PdCl_4) in

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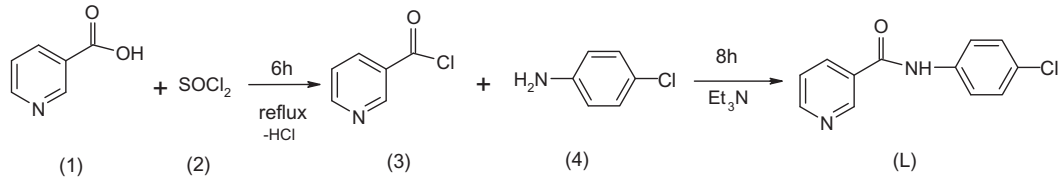
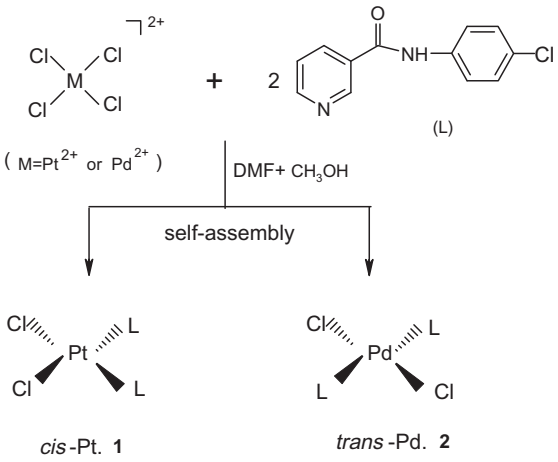


Scheme 1. The formation of *N*-(4-chlorophenyl)-3-pyridinecarboxamide (L).



Scheme 2. The synthetic route of **1** and **2**.

methanol–water solution. The precipitate was recrystallised from the mixed solvents DMF and methanol, and orange crystals of X-ray quality were obtained and identified as complex **1** and yellow crystals as complex **2** (Scheme 2). Crystal data and structure refinement details of complexes **1** and **2** are summarised in Table S1. Selected bond lengths and angles are listed in Table S2.

The starting hypothesis for this work is that complexes with pyridine carboxamide ligands should have hydrogen bonds between the ligand NH group (as H-bond donor) and Cl atom (as H-bond acceptor) and *cis* or *trans* configuration of the complex might also arise from the influence of solvent molecule taking part in hydrogen bonding interactions. In that case, they could be used as supramolecular synthons for designing complexes with extended arrays whose shapes and bonding structures are controlled by the geometrical configuration of the synthons and direction and number of hydrogen bonds. Figure 1 shows the different intermolecular hydrogen bonding patterns of complexes **1** and **2**, respectively.

In the structure of complex **1**, each platinum atom has *cis*-$PtCl_2N_2$ co-ordination. The atoms involved in square co-ordination of Pt(II) deviate 0.037 Å from the average mean plane $PtCl_2N_2$ [Pt(1), Cl(1), Cl(2), N(1), N(3)]. Average value for Pt–Cl distances is 2.3009(17) Å while the average Pt–N distance [2.028(5) Å] is in the expected region.[8] The dihedral angle between the two phenyl rings is 65.75° and the angle between the two pyridine rings is 69.87°. Both of the molecules form hydrogen-bonded dimers with Pt...Pt distance of 4.000 Å (Fig. 1). The arrangement is supported by intermolecular H-bond between NH centre of one pyridinecarboxamide ligand and Cl atom of the neighbouring molecules (distance N(2)–H...Cl(2) is 2.620 Å) and also between NH centre of the other pyridinecarboxamide ligand and O atom of the solvent DMF (distance N(4)–H...O(3) is 2.141 Å). It is notable that these dimeric entities are interlinked to form a 2D framework via intricate hydrogen bonds with solvent DMF and methanol molecules as well as weak π–π interactions (the shortest interplanar atom–atom separation of ca. 3.906 Å) (Fig. 2a). The sheets are further connected by very weak C(1)–H...Cl(2) (2.938 Å) and C(2)–H...O(1) (2.574 Å) hydrogen bonds extending along the *a*-axis to form a 3D network.

As can be seen from Figure 1, each palladium atom also adopted square-planar geometry co-ordinated by 2 equiv pyridine nitrogen atoms [N(1) and N(1A)] from two ligands and two chloride anion [Cl(1) and Cl(1A)]. However, there are the difference in the conformation of the ligand in the palladium complex relative to the platinum complex. The two ligands are *trans* to each other (i.e., N1 is *trans* to N(1A)). The Pd–Cl bond length is 2.2995(6) Å and the Pd–N bond length (2.0129(17) Å) is that expected for normal Pd–N single-bond distance.[18] The two pyridine rings and two phenyl rings of two ligands are both parallel to each other. The dihedral angle between phenyl ring and pyridine ring from the same ligand is 20.38°. By contrast, in the palladium complex, the hydrogen bond interactions manifested by N–H...O contact of 2.879 Å in-

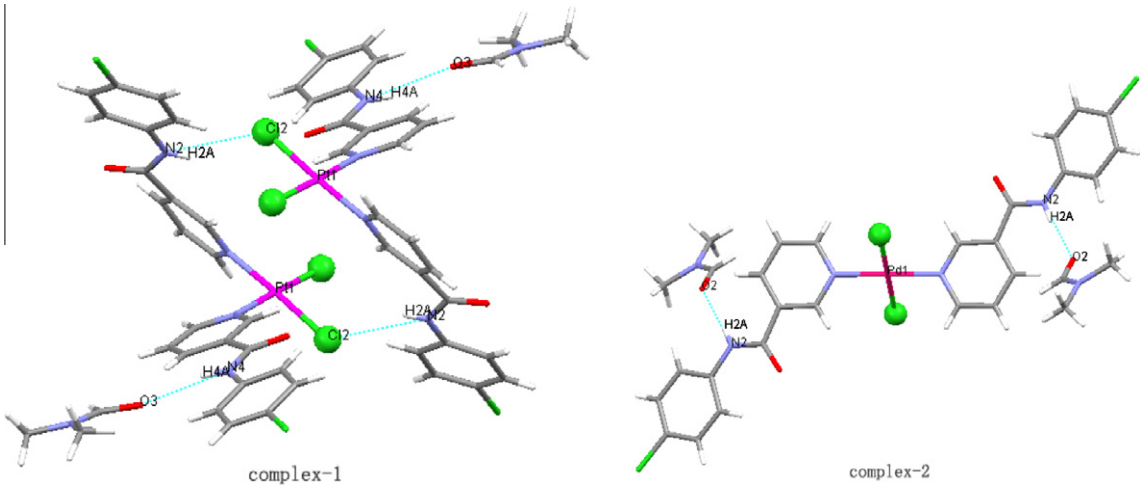


Figure 1. Intermolecular contacts in complexes **1** and **2**.