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Palladium(II) and platinum(II) complexes of ((2-pyridyl)pyrazol-1-ylmethyl)benzoic acids: Synthesis, Solid state characterisation and biological cytotoxicity

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ABSTRACT

The new ligands 3-(3-(2-pyridyl)pyrazol-1-ylmethyl)benzoic acid (**L2**) and 5-(3-(2-pyridyl)pyrazol-1-ylmethyl)benzene 1,3-dicarboxylic acid (**L3**) are reported and the synthesis and characterisation of [$PdCl_2$(**L**)] and [$PtCl_2$(**L**)] complexes of these and the previously reported 4-(3-(2-pyridyl)pyrazol-1-ylmethyl)benzoic acid (**L1**) are described. In the solid state, the square planar complexes assemble *via* hydrogen bonding interactions involving COOH and M–Cl groups as well as by various π-stacking interactions involving the aromatic rings on the ligands and, notably, the chelate rings. Hirshfeld surface analysis has been used to gain insight into the assembly of the molecules. Preliminary studies of the biological cytotoxicity of the [$PtCl_2$(**L**)] complexes against A549 and MDA-MB-231 cancer cell lines are reported.

1. Introduction

The development of an understanding of the myriad factors that drive how molecules assemble together into the solid state continues to be an important area of study in chemistry [1–6]. Key to such an understanding is a cataloging of the different possible interactions for a given set of molecular functionalities, or synthons, and a determination of the predictability of assembly motifs for such functionalities. Central to such a determination is the nature of the intermolecular force that drives the synthon–synthon interaction. Of the various intermolecular forces available, hydrogen bonding has emerged as an important player, due to the strength and directionality of the interaction, and also the ease with which hydrogen bond donors and/or acceptors can be synthetically incorporated into molecules of interest [7]. The carboxylic acid (COOH) group, for example, has been shown to form $R_2^2(8)$ homodimers [8] in half of all structurally characterised compounds containing only carboxylic acid functionalities [9]. Interactions involving π systems have also received increasing attention [10]. While these tend to be weaker than hydrogen bonds, they also have a degree of directionality and, given the widespread use of aromatic rings in the frameworks of organic and inorganic molecules, π-stacking interactions play a significant role in the solid state assembly of many reported structures.

As the field of crystal engineering matures, systems that include more than one type of hydrogen bonding motif have begun to be explored, with the aim of determining a hierarchy of functionalities in terms of their hydrogen bond donor or acceptor abilities. For example, Vishweshwar et al. have shown that, in structural studies on pyridine and pyrazine monocarboxylic acids, the OH···N hydrogen bonding drives molecular assembly, rather than $R_2^2(8)$ dimer formation [11] and Du et al. have reported similar results in their studies on cocrystallisation of dipyridyl species with dicarboxylic acids [12]. Very recently, Duggirala et al. have shown that charge assisted hydrogen bonds between phenol groups and chloride anions prevail over COOH···Cl hydrogen bonds or $R_2^2(8)$ dimer formation in cocrystallisation experiments [13]. Such studies allow for the development of a quantitative ranking of, for example, hydrogen bond donors, where structural data from the Cambridge Structural Database (CSD) is used in combination with appropriate calculations [14].

We have recently reported the synthesis of 4-(3-(2-pyridyl)pyrazol-1-ylmethyl)benzoic acid (**L1**), which combines two nitrogen donors in a potential metal-chelating motif and a distal

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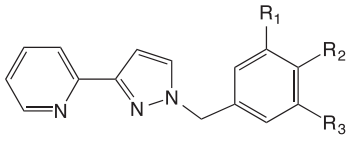
carboxylic acid group separated by a flexible methylene hinge [15]. The X-ray structure of **L1** showed that the molecules assembled *via* OH···N hydrogen bonds (between the COOH group of one molecule and the pyridine nitrogen of the next) into helical chains (consistent with the results of Vishweshwar et al. and Du et al.) – the helicity arising from the prochirality that the methylene hinge imparts to the ligand. Upon reaction of silver(I) salts with **L1**, $[Ag(\mathbf{L1})_2]^+$ complexes were obtained, in which the silver ion adopted a distorted tetrahedral geometry and the **L1** ligands wrapped around the metal such that chiral metallosynthons were generated. Hydrogen bonding interactions, either directly between the COOH groups of adjacent molecules or between COOH and solvent or counterion species, assemble these into either one-dimensional helical or *meso*-helical chains.

We were interested in extending these studies to square planar metal-based systems, and also in modifying the basic structure of the ligand. To this end, we herein report the new ligands 3-(3-(2-pyridyl)pyrazol-1-ylmethyl)benzoic acid (**L2**) and 5-(3-(2-pyridyl) pyrazol-1-ylmethyl)benzene 1,3-dicarboxylic acid (**L3**), where the position, and number, of the COOH group(s) has been varied compared to **L1** (Scheme 1). Initially we attempted to prepare $[Pd(\mathbf{L})_2]^{2+}$ complexes, expecting that the palladium(II) ions would prefer a square planar geometry. However, these attempts were unsuccessful, due, we believe, to the steric clash between the methylene groups on the two ligands (in a *trans* arrangement) or the methylene group and a pyridine CH group (in a *cis* arrangement). This result is consistent with the literature: while a small number of palladium(II) and/or platinum(II) complexes containing pyridylpyrazole-type ligands have been reported [16–21], the only reports of $[M(\mathbf{L})_2]^{2+}$ systems are those where the N2 nitrogen of the pyrazole is unsubstituted [22–29]. We therefore moved our focus to square planar complexes of the type $[PdCl_2(\mathbf{L})]$ and $[PtCl_2(\mathbf{L})]$. These should not suffer the same steric issues as the $[M(\mathbf{L})_2]^{2+}$ complexes and also, being neutral rather than cationic, should modify the ways in which molecules will interact with each other in the solid state compared with the silver(I) complexes, where the role of the counterion was important. While intermolecular hydrogen bonding between COOH groups might be expected, as has been observed in related palladium systems [30–32], the potential M–Cl hydrogen bond acceptor might also be expected to play a role [5,7,33].

Synthesis and characterisation of the six $[MCl_2(\mathbf{L})]$ (M = Pd(II), Pt(II)) complexes is reported. The X-ray crystal structures of four of these, along with that of **L2**, were obtained and show a variety of packing arrangements, facilitated by a variety of intermolecular hydrogen bonding interactions (OH···N, OH···Cl, OH···O) as well as by π–π stacking interactions involving the chelate rings, a recently recognised [34–40] but probably not uncommon type of supramolecular motif. Indeed, it has been shown that, in certain cases, such interactions can be as strong as hydrogen bonds [38]. Hirshfeld surface analysis provides further insight into the nature of the intermolecular interactions in the complexes. Finally, given their similarity to the well-known chemotherapeutic agent cisplatin, the cytotoxicity of the complexes was explored.



L1: R_1 = H, R_2 = COOH, R_3 = H
L2: R_1 = COOH, R_2 = H, R_3 = H
L3: R_1 = COOH, R_2 = H, R_3 = COOH

Scheme 1. The 2-pyridylpyrazole-based ligands discussed in this work.

2. Experimental

2.1. General methods

The ligand 4-(3-(2-pyridyl)pyrazol-1-ylmethyl)benzoic acid (**L1**) [15] and the ligand precursors 3-bromomethylbenzoic acid [41], 1,3-dimethyl-5-(bromomethyl)benzene-1,3-dicarboxylate [42] and 2-(1*H*-pyrazol-3-yl)pyridine [43] were prepared by published procedures. *cis*-$[PdCl_2(CH_3CN)_2]$ was prepared by heating $PdCl_2$ in acetonitrile and *cis*-$[PtCl_2(dmso)_2]$ was prepared by adding dmso to an aqueous solution of K_2PtCl_4. All other chemicals were purchased commercially and used as received. ^{1}H NMR and ^{1}H–^{1}H COSY spectra were recorded on a 400 MHz Varian spectrometer at 298 K, referenced to the residual solvent signal. Microanalyses were performed at the Campbell Microanalytical Laboratory at the University of Otago. Mass spectra were collected on a Bruker micrOTOF-Q spectrometer. Infrared spectra were recorded on a Bruker ALPHA FT-IR spectrometer with an ALPHA P ATR measurement module.

2.2. Synthesis of 3-(3-(2-pyridyl)pyrazol-1-ylmethyl)benzoic acid (*L2*)

2-(1*H*-Pyrazol-3-yl)pyridine (0.339 g, 2.33 mmol) and 3-bromomethylbenzoic acid (0.500 g, 2.33 mmol) were added to a solution of 40% aqueous NaOH (3.5 mL), benzene (10 mL), and Bu_4NOH (4 drops), and the resulting solution was refluxed at 80 °C overnight. After cooling to room temperature, the colourless organic layer was separated from the yellow aqueous layer. The aqueous layer was then washed with ethyl acetate (2 × 10 mL) before being acidified to pH 3 using aqueous HCl (6 M), at which point a yellow precipitate formed. This precipitate was extracted into ethyl acetate (3 × 60 mL) that was then washed with water (2 × 50 mL) and brine (50 mL). The organic layer was then dried over magnesium sulfate before having the solvent removed under reduced pressure. Recrystallization from ethyl acetate/petroleum ether (40–60 °C) gave **L2** as a pale brown solid (0.224 g, 34%). *Anal.* Calc. for $C_{16}H_{13}N_3O_2{\cdot}0.25H_2O$ C, 67.71; H, 4.80; N, 14.80. Found: C, 67.94; H, 4.67; N, 14.72%. ^{1}H NMR (400 MHz, dmf-d_7): δ (ppm) = 5.61 (2H, s, H_g), 6.95 (1H, d, J = 2.3 Hz, H_e), 7.30 (1H, ddd, J = 7.4, 4.8, 1.2 Hz, H_b), 7.54 (1H, t, J = 7.7 Hz, H_h), 7.64 (1H, dt, J = 7.7, 1.5 Hz, H_k), 7.83 (1H, td, J = 7.7, 1.8 Hz, H_c), 8.01–7.95 (3H, m, H_d, H_j and H_i), 8.05 (1H, d, J = 2.3 Hz, H_f), 8.60 (1H, dt, J = 4.9, 1.3 Hz, H_a). HRESI-MS (dmf/MeOH): m/z calcd for $C_{16}H_{12}N_3O_2^-$: 278.0935 $[\mathbf{L2}-H]^-$: found: 278.0930. Selected IR ν_{max}/cm^{-1}: 2415, 1690, 1598, 1566, 1492, 1294, 768.

2.3. 5-(3-(2-Pyridyl)pyrazol-1-ylmethyl)benzene 1,3-dicarboxylic acid (*L3*)

2-(1*H*-pyrazol-3-yl)pyridine (0.500 g, 3.45 mmol) and 1,3-dimethyl-5-(bromomethyl)benzene-1,3-dicarboxylate (0.990 g, 3.45 mmol) were added to a solution of 40% aqueous NaOH (5 mL), benzene (15 mL), and Bu_4NOH (5 drops), and the resulting solution was refluxed at 80 °C overnight. After cooling to room temperature, the colourless organic layer was separated from the yellow aqueous layer. The aqueous layer was then washed with ethyl acetate (2 × 10 mL) before being acidified to pH 3 using aqueous HCl (6 M), at which point a white precipitate formed. The solvents were then removed *in vacuo* and the residue dissolved in *ca.* 1 mL of dmf. Addition of ethyl acetate gave a pale yellow solid, which was filtered off, washed with ethyl acetate and diethyl ether and dried (0.354 g, 32%). *Anal.* Calc. for $C_{17}H_{13}N_3O_4{\cdot}2H_2O$: C, 56.83; H, 4.77; N, 11.69. Found: C, 56.78; H, 3.82; N, 11.55%. ^{1}H NMR (400 MHz, dmf-d_7): δ (ppm) = 5.71 (2H, s, H_g), 6.96 (1H, d, J = 2.3 Hz, H_e), 7.30 (1H, ddd, J = 7.5, 4.9, 1.2 Hz, H_b), 7.83 (1H, td,