Inorganica Chimica Acta 368 (2011) 252–256

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Note

# A report describing the effect of di-2-pyridyl ligand architecture on the coordination properties with gold(III)

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ARTICLE INFO

*Article history:*
Received 12 October 2010
Received in revised form 7 December 2010
Accepted 20 December 2010
Available online 6 January 2011

*Keywords:*
Gold(III)
Anticancer
Metallotherapy
DNA binding
Di-2-pyridyl ligands

ABSTRACT

In an effort to develop novel gold-based chemotherapies, gold(III) coordination complexes possessing a series of di-2-pyridyl ligands were targeted as synthetic products. It was found that di-2-pyridyl ligands linked by different groups exhibited varying coordination to gold(III). Di-2-pyridyl sulfide (DPS) exhibited bidentate binding to gold(III), and formed a complex ion with a gold tetrachloride counter ion {[(DPS)$AuCl_2$]$AuCl_4$; compound **3**}; di-2-pyridyl ether (DPO) formed a neutral monodentate coordination complex with gold(III) {[(DPO)($AuCl_3$)]; compound **4**}; and attempts to make a gold(III) complex with di-2-pyridyl ketone (DPK) were unsuccessful, as a complex ion possessing the protonated ligand and a gold tetrachloride anion was isolated {[HDPK][$AuCl_4$]; compound **5**}. Compounds **3**–**5** were structurally characterized using X-ray crystallography, which confirmed the different coordination environments around the gold(III) metal centers.



## 1. Introduction

Numerous reports describing the ongoing effort to develop gold-based anticancer compounds have been published in the last decade [1–5], and recent studies have demonstrated that polydentate ligands can be used to synthesize gold(III) complexes that have *in vitro* and *in vivo* anticancer activity [3,6,7]. Given the fact that bipyridyl ligands have been used to synthesize a variety of gold(III) compounds possessing promising antitumor properties [8], our group sought to explore the use of di-2-pyridyl moieties as ligands for gold(III) coordination complexes. The ability to synthesize di-2-pyridyl ligands with different linking groups provides an opportunity to synthesize a ligand series with varying electronic properties and/or structural characteristics, and our long term interest in this class of ligands lies in determining if the ligand design impacts the cytotoxicity of the corresponding gold(III) complexes.

Numerous metal di-2-pyridyl complexes have been previously reported, including silver(I) and copper(II) complexes possessing bidentate di-2-pyridyl sulfide (DPS) ligands [9,10], Co(II) complexes with bidentate di-2-pyridyl ether (DPO) ligands [11], and Rh(III) metal ions found to form coordination complexes with bidentate di-2-pyridyl ketone (DPK) ligands [12]. However, these three classes of ligands have not to date been reported with gold (III), though gold(III) complexes possessing structurally analogous di-2-pyridyl amine [13] and (pyrazolylmethyl) pyridine [14] ligands have been reported. Therefore, we have attempted to make gold(III) complexes with DPS, DPO, and DPK ligands, and report herein the different modes of coordination that occur upon reaction with gold(III) (see Scheme 1).

## 2. Experimental

### 2.1. General experimental procedures

Di-2-pyridyl ketone, 2-bromopyridine, 2-hydroxypyridine, 2-mercaptopyridine, potassium carbonate, $AgBF_4$, and $NaAuCl_4{\cdot}2H_2O$ were purchased from Sigma–Aldrich, Inc., and used without further purification. $^1$H NMR spectra were recorded on a Varian Mercury spectrometer at 300 MHz in $CDCl_3$ or DMSO-$d_6$, using the chloroform singlet at 7.20 ppm or DMSO pentet at 2.50 ppm, respectively, as internal references. UV–Vis spectra were recorded on a Cary 50 UV–Vis spectrophotometer, and elemental analyses were performed by Atlantic Microlab, Inc.

### 2.2. Synthesis of di-2-pyridyl sulfide (DPS, **1**)

The di-2-pyridyl sulfide ligand was synthesized as previously reported [15]; 1.00 g (6.33 mmol) of 2-bromopyridine was reacted

*Abbreviations:* DPS, di-2-pyridyl sulfide; DPO, di-2-pyridyl ether; DPK, di-2-pyridyl ketone; LMCT, ligand-to-metal-charge transfer; $^{methyl}$bipy, 4,4′-dimethyl bipyridine; pyz-$CH_2$-pyr, (pyrazolylmethyl)pyridine.

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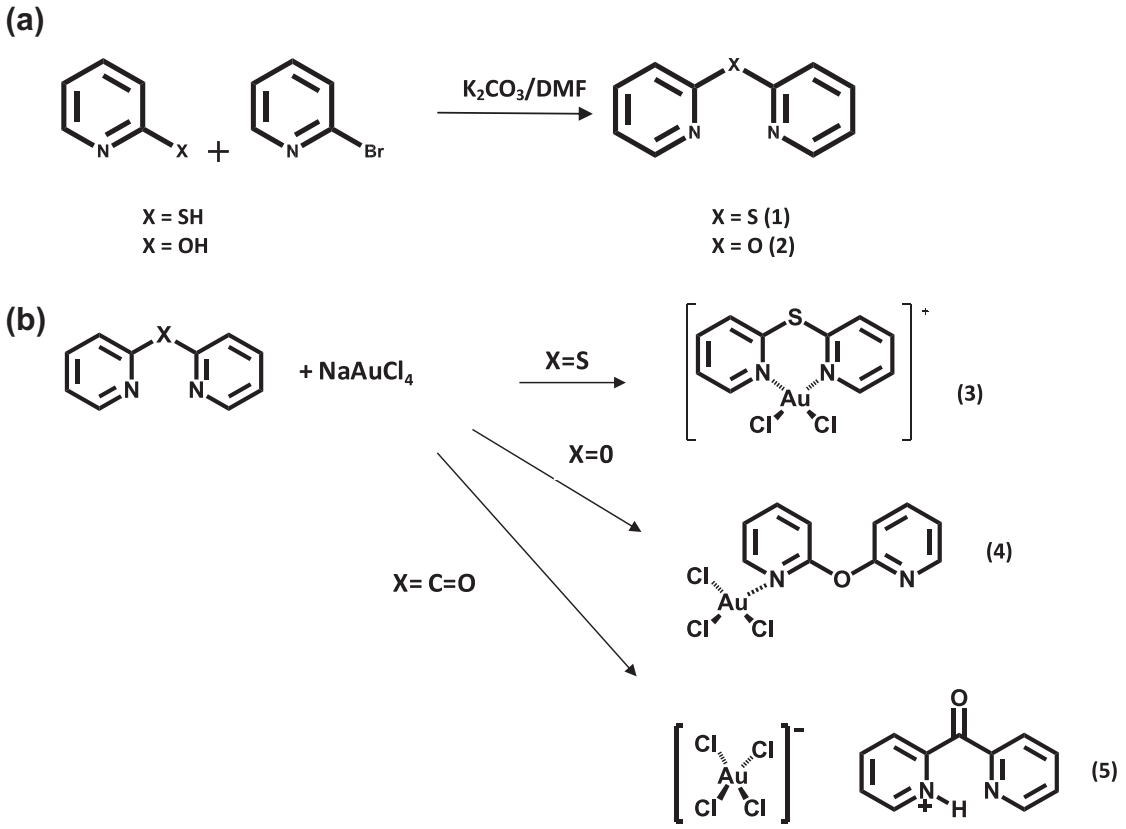
doi:10.1016/j.ica.2010.12.052




**Scheme 1.**

with 0.703 g (6.33 mmol) of 2-mercaptopyridine. The product (0.323 g, 27.1% yield) was purified via Kugelrohr distillation (approximately 0.1 Torr/150 °C). $^1$H NMR ($CDCl_3$, 300 MHz)/ppm: 8.52 (dq, 2H); 7.78 (td, 2H); 7.47 (dt, 2H); 7.30 (qd, 2H).

### 2.3. Synthesis of di-2-pyridyl ether (DPO, **2**)

Di-2-pyridyl ether has been synthesized previously, originally by the reaction of the silver salt of 2-hydroxypyridine and 2-iodopyridine [16], and subsequently by a protocol requiring the use of high temperatures and an autoclave reactor [17]. In an effort to synthesize this ligand under more convenient conditions, a protocol analogous to the synthesis of compound **1** was used. 1.00 g of 2-bromopyridine (6.33 mmol) was combined with 0.600 g of 2-hydroxopyridine (6.33 mmol) and 0.870 g of $K_2CO_3$ (6.33 mmol) in DMF (approximately 30 mL) and refluxed overnight. The resulting orange colored solution was filtered and the solvent removed *in vacuo* using a rotary evaporator. The resulting oil was purified via Kugelrohr distillation (approximately 0.1 Torr/150 °C), and then column chromatography (silica, 10% ethyl acetate in hexane). The final yield of **2** was 0.100 g (9.2% yield). $^1$H NMR ($CDCl_3$, 300 MHz)/ppm: 8.22 (dd, 2H); 7.69 (td, 2H); 7.02 (m, 4H).

### 2.4. Synthesis of [(DPS)$AuCl_2$][$AuCl_4$] (**3**)

0.211 g (0.530 mmol) of $NaAuCl_4{\cdot}2H_2O$ was measured and added to 0.100 g (0.530 mmol) of **1** in acetonitrile and refluxed for an hour, and then an acetonitrile solution containing 0.103 g (0.530 mmol) of $AgBF_4$ was added and the resulting reaction mixture refluxed overnight. The AgCl precipitate was filtered off with a celite pad and acetonitrile was removed by rotary evaporation. The yellow solid was redissolved in a minimum amount of hot methanol, and 0.075 g of X-ray quality crystals were obtained by slowly evaporating the methanol (17.9% yield). The experiment was repeated with two equivalents of $AgBF_4$, resulting in the isolation of the same product (based on elemental analysis). $^1$H NMR (DMSO-$d_6$, 300 MHz)/ppm: 8.53 (d, 2H); 7.79 (td, 2H); 7.48 (d, 2H);7.32 (q, 2H); UV–Vis: $\lambda_{max}$ (acetonitrile, 20 °C)/nm: 230, 295, 325–400 (sh). Elemental *Anal.* Calc. for $C_{10}H_8Au_2Cl_6N_2S$: C, 15.33; H, 0.92. Experimental: C, 15.11; H, 1.01%.

### 2.5. Synthesis of [(DPO)$AuCl_3$] (**4**)

0.100 g (0.581 mmol) of compound **2** was dissolved in acetonitrile and added to 0.231 g (0.581 mmol) of $NaAuCl_4{\cdot}2H_2O$ in acetonitrile and refluxed for an hour, and then an acetonitrile solution containing 0.113 g (0.581 mmol) of $AgBF_4$ was added and the resulting reaction mixture was refluxed overnight. The AgCl precipitate was filtered off with a celite pad and the acetonitrile was removed by rotary evaporation. The yellow solid was redissolved in a minimum amount of hot methanol, and 0.050 g (18.1% yield) of X-ray quality crystals were obtained by slow evaporation. $^1$H NMR (DMSO-$d_6$, 300 MHz)/ppm: 8.46 (d, 1H); 8.28 (d, 1H); 8.09 (d, 1H);7.91 (t, 1H); 7.67 (d, 1H); 7.46 (t, 1H); 7.34 (d, 1H); 7.28 (t, 1H); UV–Vis: $\lambda_{max}$ (acetonitrile, 20 °C)/nm: 225, 275, 325. Elemental *Anal.* Calc. for $C_{10}H_8AuCl_3N_2O$: C, 25.16; H, 1.60. Experimental: C, 25.26; H, 1.70%. Attempts to synthesize the bidentate complex, via the addition of two equivalents of $AgBF_4$, were unsuccessful.

### 2.6. Synthesis of [HDPK] [$AuCl_4$] (**5**)

0.200 g (1.09 mmol) of di-2-pyridylketone was dissolved in acetonitrile and added to an acetonitrile solution of 0.432 g