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Different reaction products as a function of solvent: NMR spectroscopic and crystallographic characterization of the products of the reaction of gold(III) with 2-(aminomethyl)pyridine

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ABSTRACT

The reaction between equimolar amounts of hydrogen tetrachloridoaurate(III) trihydrate ($H[AuCl_4]\cdot 3H_2O$) and 2-(aminomethyl)pyridine (AMP) has been investigated under different reaction conditions. When these reactants were mixed in ethanol with an equimolar amount of HCl and at room temperature, the reaction yielded a gold(III) complex having bidentate coordinated AMP ligand, $[Au(AMP)Cl_2]Cl\cdot H_2O$ (**1**). However, in the aqueous solution of HCl (pH $\leqslant$ 1.00) at 50 °C no coordination of AMP ligand to Au(III) ion was observed and only $H_2AMP^{2+}Cl^-[AuCl_4]^-\cdot 0.5H_2O$ (**2**) was obtained as the final product. While chelation by AMP ligand in ethanol has stabilized the Au(III) oxidation state, dominant reaction process occurring in water solvent at pH range 1.00–5.00 was reduction of Au(III) to the elemental gold, Au(0), which was rapidly accelerated by increasing pH. Both products **1** and **2** have been characterized by NMR spectroscopic and X-ray diffraction techniques. In crystals, the square-planar coordination around the Au(III) centers is supplemented to elongated square pyramidal (**1**) or octahedral (**2**) by means of Au···Cl interactions. This is achieved by either arranging the neighboring Au–Cl dipoles in antiparallel (**1**) or herring-bone (**2**) mode and additionally engaging in these interactions of the uncoordinated chloride ion (**2**).

1. Introduction

The clinical success of cisplatin (*cis*-$[PtCl_2(NH_3)_2]$) in the treatment of a variety of cancer diseases has stimulated extensive studies on the evaluation of other metal complexes as potential antitumor agents [1]. As Au(III) ion has a configuration isoelectronic with Pt(II) (d^8), gold(III) complexes were among the first non-platinum complexes explored for antitumor potential [2]. However, gold(III) complexes were shown to act in a fashion significantly different from platinum(II) analogues under physiologically relevant conditions, being kinetically more labile and easily reducible to Au(I) and metallic gold, Au(0) [3]. Despite that, the stability of the Au(III) ion has been achieved by an appropriate choice of the ligands [4–18]. Thus, different nitrogen-containing ligands such as polyamines, pyridine, bipyridine, terpyridine, phenanthroline, macrocyclic ligands (cyclam) and porphyrins have been used and a number of mononuclear and dinuclear gold(III) complexes have been synthesized showing remarkable stability under physiological conditions and relevant cytotoxic activity toward different human tumor cell lines [4–18].

Among others, special attention was devoted to the synthesis and evaluation of the gold(III) complexes containing 2-substituted pyridine ligands [19–35]. Coordination of this type of ligands to the Au(III) ion can result in the formation of chelate rings or aurocycles, incorporating atom of the side chain and the pyridine nitrogen. Thus, various organometallic gold(III) complexes of the general formula $[AuX_2(L)]$ have been synthesized, in which L is a 2-substituted pyridine ligand, such as 2-phenylpyridine [19], 2-benzylpyridines [20], 2-anilinopyridine [21], 2-phenoxypyridines [21b,22], 2-phenylsulfanylpyridine [21b], 2-benzoylpyridine [23], 2-thienylpyridine [24], 2-phenylthiazole [25] and 1-ethyl-2-phenylimidazole [26]. All these ligands form the Au–C σ-bond, as well as a coordinate Au–N(pyridine) bond, while the two remaining positions at the square planar gold(III) center are usually occupied by two monodentate or one bidentate anion. Furthermore, various

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gold(III) complexes with 2-substituted pyridine ligands containing nitrogen donor atom in the side chain have been synthesized and structurally characterized [27–35]. Thus, the gold(III) complex containing pyridine-2-carboxamide (picolinamide, Hpla), [Au(pla)Cl_2] was prepared by the reaction of this ligand with either H[$AuCl_4$]·3H_2O or Na[$AuCl_4$] in water solvent at ambient or elevated temperature and characterized by spectroscopic and crystallographic methods [27,28]. The obtained results showed that the formation of [Au(pla)Cl_2] complex proceeded through the coordination of the pyridine nitrogen, followed with the deprotonation and subsequent coordination of the amide nitrogen atom. This gold(III) complex showed structural similarity with cisplatin and *in vitro* cytotoxic activity against the MOLT-4 human leukemia and C2C12 mouse tumour cell lines comparable to this platinum(II) complex [28]. Moreover, recent study by Puddephatt and Nasser showed that gold(III) complex with *N*-substituted pyridine-2-carboxamide was an effective catalyst for oxidative α-cyanation of tertiary amines, which is a useful methodology for C–C coupling steps in organic synthesis [35].

Considering the great importance of gold(III) complexes with nitrogen donor ligands, in the present paper, we report the synthesis, NMR spectroscopic and X-ray crystallographic characterization of [Au(AMP)Cl_2]Cl·H_2O and $H_2AMP^{2+}Cl^-[AuCl_4]^-$·0.5$H_2O$ complexes, AMP is 2-(aminomethyl)pyridine (picolinamine).

2. Experimental

2.1. Materials

Distilled water was demineralized and purified to a resistance of greater than 10 MΩ·cm^{-1}. Hydrogen tetrachloridoaurate(III) trihydrate (H[$AuCl_4$]·3H_2O), 2-(aminomethyl)pyridine (AMP), ethanol and deuterium oxide (99.8%) were purchased from the Sigma–Aldrich Chemical Co. Hydrochloric acid was obtained from Zorka Pharma. All the employed chemicals were of analytical reagent grade and used without further purification.

2.2. Synthesis of [Au(AMP)Cl_2]Cl·H_2O (**1**)

The [Au(AMP)Cl_2]Cl·H_2O complex (**1**) was synthesized according to the modified procedure for preparation of [Au(phen)Cl_2]Cl complex (phen is bidentate coordinated *o*-phenanthroline) [36]. To the solution of 0.5 mmol of H[$AuCl_4$]·3H_2O (196.9 mg) in ethanol (10.0 mL), a solution containing an equimolar amounts of AMP (52.2 μL, 98%, ρ = 1.057 g/mL) and HCl (42.7 μL, 36.2%, ρ = 1.18 g/mL) in 1.0 mL of ethanol was added. The resulting yellow solution was stirred in the dark for 24 h at room temperature. Any colloidal gold formed was removed by filtration and filtrate was stored in a refrigerator to slowly evaporate. Yellow crystals of **1** formed after 2 days were filtered off and air-dried. The yield was 52% (111.7 mg). *Anal.* Calc. for [Au(AMP)Cl_2]Cl·H_2O = $C_6H_{10}AuCl_3N_2O$ (M_r = 429.48): C, 16.78; H, 2.35; N, 6.52. Found: C, 17.14; H, 2.46; N, 7.03%.

2.3. Synthesis of $H_2AMP^{2+}Cl^-[AuCl_4]^-$·0.5$H_2O$ (**2**)

The $H_2AMP^{2+}Cl^-[AuCl_4]^-$·0.5$H_2O$ (**2**) was prepared from equimolar amounts of H[$AuCl_4$]·3H_2O and AMP in the aqueous solution of HCl. 0.5 mmol of H[$AuCl_4$]·3H_2O (196.9 mg) was dissolved in 2.0 mL of 2 M HCl at room temperature and 52.2 μL (98%) of AMP was added to this solution. The resulting solution (pH ∼ 0.80) was stirred in the dark at 50 °C for 3 h. The Au(0) particles were filtered off and yellow filtrate was left standing at room temperature in the dark for several days. The pale yellow crystals of **2** were removed by filtration and dried in the dark at ambient temperature. The yield was 35% (86.3 mg). *Anal.* Calc. for $H_2AMP^{2+}Cl^-[AuCl_4]^-$·0.5$H_2O$ = $C_6H_{11}AuCl_5N_2O_{0.5}$ (M_r = 493.38): C, 14.61; H, 2.25; N, 5.68. Found: C, 14.61; H, 2.36; N, 5.68%.

2.4. pH measurements

All pH measurements were performed at ambient temperature. The pH meter (Iskra MA 5704) was calibrated with Fischer certified buffer solutions of pH 4.00 and 7.00. No corrections were made for the use of D_2O.

2.5. Elemental microanalyses

Elemental microanalyses for carbon, hydrogen and nitrogen were performed by the Microanalytical Laboratory, Faculty of Chemistry, University of Belgrade.

2.6. NMR spectroscopy

All the ^1H and ^{13}C NMR spectra were recorded at 25 °C on a Varian Gemini 2000 spectrometer at 200 and 50.3 MHz, respectively, in D_2O as solvent with TSP (sodium 3-(trimethylsilyl)propionate) as an internal reference. The concentration of the final solution was 20 mM in each compound and the total volume was 0.6 mL. All the NMR spectra were processed using Varian V NMR software (version 6.1, revision C).

2.7. Crystallographic data collection and refinement of the structures

Crystals of **1** and **2** suitable for X-ray analysis were grown from ethanol and water, respectively. Reflection intensities were measured on an Xcalibur diffractometer equipped with a Mo source (λ = 0.71073 Å) and Sapphire2 CCD detector at 295(2) K. Data reduction and analysis was carried out with CrysAlisPro program v.171.37.31 [37]. For **1** analytical numeric absorption correction using a multifaceted crystal model based on expressions derived by Clark & Reid [38] was applied, while for **2** multi-scan empirical absorption correction using spherical harmonics (implemented in SCALE3 ABSPACK scaling algorithm) was used. Further crystallographic and refinement data can be found in Table 1. Space group symmetry for the crystals of **1** was established unequivocally as $P2_1/c$. The crystals of **2** belonged to the orthorhombic system, and systematic absences of 0*kl* for $k+l$ odd and *hk*0 for *h* odd indicated the space groups $Pn2_1a$ or *Pnma*. The structure was solved by direct methods (SHELXS-97) [39] in both space groups, but the more reasonable shape of the thermal ellipsoids of the centrosymmetric refinement strongly suggested that the space group is *Pnma*. For the crystal with Z = 4 to be in the space group *Pnma*, both cations and anions would be constrained to lie on the mirror plane at y = ¼. The plane was passing through Au(III) and two chloride ions of the $[AuCl_4]^-$ complex anion and a non-coordinated chloride ion, and through the substituted C2 atom of the pyridine ring. This indicated a disorder across the mirror plane for the ammonium group as well as the pyridine nitrogen. However, it soon became apparent that the whole 2-(ammoniomethyl)pyridinium cation H_2AMP^{2+} was disordered around the mirror plane in such a way that no atom would reflect into each other across this plane. Therefore the disorder model applied for the refinement in the centrosymmetric space group *P*nma contained two H_2AMP^{2+} cations with half occupancy disordered over the mirror plane. The further refinement of both these fragments was carried out with AFIX 66 constraint. The structures of **1** and **2** were both refined by full-matrix least-squares on F^2 (SHELXL-97) [39]. The H atoms, except for water hydrogens, were calculated geometrically and a riding model was applied during