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Gold(I) and silver(I) complexes of 2,3-bis(diphenylphosphino)maleic acid: Structural studies and antitumour activity

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This contribution is dedicated to Prof. Hubert Schmidbaur.

Abstract

The 2:1 and 1:2 adducts of Au(I) and 1:2 adducts of Ag(I) with the diphosphine 2,3-bis(diphenylphosphino)maleic acid (dpmaa) have been prepared in high yields. Crystal structures have been determined for the neutral digold complex $(AuCl)_2(dpmaa) \cdot 2thf$ (**1**) and the bis-chelated complex $[Au(dpmaa)_2]Cl \cdot H_2O \cdot CH_3OH$ (**2**). For **1**, conformational rigidity imposed by the ethylenic bridge facilitates the formation of short intramolecular Au–Au contacts with no evidence of similar intermolecular contacts. Complex **2** crystallizes with $[Au(dpmaa)_2]^+$ cations hydrogen bonded through the carboxyl groups to a water molecule and chloride anion to form a H-bonded chain along the a axis. ^{31}P NMR titration of **1** with dpmaa in acetone shows conversion to **2** at Au:P–P ratios less than 1:1 indicating similar high thermodynamic and kinetic stabilities to other bis-chelated $[Au(P–P)_2]^+$ complexes containing 5- or 6-membered chelate rings. The ionic Au(I) complex **2** and the analogous Ag(I) complex $[Ag(dpmma)_2]NO_3$ (**3**) are highly water soluble. The in vitro cytotoxic activity of **2** was assessed against eight different cell lines and no significant activity was found. The solubility properties and solution behaviour of the complexes are compared to the analogous 1,2-bis(diphenylphosphino)ethane (dppe) complexes and the potential significance of these results to the antitumour properties of chelated 1:2 Au(I)diphosphine complexes are discussed.

Keywords: Gold complexes; Silver complexes; Phosphine ligands; Antitumour agents

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1. Introduction

Generally, bis-chelated 1:2 M(I) diphosphine complexes of the type $[M\{R_2P(CH_2)_nPR_2\}]^+$, where M = Au(I), Ag(I) or Cu(I) and R = aryl, $n = 2$ or 3 and analogous complexes with *cis*-$R_2PCH{=}CHPR_2$, exhibit antitumour activity [1]. In particular, the Au(I) complex $[Au(dppe)_2]Cl$ (where dppe is 1,2-bis(diphenylphosphino)ethane) showed potent activity against a range of tumour models in mice, including a cisplatin-resistant subline of P388 leukaemia [2]. While there is evidence that mitochondria are implicated in the mechanism of cytotoxicity for this class of lipophilic cations [3], the clinical development of $[Au(dppe)_2]Cl$ was precluded

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as a result of toxic side effects associated with altered mitochondrial function [4]. The lipophilic cationic properties of $[Au(dppe)_2]^+$ promote its non-selective uptake into mitochondria in all cells, with heart and liver tissue being particularly sensitive owing to the high numbers of mitochondria. For other large lipophilic cations, such as bis quarternary ammonium heterocycles [5] and trialkylphosphonium salts [6] a relationship between antitumour selectivity and lipophilic–hydrophilic balance was demonstrated. Our strategy has been to develop more hydrophilic analogues of $[Au(dppe)_2]^+$ that may be less toxic than the parent compound and retain the antitumour activity. We have shown previously for Au(I) and Ag(I) complexes of type $[M\{R_2P(CH_2)_nPR_2\}_2]^+$ that replacing the phenyl groups with pyridyl substituents [7,8], resulted in a series of complexes with different hydrophilic–lipophilic balance, which exhibited differences in cellular uptake and hence differences in antitumour selectivity, potency and hepatotoxicity [9–11].

In this work, we have adopted a different approach, which also retains the aromatic substituents, which appear to be important for antitumour activity [1] but introduces hydrophilic groups into the ethane bridge of dppe to increase water solubility. Here, we describe the preparations, stabilities and structural studies in both solid state and in solution of the Au(I) and Ag(I) complexes of the known ligand, 2,3-bis(diphenylphosphino)maleic acid (dpmaa) [12]. The results obtained from cytotoxicity assays of the Au(I) complex against tumour cell lines in vitro are also discussed.

2. Experimental

All manipulations were carried out under argon, using standard Schlenk techniques. Solvents were distilled from drying agents and degassed. The NMR spectra were recorded on the following Bruker instruments: DRX 400 (^{1}H, 400.32; ^{31}P, 161.98 MHz), Avance 300 (^{1}H, 300.13; ^{13}C, 75.5; ^{31}P 121.5 MHz) or AC 200 (^{1}H, 200.13 MHz). ^{1}H and ^{13}C{^{1}H}NMR spectra were referenced using the residual solvent signal as the internal standard, whereas ^{31}P–{^{1}H}NMR spectra were referenced to external H_3PO_4 (85%). NMR data for the complexes are shown in Table 1. Elemental analyses were determined by the Institute for Soil, Climate and Water, Pretoria, South Africa or by the Australian Microanalytical Service, Victoria, Australia.

Data sets for compounds **1** and **2** were collected on a Bruker SMART 1K CCD area detector, using monochromatic Mo Kα radiation. Data reduction was carried out using the program SAINT [13a] and absorption corrections were made using the program SADABS [13b]. The structures were solved by direct methods using SHELXTL [14]. Refinement was based on F^2 with hydrogen atoms in riding mode, using SHELXTL [14]. Publication materials were generated using SHELXTL [14], PLATON [15] and SCHAKAL-97 [16]. Further details are found in Table 4.

Table 1
NMR data for dpmaa and the Au(I) complexes **1** and **2** (in $CDCl_3$)

	dpmaa	$(AuCl)_2$(dpmaa) (**1**)	$[Au(dpmaa)_2]Cl$ (**2**)
δ^{13}C (J_{PC}, Hz)[a]			
C_i	132.1	125.9 (32)	128.6 (m)
C_o	134.1 (11)	133.9 (7)	131.5 (m)
C_m	128.7 (4)	128.5 (6)	128.1 (m)
C_p	129.9	131.8	130.0
C=C	150.0 (m)	143.5 (23)	151.2 (m)
COOH	169.1 (4)	164.7 (10)	165.0 (m)
δ^1H			
ArH	7.25 (m)	7.52 (m)	7.20 (m)
COOH	9.11	–[b]	–[b]
δ^{31}P[c]			
	−10.9	21.9	28.1

[a] J_{PC} couplings (where resolved) are observed as virtual triplets for **1** and dpmaa and second-order multiplets for **2**.

[b] Not observed.

[c] In d_6-acetone.

2.1. Preparation of compounds

The ligands 2,3-bis(diphenylphosphino)maleic anhydride (dpma) [17] and 2,3-bis(diphenylphosphino)maleic acid (dpmaa) [12] were prepared by literature methods. $Na[AuCl_4] \cdot 2H_2O$ was purchased from Johnson Matthey, while $ClAuSMe_2$ was prepared by the oxidation of gold metal with dimethylsulfoxide, as described elsewhere [18].

2.1.1. $(AuCl)_2$(dpmaa) (1)

(a) Thiodiglycol (0.19 g, 1.62 mmol) in thf (2 ml) was quickly added to an orange solution of $NaAuCl_4 \cdot H_2O$ (0.307 g, 0.808 mmol) in deionised water (5 ml) at 0 °C. After stirring for 5 min, the resulting colourless solution was added to a light yellow solution of dpmaa · $1.5Et_2O$ (0.241 g, 0.404 mmol) in thf (10 ml). The solution became dark orange, and after 10 min, the solvents were removed in vacuo to give a pale yellow gum. The material was redissolved in a thf:Et_2O mixture (1:1) and after refrigeration at 4 °C overnight, yellow crystals were produced and collected by filtration. Elemental analysis *Anal.* Calc. for $C_{28}H_{22}O_4P_2Au_2Cl_2 \cdot 1.5C_4H_8O$: C, 38.7; H, 3.1. Found: C, 38.5; H, 2.9%. The presence of thf solvate was verified by ^{1}H NMR spectroscopy. IR (nujol): $\bar{\nu} = 3378$ (ν_{OH}), 2728 (ν_{COOH}), 2594 (ν_{COOH}), 1719 (ν_{CO}), 1555 (ν_{ArH}) cm^{-1}.

(b) $ClAuSMe_2$ (0.238 g, 0.808 mmol) was added to dpmaa · $1.5Et_2O$ (0.241 g, 0.404 mmol) in thf (20 ml) at room temperature. The reaction mixture was stirred for 30 min, the solvents removed in vacuo, and the resultant residue re-dissolved in a 1:1 thf:Et_2O mixture (30 ml