DALTON COMMUNICATION

Mononuclear gold(I) complex of a chiral tetra(tertiary phosphine). Crystal and molecular structure of [*T*-4-(R_P*,R_P*)]-(±)-1,2-bis-[(2-diphenylphosphinophenyl)methylphosphino]benzene-*P*,*P*′,*P*″,*P*‴gold(I) hexafluorophosphate

Swarup Chatterjee,[a] Felicity K. E. Moore,[a] Geoffrey Salem,[a] Paul Waring[b] and Anthony C. Willis[c]

[a] *Chemistry Department, The Faculties, Australian National University, Canberra, A. C. T. 0200, Australia. E-mail: Geoff.Salem@anu.edu.au*
[b] *John Curtin School of Medical Research, Australian National University, Canberra, A. C. T. 0200, Australia*
[c] *Research School of Chemistry, Australian National University, Canberra, A. C. T. 0200, Australia*

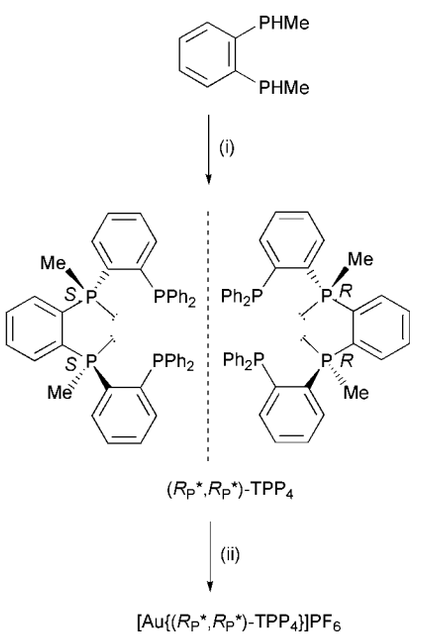
Received 11th September 2000, Accepted 15th November 2000
First published as an Advance Article on the web 30th November 2000

A mononuclear tetra(tertiary phosphine)gold(I) complex has been isolated *via* the reaction of (R_P*,R_P*)-1,2-bis-[(2-dimethylphosphinophenyl)methylphosphino]benzene, (R_P*,R_P*)-TPP$_4$, with NBu$^n_4$[AuI$_2$] in ethanol followed by metathesis with aqueous NH$_4$PF$_6$; as confirmed by a crystal structure determination of [Au{(R_P*,R_P*)-TPP$_4$}]PF$_6$.

Much of the current interest in (tertiary phosphine)gold(I) complexes has focussed on compounds containing two or more metal centres.[1] The luminescence behaviour associated with polynuclear d^{10} metal complexes has been a major contributing factor as compounds of this type are seen as potential luminescent sensors.[2] The observation of short metal–metal distances in compounds of this type and, in particular, in a range of gold(I) complexes has also helped to kindle interest in this area of research.[2,3] The tertiary phosphines associated with the gold(I) centres in these compounds are typically unidentate or bidentate ligands although there are several examples containing bridging polydentate ligands. Examples of the latter include the tri(tertiary phosphines) RP[(CH$_2$)$_n$PR$_2$]$_2$ (where n = 1 and R = Me or Ph, or n = 2 and R = Ph),[2,4] RC(PPh$_2$)$_3$ (where R = H or Me),[5] PhP(C$_6$H$_4$PPh$_2$-2)$_2$,[6] and N(CH$_2$CH$_2$PPh$_2$)$_3$.[7] The latter two ligands also form monomeric gold(I) complexes. The tetra(tertiary phosphine) 1,2-bis[(diphenylphosphinoethyl)-phenylphosphino]ethane, tetraphos, forms bimetallic helicates on complexation to gold(I).[8]

In this communication we report on the synthesis and crystal structure determination of [*T*-4-(R_P*,R_P*)]-(±)-{1,2-bis[(2-diphenylphosphinophenyl)methylphosphino]benzene-*P*,*P*′,*P*″,*P*‴} gold(I) hexafluorophosphate, [Au{(R_P*,R_P*)-TPP$_4$}]PF$_6$, the first example of a structurally authenticated mononuclear tetra(tertiary phosphine)gold(I) complex. The presence of three 1,2-phenylene linkages in the backbone of the ligand, coupled with the two stereogenic phosphorus centres having the same relative configuration, precludes formation of anything but a mononuclear tetrahedral gold(I) complex. We have recently reported on the completely stereoselective synthesis of the related ligand (R_P*,R_P*)-1,2-bis[(2-dimethylphosphinophenyl)methylphosphino]benzene, the first example of a tetra(tertiary phosphine) in which the four phosphorus centres are linked by three 1,2-phenylene linkages. The presence of the latter is the key to the high stereoselectivity observed in the synthesis of the ligand and also for the exclusive formation of the *cis*–*α* diastereomer on complexation of the tetra(tertiary phosphine) to cobalt(III).[9]

Tetra(tertiary phosphine) (R_P*,R_P*)-TPP$_4$ was synthesised *via* double-deprotonation of the bis(secondary phosphine) (R_P*,R_P*)- and (R_P*,S_P*)-1,2-phenylenebis(methylphosphine)[10] using two equivalents of sodium in THF followed by the addition of two equivalents of (2-chlorophenyl)diphenylphosphine (Scheme 1).† It was isolated as an air-stable, white crystal-



Scheme 1 Only one of the enantiomers of (R_P*,R_P*)-TPP$_4$ is depicted. Reagents and conditions: i, 2 Na, THF; 2 (2-ClC$_6$H$_4$)PPh$_2$, THF; ii, NBu$_4$[AuI$_2$], EtOH; NH$_4$PF$_6$ in water.

line solid from hot methanol. The ^{1}H NMR spectrum of (R_P*,R_P*)-TPP$_4$ exhibited a single PMe resonance and the ^{31}P-{^{1}H} NMR spectrum revealed a spectral pattern for an AXX′A′ spin system, consistent with the presence of a single diastereomer of the tetra(tertiary phosphine). The complex [Au{(R_P*,R_P*)-TPP$_4$}]PF$_6$ was subsequently prepared *via* reaction of (R_P*,R_P*)-TPP$_4$ with NBu$_4$[AuI$_2$] in ethanol followed by metathesis with aqueous NH$_4$PF$_6$.† The structure of the complex has been determined by an X-ray analysis (Fig. 1).‡ The structural data clearly show the presence of a mononuclear gold(I) complex in which the metal centre is surrounded by a pseudo-tetrahedral arrangement of phosphorus donor atoms.

DOI: 10.1039/b007363f

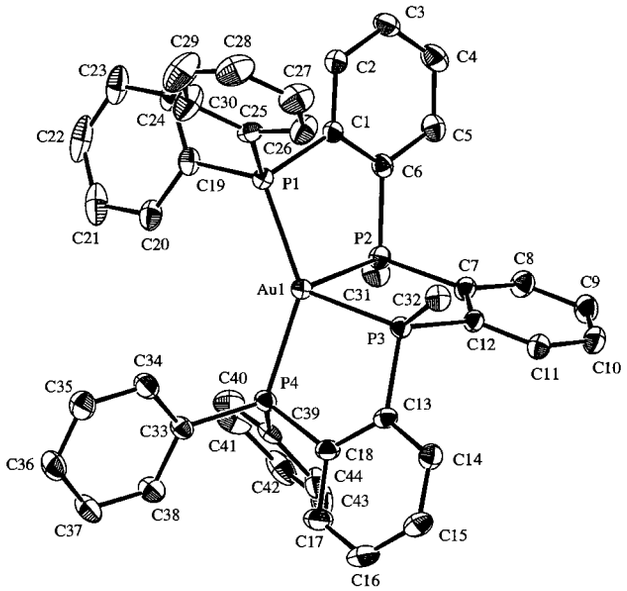


Fig. 1 Molecular structure of the cation $[Au\{(R_P^*,R_P^*)\text{-}TPP_4\}]^+$. Selected bond distances and angles are as follows: Au–P(1) 2.320(1), Au–P(2) 2.414(1), Au–P(3) 2.382(1), Au–P(4) 2.333(1) Å; P(1)–Au–P(2) 87.41(5), P(1)–Au–P(3) 124.82(5), P(1)–Au–P(4) 143.32(5), P(2)–Au–P(3) 86.22(5), P(2)–Au–P(4) 113.42(5), P(3)–Au–P(4) 87.89(5)°. (The complex has non-crystallographic C_2 symmetry.)

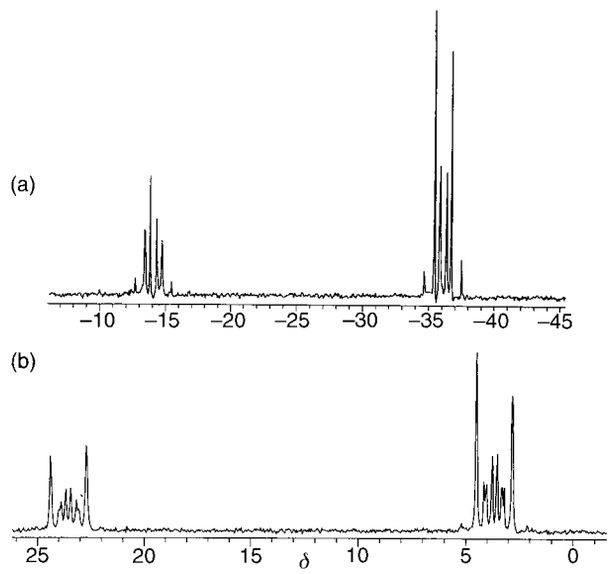


Fig. 2 $^{31}P\text{-}\{^1H\}$ NMR spectra of (a) $(R_P^*,R_P^*)\text{-}TPP_4$ in C_6D_6 and (b) $[Au\{(R_P^*,R_P^*)\text{-}TPP_4\}]PF_6$ in $CDCl_3$.

The P–Au–P bond angles range from 86.22(5) to 143.32(5)°, the largest angle being that subtended by the two coordinated phosphorus atoms of the terminal diphenylphosphino groups. It is noteworthy that the Au–P bond lengths associated with the latter are shorter than that between the internal stereogenic phosphorus donor atoms and the metal centre. The two phosphorus stereocentres also have the same relative configuration, with both $\Delta(R,R)$ and $\Lambda(S,S)$ forms of the cation being present in the unit cell. Only the former is shown in Fig. 1. As expected there was no evidence of an aurophilic interaction between neighbouring gold(I) centres, a consequence of the bulky nature of the three 1,2-phenylene units in the backbone of the ligand combined with that of the terminal diphenylphosphino moieties.

The $^{31}P\text{-}\{^1H\}$ NMR spectrum of $[Au\{(R_P^*,R_P^*)\text{-}TPP_4\}]PF_6$ can be rationalised in terms of its solid state structure, a spectral pattern for an AXX′A′ spin system being observed. The $^{31}P\text{-}\{^1H\}$ NMR spectra of $[Au\{(R_P^*,R_P^*)\text{-}TPP_4\}]PF_6$ and $(R_P^*,R_P^*)\text{-}TPP_4$ are shown in Fig. 2. Redistribution reactions between free $(R_P^*,R_P^*)\text{-}TPP_4$ and its gold(I) complex also appear to be slow on the NMR time scale and there is no evidence for an equilibrium between monomeric and dimeric species in solution. Similar behaviour was observed between free tetraphos and its gold(I) complex; however, the possibility of an equilibrium between monomeric and dimeric species in solution could not be completely discounted.[8,11]

Our particular interest in gold(I) complexes containing tetra(tertiary phosphines) is that they are seen as potential antitumour agents. A number of related bis[di(tertiary phosphine)]gold(I) complexes have previously been shown to display antitumour activity comparable to that of cisplatin, for example, bis[1,2-bis(diphenylphosphino)ethane]gold(I) chloride, $[Au(dppe)_2]Cl$.[12] The mechanism of action of compounds of this type is not known with any certainty but is believed to be fundamentally different to that of the platinum-based anticancer drugs. The complexes are believed to target the cell mitochondria. For example, the complex $[Au(dppe)_2]Cl$ was shown to induce a rapid, dose-related collapse of the inner mitochondrial potential (mmp) that led to an increase in cellular respiration and a disruption of ATP synthesis and finally a swelling of the mitochondria. It was subsequently shown to be too toxic for clinical use due to side-effects related to the disruption of mitochondrial function in hepatocytes and acute cardiotoxicity in dogs.[13] We have recently reported that the gold(I) complex of tetraphos exhibited potent *in vitro* cytotoxicity against the mouse tumour cell lines P815 mastocytoma, B16 melanoma and P388 leukaemia, and the cisplatin-resistant 41McisR, CH1cisR and SKOV-3 tumour models.[11] *In vivo* antitumour activity has also been recently reported for bis(bidentate)gold(I) complexes containing di(tertiary phosphine) ligands bearing pyridyl substituents against cisplatin-resistant cell lines and purported too for gold(I) complexes containing a range of linear tetra(tertiary phosphines) with one or more methylene units between the phosphorus atoms, including tetraphos, against the murine P388 leukaemia cell line.[14,15] In the present work the complex $[Au\{(R_P^*,R_P^*)\text{-}TPP_4\}]PF_6$ was found to exhibit potent *in vitro* cytotoxicity against the mouse tumour cell line P388 leukaemia. Both $[Au\{(R_P^*,R_P^*)\text{-}TPP_4\}]PF_6$ and $[Au_2\{(R_P^*,R_P^*)\text{-tetraphos}\}_2](PF_6)_2$ have also been shown to inhibit colony formation of the human breast tumour cell line MCF-7 [relatively high mitochondrial membrane potential (mmp)] to a significantly greater extent than that of monkey kidney epithelial CV-1 cells (significantly lower mmp). These preliminary studies augur well for the eventual goal of designing a gold(I)-based agent which selectively targets the mitochondria of tumour cells.

Acknowledgements

The authors gratefully acknowledge the financial support of this project by the Australian Research Council.

Notes and references

† Preparations. $(R_P^*,R_P^*)\text{-}TPP_4$: Excess sodium foil (1.48 g, 0.064 mol) was added to (R_P^*,R_P^*)- and (R_P^*,S_P^*)-1,2-phenylenebis(methylphosphine) (4.66 g, 0.027 mol) in THF (120 cm^3) and the solution stirred for 48 h. The reaction mixture was cooled to −78 °C and a solution of (2-chlorophenyl)diphenylphosphine (18.26 g, 0.062 mol) in THF (250 cm^3) was added over a period of 1.5 h. The solution was stirred at room temperature for 15 days. The reaction mixture was cooled to 0 °C and a saturated solution of aqueous NH_4Cl (20 cm^3) was added. The solvents were distilled off under argon, and water (200 cm^3) was added to the residue. The mixture was extracted with dichloromethane (2 × 100 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed under argon. The residue was dissolved in hot methanol (400 cm^3) and gave a white crystalline material on standing at room temperature overnight. The product was collected, washed with cold methanol (50 cm^3) and dried *in vacuo* at 40 °C for 24 h (6.18 g, 33%). mp 114–116 °C; ^1H NMR data (300 MHz, C_6D_6 at 20 °C): δ 1.74 (m, 6 H, 2 PMe), 6.90–7.46 (m, 32 H, aromatics); $^{31}P\text{-}\{^1H\}$ NMR data (121.5 MHz, C_6D_6 at 20 °C): δ_A −36.1 (internal P; AA′), δ_X −14.1 (terminal P; XX′), (XAA′X′, $J_{AA'}$ 79.0 Hz, J_{AX}

149.5 Hz, $J_{AX'}$ 6.9 Hz, $J_{XX'}$ 0.5 Hz); EI-MS: *m*/*z* 690 $(M)^+$, 675 $(M - Me)^+$, 613 $(M - Ph)^+$, 505 $(M - PPh_2)^+$. Found: C, 76.36; H, 5.85. Calc. for $C_{44}H_{38}P_4$: C, 76.52; H, 5.55%.

[Au{(R_P*,R_P*)-TPP_4}]PF_6: $[NBu^n_4][AuI_2]$ (0.11 g, 0.14 mmol) was added to a solution of (R_P*,R_P*)-TPP_4 (0.11 g, 0.14 mmol) in ethanol (20 cm^3) and the mixture heated briefly on a steam bath. The volume of the solution was reduced by *ca*. 50% to give [Au{(R_P*,R_P*)-TPP_4}]I (0.14 g, 97%). The iodide salt was redissolved in acetone (20 cm^3) and a solution of NH_4PF_6 (0.11 g, 0.880 mmol) in water (10 cm^3) was added. The volume of the solution was reduced to *ca*. 10 cm^3 to give a white solid that was subsequently recrystallised from acetonitrile by the addition of diethyl ether (0.11 g, 93%). mp 288 °C. ^{1}H NMR data [300 MHz, $(CD_3)_2CO$ at 20 °C]: δ 1.97 (bs, 6H, PMe), 7.59–8.55 (m, 32 H, aromatic); ^{31}P-{^{1}H} NMR data [121.5 MHz, $(CD_3)_2CO$ at 20 °C]: δ_A 3.69 (internal P; AA′), δ_X 23.57 (terminal P; XX′), (XAA′X′, $J_{AA'}$ 41 Hz, J_{AX} 131 Hz, $J_{AX'}$ 75 Hz, $J_{XX'}$ 7 Hz). Found: C, 49.14; H, 3.60. Calc. for $C_{44}H_{38}AuF_6P_5 \cdot 2\,H_2O$: C, 49.45; H, 3.96%.

‡ Crystal data for [Au{(R_P*,R_P*)-TPP_4}]$PF_6 \cdot CH_2Cl_2$: $C_{45}H_{40}AuCl_2F_6P_5$, $M = 1117.54$, triclinic, $a = 9.7019(3)$, $b = 14.5445(4)$, $c = 16.3041(4)$ Å, $\alpha = 86.957$, $\beta = 76.013(2)$, $\gamma = 87.492(2)°$, $U = 2228.2(1)$ Å^3, $T = 200.0$ K, space group $P\bar{1}$ (no. 2), $Z = 2$, μ(Mo-Kα) = 36.7 cm^{-1}, 48690 reflections measured, 10205 unique ($R_{int} = 0.092$), 7069 with $I > 2\sigma(I)$ used in all calculations. The final R and R' values were 0.0381 and 0.0392. CCDC reference number 186/2269. See http://www.rsc.org/suppdata/dt/b0/b007363f/ for crystallographic files in .cif format.

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