DALTON

Synthesis of gold(I), silver(I) and copper(I) complexes containing substituted (2-aminophenyl)phosphines. Molecular structures of [AuI(2-$H_2NC_6H_4PPh_2$)], [AuI{(±)-2-$H_2NC_6H_4PMePh$}] and (±)-[Cu(2-$H_2NC_6H_4PPh_2$)$_2$]PF_6

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Linear gold(I) complexes of type [AuI(L)] and [AuL$_2$]I (L = 2-$H_2NC_6H_4PPhR$, R = Me or Ph) have been prepared by the reaction of the appropriate ligand with [NBu^n_4][AuI_2] in ethanol. The neutral ligand L is co-ordinated to the metal centre *via* the phosphorus donor atom. The structures of the complexes [AuI(2-$H_2NC_6H_4PPh_2$)] and [AuI{(±)-2-$H_2NC_6H_4PMePh$}] have been confirmed by X-ray analyses with the latter, but not the former, complex exhibiting auriophilicity. Metathesis of these compounds with NH_4PF_6 gave the corresponding hexafluorophosphate salts [AuL_n]PF_6 (n = 1 or 2). Tetrahedral complexes of the type [ML_n]PF_6 (L = 2-$H_2NC_6H_4PPhR$; R = Ph, M = Ag or Cu, n = 2 or 3; R = Me, M = Cu, n = 2 or 3; R = Me, M = Ag, n = 3) have also been prepared *via* reaction of the appropriate ligand with [Cu(NCMe)$_4$]PF_6 in acetonitrile or $AgNO_3$ in ethanol followed by metathesis with NH_4PF_6. The molecular structure of (±)-[Cu(2-$H_2NC_6H_4PPh_2$)$_2$]PF_6 has been confirmed by X-ray crystallography. All of the complexes have been shown by NMR spectroscopy to undergo facile ligand-exchange reactions in solution. These complexes are seen as potential anticancer agents. Preliminary biological studies have shown them to be active against three mouse tumour cell lines *in vitro* with cytotoxicities of certain of these complexes being comparable to that of *cis*-diamminedichloroplatinum(II), cisplatin, and bis[1,2-bis(diphenylphosphino)ethane]gold(I) iodide.

The coinage metals of Group 11 readily form bis(bidentate) complexes with di(tertiary phosphines) in which the univalent metal centre has a tetrahedral stereochemistry. Complexes of this type containing the dissymmetric di(tertiary phosphine) (*R**,*R**)-1,2-bis(methylphenylphosphino)benzene were found to undergo intermolecular ligand-redistribution reactions in solution, the rate of exchange increasing in the order gold(I) < copper(I) < silver(I).[1,2] In the case of gold(I) these reactions were slow enough to allow the separation by fractional crystallisation of racemic and *meso* complexes. Furthermore, the stereogenic metal centre in related tetrahedral complexes containing the (*R**,*S**) form of $C_6H_4(PMePh)_2$-1,2 underwent facile inversion, the low barriers to inversion precluding resolution of the complexes. Similar results have been reported for related tetrahedral complexes containing symmetrical di(tertiary phosphines) such as 1,2-bis(diphenylphosphino)ethane, dppe, 1,2-bis(diphenylphosphino)propane, dppp, *cis*-1,2-bis(diphenylphosphino)ethene, dppey, and 1,2-bis(diethylphosphino)ethane, depe; the unsymmetrical di(tertiary phosphine) 1-(diethylphosphino)-2-(diphenylphosphino)ethane, eppe;[3–7] the di(tertiary arsine) (*R**,*R**)- and (*R**,*S**)-1,2-bis(methylphenylarsino)benzene;[1,2] and the mixed-donor ligands (*R**,*R**)- and (*R**,*S**)-1-(methylphenylarsino)-2-(methylphenylphosphino)benzene, and 1-(diphenylphosphino)-2-(2-pyridyl)ethane, ppye.[1,8] In the latter case, only the complexes of copper(I) and silver(I) had a tetrahedral stereochemistry; the gold(I) complex was digonal.

Bis(ditertiary phosphine) complexes of gold(I), silver(I) and copper(I) have attracted much interest over the past decade as certain of these complexes, for example, bis[1,2-bis(diphenylphosphino)ethane]gold(I) chloride, [Au(dppe)$_2$]Cl, and its silver(I) and copper(I) derivatives, have been shown to display antitumour activities comparable to those of *cis*-diamminedichloroplatinum(II), cisplatin.[9] Whilst cisplatin has been highly successful in the treatment of certain cancers, there are a number of side-effects associated with the use of this drug such as nephrotoxicity, myelosuppression, ototoxicity, nausea and vomiting.[10] Continuing research into the development of other platinum-based anticancer agents as well as alternative metal-based drugs is geared to overcoming these problems. Despite the early promise of [Au(dppe)$_2$]Cl and its derivatives, the compounds have subsequently been shown to be too toxic for clinical use due to side-effects related to the disruption of mitochondrial function in hepatocytes.[11,12]

This paper describes the synthesis of gold(I), silver(I) and copper(I) complexes containing the mixed-donor ligands (2-aminophenyl)diphenylphosphine, adpp, and (±)-(2-aminophenyl)methylphenylphosphine, (±)-ampp.† The molecular structures of [AuI(2-$H_2NC_6H_4PPh_2$)], [AuI{(±)-2-$H_2NC_6H_4PMePh$}] and (±)-[Cu(2-$H_2NC_6H_4PPh_2$)$_2$]PF_6 have been confirmed by X-ray crystallography. The solution behaviour of these complexes and their *in vitro* cytotoxic properties against three mouse tumour cell lines are also reported.

Experimental

Synthetic procedures and materials

Reactions involving air-sensitive reagents were performed under argon using Schlenk techniques. Solvents were dried and purified by distillation under argon. The NMR spectra were recorded on a Varian Gemini II spectrometer operating at 300 (^{1}H) or 121 MHz (^{31}P-{^{1}H}). Chemical shifts are reported as δ

† A paper on the synthesis of related gold(I) complexes containing the ligand adpp has very recently appeared.[13]

values relative to $SiMe_4$ (^1H) or 85% H_3PO_4 (^{31}P-{^1H}). Molar conductivities were measured on 10^{-3} mol dm^{-3} solutions at 25 °C using a Radiometer Copenhagen CDM 80 conductivity meter. Elemental analyses were performed within the Research School of Chemistry.

The compounds (2-aminophenyl)diphenylphosphine,[14] (±)-(2-aminophenyl)methylphenylphosphine,[15] (*L*-2)-tetra-*n*-butylammonium diiodoaurate(I)[16] and (*T*-4)-tetrakis(acetonitrile)-copper(I) hexafluorophosphate[17] were prepared by literature procedures.

Preparations

(*L*-2)-[(2-Aminophenyl)diphenylphosphine]iodogold(I), [AuI(adpp)]. Tetra-*n*-butylammonium diiodoaurate(I) (0.25 g, 0.36 mmol) was dissolved in ethanol (15 cm^3) and adpp (0.10 g, 0.36 mmol) slowly added with stirring. The resulting white crystalline product was filtered off, washed with ethanol and dried *in vacuo* (0.15 g, 69%), m.p. 210 °C (Found: C, 35.9; H, 2.8; N, 2.0. Calc. for $C_{18}H_{16}AuINP$: C, 36.0; H, 2.7; N, 2.3%). ^1H NMR ($CDCl_3$): δ 4.40 (s, 2 H, NH_2) and 6.73–7.61 (m, 14 H, aromatics).

(*L*-2)-[(±)-(2-Aminophenyl)methylphenylphosphine]iodogold(I), [AuI{(±)-ampp}]. A solution of the racemic ligand (±)-ampp (0.17 g, 0.79 mmol) in ethanol (5 cm^3) was added to a solution of tetra-*n*-butylammonium diiodoaurate(I) (0.55 g, 0.79 mmol) in ethanol (20 cm^3) with stirring. The white crystalline product was filtered off, washed with ethanol and dried *in vacuo* (0.33 g, 77%), m.p. 164 °C (Found: C, 29.4; H, 2.9; N, 2.4. Calc. for $C_{13}H_{14}AuINP$: C, 29.0; H, 2.6; N, 2.6%). ^1H NMR ($CDCl_3$): δ 2.13 (d, 3 H, $^2J_{PH}$ 10.4 Hz, PMe), 4.28 (s, 2 H, NH_2) and 6.81–7.83 (m, 9 H, aromatics).

(*L*-2)-[(2-Aminophenyl)diphenylphosphine]gold(I) hexafluorophosphate, [Au(adpp)]PF_6. The complex [AuI(adpp)] (0.15 g, 0.25 mmol) was dissolved in acetone (15 cm^3) and a solution of NH_4PF_6 (0.10 g, 0.61 mmol) in water (5 cm^3) slowly added with stirring. The resulting white crystalline product was filtered off and dried *in vacuo* (0.11 g, 72%), m.p. 210 °C (Found: C, 35.5; H, 2.5; N, 2.4. Calc. for $C_{18}H_{16}AuF_6NP_2$: C, 34.9; H, 2.6; N, 2.3%). ^1H NMR ($CDCl_3$): δ 4.40 (s, 2 H, NH_2) and 6.68–7.59 (m, 14 H, aromatics).

(*L*-2)-[(±)-(2-Aminophenyl)methylphosphine]gold(I) hexafluorophosphate–acetone (2/1), [Au{(±)-ampp}]PF_6·0.5Me_2CO. This was prepared as for [Au(adpp)]PF_6 except using [AuI{(±)-ampp}] (0.11 g, 0.20 mmol) to give a white crystalline product (0.09 g, 79%), m.p. 168 °C (Found: C, 29.4; H, 2.7; N, 2.4. Calc. for $C_{14.5}H_{20}AuF_6NOP_2$: C, 29.7; H, 2.9; N, 2.4%). ^1H NMR ($CDCl_3$): δ 2.31 (d, 3 H, $^2J_{PH}$ 10.5 Hz, PMe), 4.28 (s, 2 H, NH_2) and 6.88–7.76 (m, 9 H, aromatics).

(*L*-2)-Bis[(2-aminophenyl)diphenylphosphine]gold(I) iodide, [Au(adpp)$_2$]I. Tetra-*n*-butylammonium diiodoaurate(I) (0.40 g, 0.56 mmol) was dissolved in ethanol (20 cm^3) and adpp (0.32 g, 1.15 mmol) slowly added with stirring. The resulting white crystalline product was filtered off, washed with ethanol and dried *in vacuo* (0.41 g, 81%), m.p. 192–194 °C (Found: C, 49.6; H, 3.6; N, 2.9. Calc. for $C_{36}H_{32}AuIN_2P_2$: C, 49.2; H, 3.7; N, 3.2%). ^1H NMR ($CDCl_3$): δ 4.29 (s, 4 H, NH_2) and 6.72–7.59 (m, 28 H, aromatics).

(*L*-2)-Bis[(±)-(2-aminophenyl)methylphenylphosphine]gold(I) iodide, [Au{(±)-ampp}$_2$]I. A solution of (±)-ampp (0.15 g, 0.70 mmol) in ethanol (5 cm^3) was added to a solution of tetra-*n*-butylammonium diiodoaurate(I) (0.24 g, 0.35 mmol) in ethanol (15 cm^3) with stirring. The white crystalline product was filtered off, washed with ethanol and dried *in vacuo* (0.14 g, 54%), m.p. 168 °C (Found: C, 41.8; H, 3.6; N, 3.4. Calc. for $C_{26}H_{28}AuIN_2P_2$: C, 41.4; H, 3.7; N, 3.7%). ^1H NMR ($CDCl_3$): δ 2.26 (d, 6 H, $^2J_{PH}$ 8.5 Hz, PMe), 4.31 (s, 4 H, NH_2) and 6.63–7.67 (m, 18 H, aromatics).

(*T*-4)-Bis[1,2-bis(diphenylphosphino)ethane]gold(I) iodide, [Au(dppe)$_2$]I. This was prepared as for [Au(adpp)$_2$]I except using tetra-*n*-butylammonium diiodoaurate(I) (0.30 g, 0.43 mmol) and dppe (0.35 g, 0.88 mmol). The product was recrystallised from methanol (3 cm^3) by the addition of water (20 cm^3) to give white crystals (0.33 g, 68%), m.p. 94 °C (Found: C, 55.4; H, 3.9. Calc. for $C_{52}H_{48}AuIP_4$: C, 55.7; H, 4.3%). ^1H NMR ($CDCl_3$): δ 2.51 (s, 4 H, CH_2) and 7.21–7.38 (m, 20 H, aromatics).

(*L*-2)-Bis[(2-aminophenyl)diphenylphosphine]gold(I) hexafluorophosphate, [Au(adpp)$_2$]PF_6. This was prepared as for [Au(adpp)]PF_6 except using [Au(adpp)$_2$]I (0.25 g, 0.28 mmol) to give a white crystalline product (0.23 g, 90%), m.p. 190 °C (Found: C, 48.6; H, 3.2; N, 2.7. Calc. for $C_{36}H_{32}AuF_6N_2P_3$: C, 48.2; H, 3.6; N, 3.1%). ^1H NMR ($CDCl_3$): δ 4.32 (s, 4 H, NH_2) and 6.68–7.48 (m, 28 H, aromatics).

(*L*-2)-Bis[(±)-(2-aminophenyl)methylphenylphosphine]gold(I) hexafluorophosphate, [Au{(±)-ampp}$_2$]PF_6. This was prepared as for [Au(adpp)]PF_6 except using [Au{(±)-ampp}$_2$]I (0.42 g, 0.57 mmol) to afford a white crystalline product (0.39 g, 91%), m.p. 186 °C (Found: C, 40.6; H, 3.6; N, 3.4. Calc. for $C_{26}H_{28}AuF_6N_2P_3$: C, 40.4; H, 3.7; N, 3.6%). ^1H NMR ($CDCl_3$): δ 2.19 (d, 6 H, $^2J_{PH}$ 6.2 Hz, PMe), 4.28 (s, 4 H, NH_2) and 6.67–7.71 (m, 18 H, aromatics).

(*T*-4)-Bis[(2-aminophenyl)diphenylphosphine]silver(I) nitrate–dichloromethane (2/1), [Ag(adpp)$_2$]NO_3·0.5CH_2Cl_2. Silver nitrate (0.07 g, 0.41 mmol) was dissolved in ethanol (20 cm^3) and adpp (0.23 g, 0.83 mmol) slowly added with stirring. *n*-Pentane (10 cm^3) was added dropwise to give white crystals which were subsequently filtered off, washed with *n*-pentane, dried *in vacuo* and stored in the dark (0.25 g, 84%), m.p. 222 °C (Found: C, 56.8; H, 4.4; N, 5.6. Calc. for $C_{36.5}H_{33}AgClN_3O_3P_2$: C, 57.1; H, 4.3; N, 5.5%). ^1H NMR ($CDCl_3$): δ 4.61 (s, 4 H, NH_2) and 6.58–7.50 (m, 28 H, aromatics).

(*T*-4)-Tris[(2-aminophenyl)diphenylphosphine]silver(I) nitrate–dichloromethane (2/1), [Ag(adpp)$_3$]NO_3·0.5CH_2Cl_2. This was prepared as for [Ag(adpp)$_2$]NO_3 except using silver nitrate (0.07 g, 0.41 mmol) and adpp (0.46 g, 1.66 mmol) to give a white crystalline product (0.31 g, 59%), m.p. 200 °C (Found: C, 63.0; H, 4.3; N, 5.0. Calc. for $C_{36.5}H_{33}AgClN_3O_3P_2$: C, 62.7; H, 4.7; N, 5.4%). ^1H NMR ($CDCl_3$): δ 4.61 (s, 6 H, NH_2) and 6.39–7.40 (m, 42 H, aromatics).

(*T*-4)-Bis[(2-aminophenyl)diphenylphosphine]silver(I) hexafluorophosphate, [Ag(adpp)$_2$]PF_6. Silver nitrate (0.15 g, 0.89 mmol) was dissolved in ethanol (100 cm^3) and adpp (0.51 g, 1.84 mmol) was slowly added with stirring. The solution was filtered, the solvent evaporated, the residue dissolved in dichloromethane (100 cm^3) and a solution of NH_4PF_6 (0.50 g, 3.05 mmol) in water (20 cm^3) added. The organic layer was separated off, dried over anhydrous $MgSO_4$, filtered and the solvent again evaporated. The residue was redissolved in dichloromethane (5 cm^3) and diethyl ether (25 cm^3) added to give a white crystalline product. The product was collected, washed with diethyl ether (5 cm^3), dried *in vacuo* and stored in the dark (0.58 g, 81%), m.p. 172–174 °C (Found: C, 54.0; H, 3.7; N, 3.2. Calc. for $C_{36}H_{32}AgF_6N_2P_3$: C, 53.6; H, 4.0; N, 3.5%). ^1H NMR [$(CD_3)_2CO$]: δ 4.99 (s, 4 H, NH_2) and 6.82–7.55 (m, 28 H, aromatics).

(*T*-4)-Tris[(2-aminophenyl)diphenylphosphine]silver(I) hexafluorophosphate, [Ag(adpp)$_3$]PF_6. This was prepared as for [Ag(adpp)$_2$]PF_6 except using silver nitrate (0.07 g, 0.41 mmol)

and adpp (0.35 g, 1.26 mmol) to give a white crystalline product (0.25 g, 56%), m.p. 228 °C (Found: C, 59.3; H, 4.4; N, 3.5. Calc. for $C_{54}H_{48}AgF_6N_3P_4$: C, 59.8; H, 4.5; N, 3.9%). ^{1}H NMR [$(CD_3)_2CO$]: δ 4.69 (s, 6 H, NH_2) and 6.76–7.55 (m, 42 H, aromatics).

(*T*-4)-Tris[(±)-(2-aminophenyl)methylphenylphosphine]-silver(I) hexafluorophosphate, [Ag{(±)-ampp}$_3$]PF$_6$. A solution of (±)-ampp (0.30 g, 1.39 mmol) in ethanol (10 cm^3) was added dropwise to a solution of silver nitrate (0.08 g, 0.47 mmol) in ethanol (90 cm^3). The solution was filtered, the solvent evaporated, the residue redissolved in dichloromethane (40 cm^3) and a solution of NH_4PF_6 (0.50 g, 3.05 mmol) in water (20 cm^3) added. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and the solvent again evaporated. The residue was redissolved in methanol (20 cm^3) and gave a white crystalline product on standing. The product was collected, washed with diethyl ether (5 cm^3), dried *in vacuo* and stored in the dark (0.34 g, 81%), m.p. 164–166 °C (Found: C, 52.0; H, 4.1; N, 4.4. Calc. for $C_{39}H_{42}AgF_6N_3P_4$: C, 52.1; H, 4.7; N, 4.7%). ^{1}H NMR ($CDCl_3$): δ 1.82 (br s, 9 H, PMe), 4.75 (s, 6 H, NH_2) and 6.80–7.54 (m, 27 H, aromatics).

(*T*-4)-Bis[(2-aminophenyl)diphenylphosphine]copper(I) hexafluorophosphate, [Cu(adpp)$_2$]PF$_6$. Tetrakis(acetonitrile)copper(I) hexafluorophosphate (1.00 g, 2.68 mmol) was dissolved in acetonitrile (50 cm^3) and adpp (1.49 g, 5.38 mmol) was slowly added with stirring. The solution was filtered, the solvent evaporated and the residue dissolved in dichloromethane (2 cm^3). A white crystalline product was obtained upon the addition of diethyl ether (25 cm^3). The product was collected, washed with diethyl ether (5 cm^3) and dried *in vacuo* (1.90 g, 93%), m.p. 186 °C (Found: C, 56.3; H, 4.0; N, 3.7. Calc. for $C_{36}H_{32}CuF_6N_2P_3$: C, 56.2; H, 4.2; N, 3.7%). ^{1}H NMR [$(CD_3)_2CO$]: δ 5.82 (s, 4 H, NH_2) and 7.31–7.50 (m, 28 H, aromatics).

(*T*-4)-Tris[(2-aminophenyl)diphenylphosphine]copper(I) hexafluorophosphine, [Cu(adpp)$_3$]PF$_6$. This was prepared as for [Cu(adpp)$_2$]PF$_6$ except using tetrakis(acetonitrile)copper(I) hexafluorophosphate (1.00 g, 2.68 mmol) and adpp (1.73 g, 6.24 mmol) to give a white crystalline product (2.00 g, 98%), m.p. 218–220 °C (Found: C, 62.0; H, 4.6; N, 3.7. Calc. for $C_{54}H_{48}CuF_6N_3P_4$: C, 62.3; H, 4.7; N, 4.0%). ^{1}H NMR [$(CD_3)_2CO$]: δ 5.82 (s, 6 H, NH_2) and 7.42–7.78 (m, 42 H, aromatics).

(*T*-4)-Bis[(±)-(2-aminophenyl)methylphenylphosphine]gold(I) hexafluorophosphate, [Cu{(±)-ampp}$_2$]PF$_6$. A solution of (±)-ampp (0.30 g, 1.39 mmol) in acetonitrile (10 cm^3) was added to a solution of tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.26 g, 0.70 mmol) in acetonitrile (25 cm^3). The colourless solution was filtered, the solvent evaporated and the residue dissolved in methanol (2 cm^3). Diethyl ether (20 cm^3) was added dropwise to give a white crystalline product which was collected, washed with diethyl ether (5 cm^3) and dried *in vacuo* (0.31 g, 70%), m.p. 188 °C (Found: C, 51.8; H, 4.9; N, 4.4. Calc. for $C_{26}H_{28}CuF_6N_2P_3$: C, 51.4; H, 4.6; N, 4.6%). ^{1}H NMR ($CDCl_3$): δ 1.61 (s, 6 H, PMe), 4.40 (s, 4 H, NH_2) and 7.00–7.42 (m, 18 H, aromatics).

(*T*-4)-Tris[(±)-(2-aminophenyl)methylphenylphosphine]gold(I) hexafluorophosphate, [Cu{(±)-ampp}$_3$]PF$_6$. This was prepared as for [Cu{(±)-ampp}$_2$]PF$_6$ except using tetrakis(acetonitrile)-copper(I) hexafluorophosphate (0.50 g, 1.34 mmol) and (±)-ampp (0.86 g, 4.00 mmol) to give a white crystalline product (0.62 g, 72%), m.p. 180 °C (Found: C, 54.7; H, 5.1; N, 4.8. Calc. for $C_{39}H_{42}CuF_6N_3P_4$: C, 54.8; H, 5.0; N, 4.9%). ^{1}H NMR ($CDCl_3$): δ 1.67 (s, 9 H, PMe), 5.05 (s, 6 H, NH_2) and 7.00–7.43 (m, 27 H, aromatics).

Biological procedures and materials

The P815 mastocytoma cells were cultured in Eagle's Minimum Essential Medium F15 with 10% foetal bovine serum, B16 cells in McCoy's medium RPMI 1640 with 10% foetal bovine serum and P388 leukaemia cells in Dulbecco's Modified Eagle Medium H16 with 10% horse serum (herein EC 10). All cells were cultured and incubated in a Forma Scientific Infrared CO_2 incubator at 37 °C in 5% CO_2. Cell suspensions were centrifuged using a model CR 4 22 Jouan centrifuge. Linbro 96 round-bottom-well tissue-culture plates were used for the thymidine incorporation assay. Cells were harvested using a Pharmacia Version 1.02 Micro Cell Harvester and incorporated thymidine was counted using a Pharmacia 1205 Betaplate liquid scintillation counter. Thymidine incorporation assays were performed following a literature procedure.[18] The compounds tested were dissolved in dimethyl sulfoxide (0.2 cm^3) to give a concentration of 0.02 mol dm^{-3} and then diluted to 2×10^{-5} mol dm^{-3} using EC 10.

X-Ray crystallography

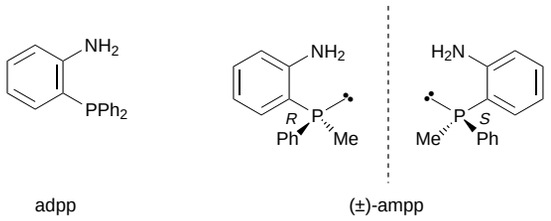
Crystal data. *Complex* [AuI(adpp)] **A**. $C_{18}H_{16}AuINP$, $M = 601.18$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 10.220(2)$, $b = 12.689(4)$, $c = 14.112(4)$ Å, $U = 1830(1)$ Å^3 (by least-squares analysis of the setting angles of 24 reflections $38.69 < 2\theta < 42.27°$), Mo-Kα radiation $\lambda = 0.710\,69$ Å with a graphite monochromator, $Z = 4$, $D_c = 2.182$ g cm^{-3}, $F(000) = 1112.00$, specimen $0.37 \times 0.28 \times 0.09$ mm, μ(Mo-Kα) = 98.38 cm^{-1}.

Complex [AuI{(±)-ampp}] **B**. $C_{13}H_{14}AuINP$, $M = 539.11$, triclinic, space group $P\bar{1}$ (no. 2), $a = 11.109(3)$, $b = 11.892(4)$, $c = 13.244(3)$ Å, $\alpha = 72.24(2)$, $\beta = 78.31(2)$, $\gamma = 62.12(2)°$, $U = 1469.0(8)$ Å^3 (by least-squares analysis of the setting angles of 24 reflections $35.02 < 2\theta < 41.50°$), Mo-Kα radiation $\lambda = 0.710\,69$ Å with a graphite monochromator, $Z = 4$, $D_c = 2.437$ g cm^{-3}, $F(000) = 984.00$, specimen $0.25 \times 0.13 \times 0.12$ mm, μ(Mo-Kα) = 121.51 cm^{-1}.

Complex (±)-[Cu(adpp)$_2$]PF$_6$ **C**. $C_{36}H_{32}CuF_6N_2P_3$, $M = 763.12$, triclinic, space group $P\bar{1}$ (no. 2), $a = 11.298(6)$, $b = 11.877(4)$, $c = 14.798(4)$ Å, $\alpha = 66.52(2)$, $\beta = 88.91(3)$, $\gamma = 74.52(3)°$, $U = 1747(1)$ Å^3 (by least-squares analysis of the setting angles of 18 reflections $82.28 < 2\theta < 86.54°$), Cu-Kα radiation $\lambda = 1.541\,78$ Å with a graphite monochromator, $Z = 2$, $D_c = 1.451$ g cm^{-3}, $F(000) = 780.00$, specimen $0.49 \times 0.21 \times 0.08$ mm, μ(Cu-Kα) = 27.15 cm^{-1}.

Data collection and processing. A unique data set was measured in each case at 296(1) K using the ω–2θ scan technique to a maximum 2θ value of 50.1 and 55.1° for **A** and **B**, respectively, on a Rigaku AFC6S diffractometer, and a maximum 2θ value of 120.5° for **C** on a Rigaku AFC6R diffractometer. Scans of width (1.78 + 0.34 tan θ), (1.52 + 0.34 tan θ) and (1.52 + 0.30 tan θ)° were made at a speed (in ω) of 8.0, 4.0 and 32.0° min^{-1} for **A**, **B** and **C**, respectively. The weak reflections [$I < 10.0\sigma(I)$] were rescanned (maximum of four scans) and the counts were accumulated to ensure good counting statistics. The number of unique reflections was 1889 for **A**, 6814 for **B** and 5200 for **C**. The intensities of three representative reflections were measured after every 150. No decay correction was required. Analytical absorption corrections were applied which resulted in transmission factors ranging from 0.14 to 0.44 for **A**, 0.24 to 0.37 for **B** and 0.56 to 0.81 for **C**. The data were corrected for Lorentz-polarisation effects.

Structure analysis and refinement. The structures were solved by direct methods and expanded using Fourier techniques.[19–21] The non-hydrogen atoms were refined anisotropically for **A** and **B**. These atoms were refined with isotropic displacement factors and then anisotropically for **C**. The hexafluorophosphate ion in **C** was found to be rotationally disordered to some degree.



adpp (±)-ampp

Hydrogen atoms attached to carbon atoms of the cations were included at calculated positions but were not refined. Similarly the amine hydrogens of **C**. Amine hydrogen atoms of **A** and **B** were not located unambiguously and have not been included. The final cycle of full-matrix least-squares refinement was based on 1223 (for **A**), 4087 (for **B**) and 3954 (for **C**) observed reflections [$I > 3.0\sigma(I)$] and 203 (for **A**), 307 (for **B**) and 452 (for **C**) variable parameters and converged [largest shift was 0.04 (for **A**), 0.01 (for **B**) and 0.22 (for **C**) times its estimated standard deviation (e.s.d.)] with final R and R' values being 0.031 an 0.030 for **A**, 0.030 and 0.031 for **B** and 0.050 and 0.060 for **C**, respectively. The maximum and minimum peaks on the final Fourier-difference map corresponded to 1.02 and −0.73 (for **A**), 1.07 and −0.90 (for **B**) and 0.49 and −0.62 e Å^{-3} (for **C**), respectively. The absolute structure of **A** was also established by refining a model with coordinates transformed by $(-x, -y, -z)$ which yielded a higher R factor of 0.059 and R' of 0.062 and thereby showed that the original model was correct. Neutral atom scattering factors were taken from Cromer and Waber.[22] Anomalous dispersion effects were included in F_c;[23] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[24] The values for the mass-attenuation coefficients were those of Creagh and Hubbell.[25] All calculations were performed using the TEXSAN package.[26]

CCDC reference number 186/600.

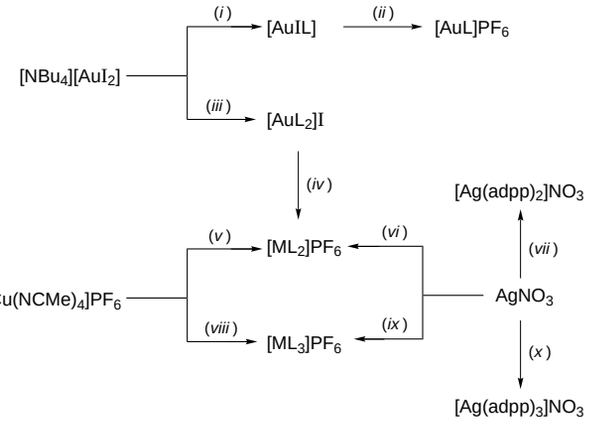
Results and Discussion

Synthesis of complexes

A number of gold(I), silver(I) and copper(I) complexes have been synthesized containing the ligands (2-aminophenyl)diphenylphosphine, adpp, and (±)-(2-aminophenyl)methylphenylphosphine, (±)-ampp. Gold(I) complexes of the type [AuI(L)] were prepared by treating equimolar quantities of the appropriate ligand L [adpp or (±)-ampp] with tetra-*n*-butylammonium diiodoaurate(I) in ethanol (Scheme 1). When 2 equivalents of L were used in the reaction the complexes $[AuL_2]I$ were isolated. Further reaction of [AuI(L)] and $[AuL_2]I$ with aqueous NH_4PF_6 gave the corresponding salts $[AuL_n]PF_6$ ($n = 1$ or 2). Copper(I) complexes of the type $[CuL_n]PF_6$ ($n = 2$ or 3) were prepared by treating 2 or 3 equivalents of L [adpp or (±)-ampp] with tetrakis(acetonitrile)copper(I) hexafluorophosphate in acetonitrile. The analogous silver(I) complexes $[AgL_n]PF_6$ (where $n = 2$ or 3) were obtained from the appropriate form of the ligand and silver nitrate in ethanol followed by treatment with aqueous NH_4PF_6. In the case of adpp the intermediate nitrate salts were also isolated. The complex $[Ag\{(\pm)\text{-ampp}\}_2]PF_6$, however, could not be isolated in a pure form; the product was invariably contaminated with $[Ag\{(\pm)\text{-ampp}\}_3]PF_6$.

No evidence was found for the co-ordination of more than 2 equivalents of adpp or (±)-ampp to gold(I) or of 4 equivalents to copper(I) and silver(I). Furthermore, the complex $[Cu\{(\pm)\text{-ampp}\}_2]PF_6$ was unstable in the solid state and particularly so in solution. This, coupled with the failure to prepare the analogous complex of silver(I), suggests that these two metal centres preferentially bind 3 equivalents of (±)-ampp. The greater steric bulk of adpp probably accounts for the enhanced stability of (±)-$[M(adpp)_2]PF_6$ (where M = Cu^{I} or Ag^{I}).

Selected data for the complexes are given in Table 1. The



Scheme 1 (*i*) L, EtOH; (*ii*) acetone, NH_4PF_6 in water; (*iii*) 2 L, EtOH; (*iv*) acetone, NH_4PF_6 in water; (*v*) 2 L, MeCN; (*vi*) 2 adpp, EtOH, NH_4PF_6 in water; (*vii*) 2 adpp, CH_2Cl_2; (*viii*) 3 L, MeCN; (*ix*) 3 L, EtOH, NH_4PF_6 in water; (*x*) 3 adpp, CH_2Cl_2

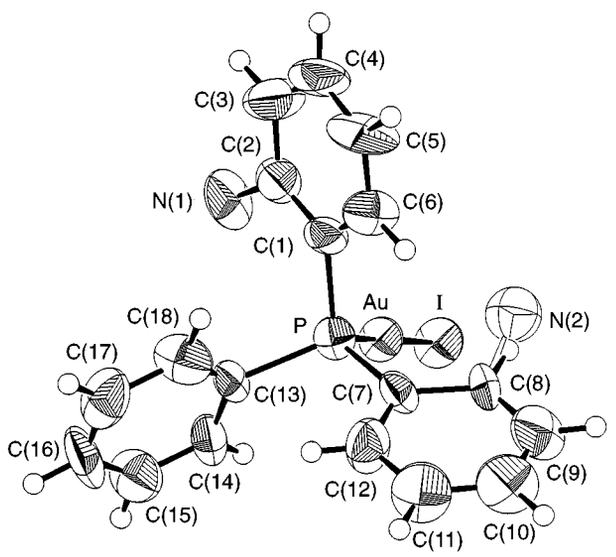


Fig. 1 Molecular structure of [AuI(adpp)] [both locations of the disordered amine nitrogen atom are shown, *vis-à-vis* N(1) and N(2)]

molar conductance data are entirely consistent with the given formulations;[27] the complexes [AuI(L)] behaving as non-electrolytes in nitromethane and acetonitrile and those of the type $[ML_n]X$ as 1:1 electrolytes in the same solvents. A linear geometry about the metal centre is proposed for the gold(I) complexes and a tetrahedral stereochemistry for their copper(I) and silver(I) counterparts. The related complex $[Au(ppye)_2]PF_6$ has been structurally authenticated and shown to have a two-co-ordinate gold(I) centre with the ppye ligands bound in a monodentate fashion *via* the phosphorus donor atom.[8] Complexes of the type $[ML_3]PF_6$ [M = Cu^{I} or Ag^{I}, L = adpp or (±)-ampp] are believed to contain one bidentate ligand and two ligands bound in a monodentate fashion *via* the phosphorus donor atom.

Crystal structures of complexes [AuI(adpp)], [AuI{(±)-ampp}] and (±)-$[Cu(adpp)_2]PF_6$

The molecular structures of [AuI(adpp)], [AuI{(±)-ampp}] and (±)-$[Cu(adpp)_2]PF_6$ have been confirmed by X-ray analyses. The stereochemistries of the gold(I) complexes and the cation (±)-$[Cu(adpp)_2]^+$ are shown in Figs. 1, 2 and 3, respectively; and selected bond lengths and angles in Table 2.

It is clear from the structural data that the molecular structures of the two gold(I) complexes are significantly different. Only one molecule of [AuI(adpp)] was present in the asymmetric unit whereas two were found for [AuI{(±)-ampp}]. In

Table 1 Selected data for the ligands adpp and (±)-ampp, and their gold(I), silver(I) and copper(I) complexes

	Λ_M [a]/S cm^2 mol^{-1}		^{1}H NMR,[b] δ		^{31}P-{^{1}H} NMR [b]
Compound	$MeNO_2$	MeCN	PMe [c]	NH_2	δ
adpp	—	—	—	3.90 (br s)	−20.9 (s)
(±)-ampp	—	—	1.56 (d, 3.5)	4.07 (br s)	−42.8 (s)
[AuI(adpp)]	0.4	0.5	—	4.40 (s)	28.1 (s, 1P)
$[Au(adpp)]PF_6$	91	91	—	4.40 (s)	28.2 (s, 1P)
$[Au(adpp)_2]I$	90	90	—	4.29 (s)	19.9 (s, 2P)
$[Au(adpp)_2]PF_6$	91	90	—	4.32 (s)	23.4 (s, 2P)
[AuI{(±)-ampp}]	0.8	0.8	2.13 (d, 10.4)	4.28 (s)	13.7 (s, 1P)
$[Au\{(\pm)\text{-ampp}\}]PF_6$	93	93	2.13 (d, 10.5)	4.28 (s)	15.5 (s, 1P)
$[Au\{(\pm)\text{-ampp}\}_2]I$	92	93	2.26 (d, 8.5)	4.31 (s)	11.1 (s, 2P)
$[Au\{(\pm)\text{-ampp}\}_2]PF_6$	92	93	2.19 (d, 6.2)	4.28 (s)	14.2 (s, 2P)
$(\pm)\text{-}[Ag(adpp)_2]NO_3$	82	83	—	4.61 (s)	−2.3 (br s, 2P) [d]
$[Ag(adpp)_3]NO_3$	80	80	—	4.61 (s)	−5.1 (br s, 2P) [d]
$(\pm)\text{-}[Ag(adpp)_2]PF_6$ [d]	83	82	—	4.99 (s)	−1.1 (s, 2P)
$[Ag(adpp)_3]PF_6$ [d]	80	81	—	4.69 (s)	−1.9 (s, 3P)
$[Ag\{(\pm)\text{-ampp}\}_3]PF_6$	84	84	1.82 (br s)	4.75 (s)	−24.2 (s, 3P)
$(\pm)\text{-}[Cu(adpp)_2]PF_6$ [d]	89	92	—	5.82 (s)	−10.6 (br s, 2P)
$[Cu(adpp)_3]PF_6$ [d]	86	89	—	5.82 (s)	−9.0 (br s, 3P)
$[Cu\{(\pm)\text{-ampp}\}_2]PF_6$	90	91	1.61 (s)	4.40 (br s)	−24.6 (br s, 2P)
$[Cu\{(\pm)\text{-ampp}\}_3]PF_6$	89	91	1.67 (s)	5.05 (br s)	−23.8 (br s, 3P)

[a] Molar conductance for 10^{-3} mol dm^{-3} solutions at 298 K. [b] In $CDCl_3$. [c] Coupling constants ($^2J_{PH}$/Hz) are given in parentheses. [d] In $(CD_3)_2CO$.

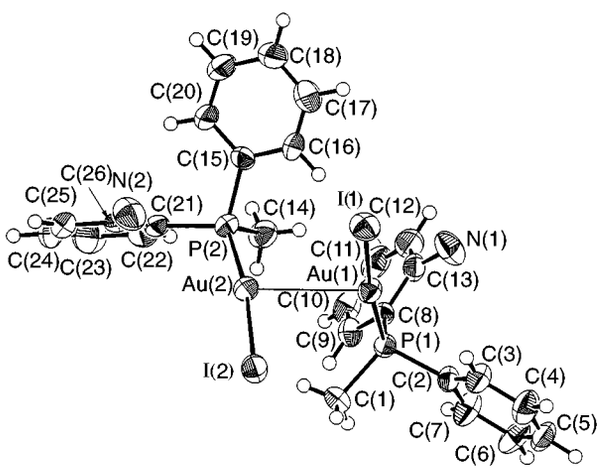


Fig. 2 Molecular structure of [AuI{(±)-ampp}]

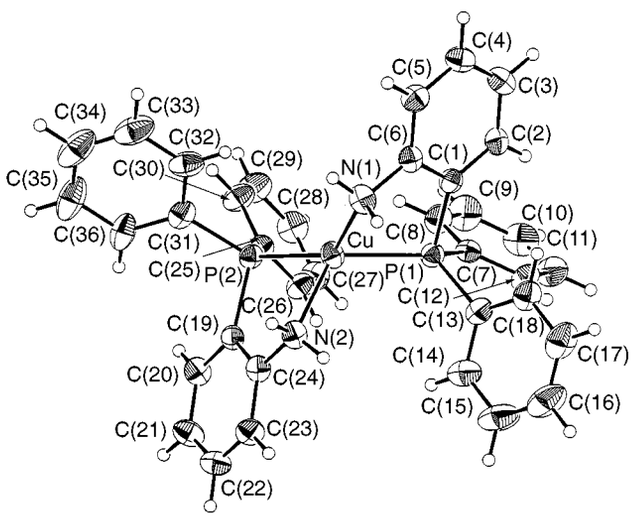


Fig. 3 Molecular structure of the cation $(\pm)\text{-}[Cu(adpp)_2]^+$

the latter case a weak interaction between the Au(1) and Au(2) centres was present. Auriophilicity has been observed in a number of gold(I) complexes;[28] the absence of this effect in the crystal structure of [AuI(adpp)] is presumably a direct result of the greater steric bulk of the adpp ligand. The geometry about the gold(I) centres is essentially linear in the two structures, the largest deviation from linearity being found for [AuI{(±)-ampp}] {where the P–Au–I angle was 170.9 and 173.2° compared with 177.9° for [AuI(adpp)]}. The Au–P and Au–I bond lengths in the two structures were similar and comparable to other values in the literature.[24] Furthermore, the complex [AuI{(±)-ampp}] is racemic with both (*R*,*R*) and (*S*,*S*) dimeric units being present in the unit cell. Only the former is shown in Fig. 2. In addition, the NH_2 group, which was not co-ordinated to the gold(I) metal centre, was found to be disordered over two sites in the crystal lattice of [AuI(adpp)]. For 70% of the time this group was found bound to the C(2) atom [*vis-à-vis* N(1)] while for the other 30% it was bound to the C(8) atom [*vis-à-vis* N(2)].

The structural data for the cation $(\pm)\text{-}[Cu(adpp)_2]^+$ revealed a distorted tetrahedral co-ordination geometry with angles about the copper(I) centre of P(1)–Cu–P(2) 129.11(5), P(1)–Cu–N(1) 84.2(1), P(2)–Cu–N(2) 86.0(1), P(1)–Cu–N(2) 119.0(1), P(2)–Cu–N(1) 134.9(1) and N(1)–Cu–N(2) 104.6(1). The Cu–P and Cu–N bond lengths in this structure were similar and comparable to other values in the literature.[24] Furthermore, the complex $(\pm)\text{-}[Cu(adpp)_2]PF_6$ is a racemic compound with both *R* and *S* forms of the cation being present in the unit cell. Only the *S* form is shown in Fig. 3.

NMR spectra

Selected NMR data for adpp and (±)-ampp and their gold(I), silver(I) and copper(I) complexes are given in Table 1. In all cases singlet NH_2 and single PMe [for (±)-ampp and its complexes] resonances were observed in the ^{1}H NMR spectra at 293 K and singlet ^{31}P resonances in the ^{31}P-{^{1}H} NMR spectra at the same temperature. The chemical shifts of the singlet NH_2 resonances for the gold(I) complexes were very similar to those recorded for the free phosphines, this being consistent with the interpretation that the ligands bind to the gold(I) centre in a monodentate fashion through the phosphorus donor atom. For the silver(I) and copper(I) complexes the NH_2 resonances occurred further downfield indicating some degree of metal–nitrogen interaction. Both these results were consistent with the solid-state structures of the gold(I) and copper(I) complexes and indicated that the configuration about the metal centre was retained in solution. Ligand-redistribution reactions, however, are rife for these complexes in solution.

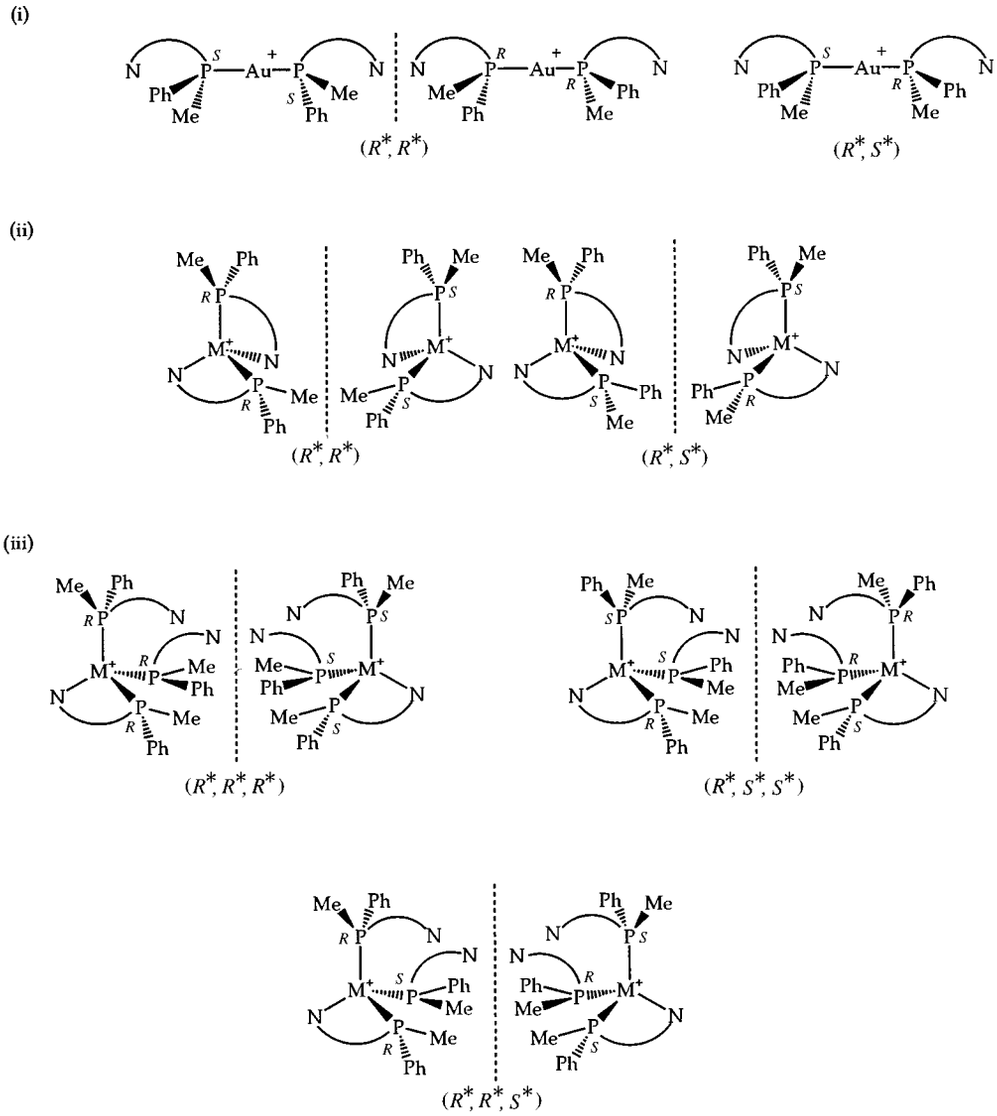


Fig. 4 Diastereomerism in the cations (i) $[Au\{(\pm)\text{-ampp}\}_2]^+$, (ii) $[M\{(\pm)\text{-ampp}\}_2]^+$ and (iii) $[M\{(\pm)\text{-ampp}\}_3]^+$ (M = Cu^I or Ag^I)

The observation of singlet ^{31}P resonances for the silver(I) complexes in the $^{31}P\text{-}\{^1H\}$ NMR spectra at 293 K is only consistent with rapid intermolecular exchange of the ligands. For kinetically inert complexes containing silver(I) two doublets should be observed for each ^{31}P resonance in the $^{31}P\text{-}\{^1H\}$ NMR spectrum as a result of coupling of the ^{31}P nucleus to ^{107}Ag and ^{109}Ag nuclei.[29] The observation of single NH_2 and PMe resonances for the cations $[M\{(\pm)\text{-ampp}\}_2]^+$ and $[M\{(\pm)\text{-ampp}\}_3]^+$ in the respective ^1H NMR spectra and singlet ^{31}P resonances in the $^{31}P\text{-}\{^1H\}$ NMR spectra at 293 K was also indicative of the species undergoing facile rearrangement in solution. Whereas complexes of the type [AuI(L)], $[AuL]PF_6$ and $[M(adpp)_n]X$ can only exist as a single stereoisomer, or as a pair of enantiomers in the case of tetrahedral $[M(adpp)_2]X$, two diastereomers are possible for $[M\{(\pm)\text{-ampp}\}_2]PF_6$ and three for $[M\{(\pm)\text{-ampp}\}_3]PF_6$. The diastereomeric forms of the cations $[M\{(\pm)\text{-ampp}\}_2]^+$ and $[M\{(\pm)\text{-ampp}\}_3]^+$ are depicted in Fig. 4. Similarly, two distinct NH_2 resonances and ^{31}P resonances would be expected for kinetically inert cations of the type $[M(adpp)_3]^+$ in the appropriate spectra.

Variable-temperature NMR spectroscopy has been used to probe the dynamic behaviour of certain of these complexes in solution. For example, $^{31}P\text{-}\{^1H\}$ NMR spectra of (±)-$[Ag(adpp)_2]PF_6$ and $[Ag(adpp)_3]PF_6$ in CD_2Cl_2 were recorded over the temperature range 183–298 K (Fig. 5). The slow-exchange limit for (±)-$[Ag(adpp)_2]PF_6$ was attained at 213 K: the $^{31}P\text{-}\{^1H\}$ NMR spectrum at this temperature exhibited a pair of doublets centred at δ −3.38 [with $^1J(^{107}Ag\text{–}^{31}P)$ −312 and $^1J(^{109}Ag\text{–}^{31}P)$ −361 Hz]. The sign of the coupling constants was assumed to be negative by analogy with other silver(I) complexes containing tertiary phosphine ligands.[29] In the case of $[Ag(adpp)_3]PF_6$ two pairs of doublet ^{31}P resonances (in the ratio of 1:2) would be expected in the $^{31}P\text{-}\{^1H\}$ NMR spectrum at the slow-exchange limit (assuming the spectrum is amenable to first-order analysis). The $^{31}P\text{-}\{^1H\}$ NMR spectrum of the complex at 213 K exhibited a pair of doublets centred at δ −3.31 [with $^1J(^{107}Ag\text{–}^{31}P)$ −313 and $^1J(^{109}Ag\text{–}^{31}P)$ −361 Hz] as well as unresolved signals at δ −0.47 and −4.70, respectively. On further cooling of the NMR sample to 183 K a second pair of doublets centred at δ −2.87 [with $^1J(^{107}Ag\text{–}^{31}P)$ −491 and $^1J(^{109}Ag\text{–}^{31}P)$ −567 Hz] was observed in the $^{31}P\text{-}\{^1H\}$ NMR spectrum. Presumably the upfield signal arose from the phosphorus donor atom of the chelating adpp ligand and the other signal from the equivalent phosphorus nuclei of the two unidentate adpp ligands. The $^{31}P\text{-}\{H\}$ NMR spectrum of the related complex $[Ag\{(\pm)\text{-ampp}\}_3]PF_6$ in CD_2Cl_2 at 183 K similarly contained a number of peaks, however they were insufficiently well resolved for an unequivocal assignment to be made.

A series of $^{31}P\text{-}\{^1H\}$ NMR spectra was similarly recorded for each of the complexes $[Cu(adpp)_3]PF_6$, $[Cu\{(\pm)\text{-ampp}\}_3]PF_6$ and $[Au\{(\pm)\text{-ampp}\}_2]PF_6$ in CD_2Cl_2 over the temperature range 183–298 K. For the two copper(I) complexes singlet ^{31}P resonances were observed with $\nu_{\frac{1}{2}}$ decreasing from 90 to 50 Hz for $[Cu(adpp)_3]PF_6$ and 170 to 80 Hz for $[Cu\{(\pm)\text{-ampp}\}_3]PF_6$ on

Table 2 Selected non-hydrogen interatomic distances (Å) and interatomic angles (°) for [AuI(adpp)], [AuI{(±)-ampp}] and (±)-$[Cu(adpp)_2]PF_6$

[AuI(adpp)]			
Au–P	2.260(4)	Au–I	2.553(1)
I–Au–P	177.9(1)		
[AuI{(±)-ampp}]			
Au(1)–P(1)	2.262(2)	Au(1)–Au(2)	3.1709(5)
Au(1)–I(1)	2.5644(9)	Au(1)···I(2)	3.7891(9)*
Au(2)–P(2)	2.256(2)	Au(2)···I(1)	4.0820(7)*
Au(2)–I(2)	2.5708(7)		
I(1)–Au(1)–P(1)	173.13(6)	I(2)–Au(1)–P(2)	170.86(6)
(±)-$[Cu(adpp)_2]PF_6$			
Cu–P(1)	2.256(1)	Cu–N(1)	2.131(4)
Cu–P(2)	2.207(2)	Cu–N(2)	2.152(4)
P(1)–Cu–P(2)	129.11(5)	P(1)–Cu–N(2)	119.0(1)
P(1)–Cu–N(1)	84.2(1)	P(2)–Cu–N(1)	134.9(1)
P(2)–Cu–N(2)	86.0(1)	N(1)–Cu–N(2)	104.6(1)

* Non-bonded interatomic distance.

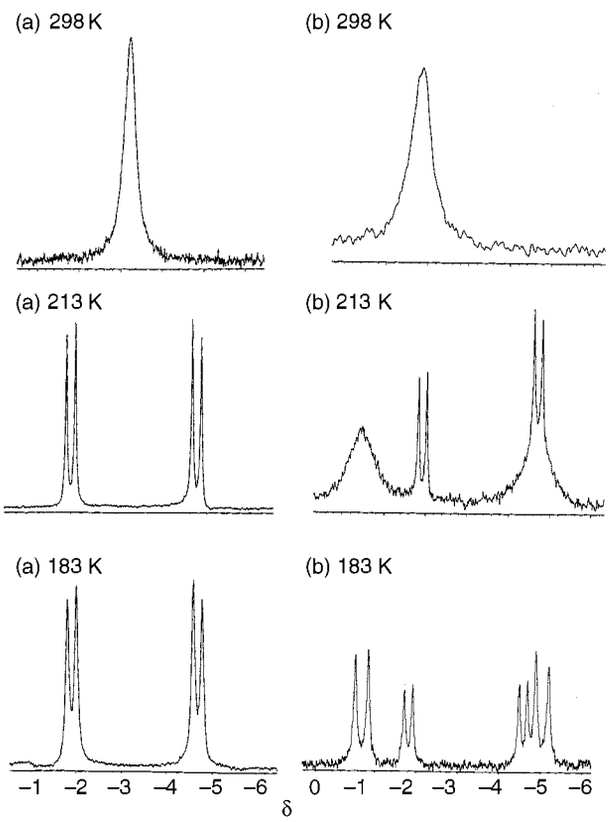


Fig. 5 Variable-temperature $^{31}P-\{^1H\}$ NMR spectra for the complexes (a) (±)-$[Ag(adpp)_2]PF_6$ and (b) $[Ag(adpp)_3]PF_6$ in CD_2Cl_2

cooling the respective NMR samples from 298 to 183 K, consistent with the complexes undergoing facile ligand redistribution in solution. In the case of $[Au\{(\pm)\text{-ampp}\}_2]PF_6$ two singlet resonances at δ 13.40 and 14.05 were observed in the $^{31}P-\{^1H\}$ NMR spectrum at 213 K, consistent with the presence of racemic and *meso* diastereomers. The observation of facile racemic–*meso* interconversion in the room-temperature spectrum of $[Au\{(\pm)\text{-ampp}\}_2]PF_6$ in CD_2Cl_2 is only consistent with rapid intermolecular ligand exchange. Furthermore, when a trace of free phosphine was added to either of the three NMR samples a single ^{31}P resonance was observed in the respective $^{31}P-\{^1H\}$ NMR spectrum at 293 K, upfield of that recorded for

Table 3 The IC_{50} values for gold(I), silver(I) and copper(I) complexes against P815 mastocytoma, B16 melanoma, and P388 leukaemia mouse tumour cell models

	IC_{50}/mmol dm^{-3}		
Complex	P815	B16	P388
[AuI(adpp)]	8.00	2.12	4.50
$[Au(adpp)]PF_6$	10.00	3.00	18.00
$[Au(adpp)_2]I$	8.50	0.97	4.80
$[Au(adpp)_2]PF_6$	5.00	1.65	5.50
[AuI{(±)-ampp}]	32.40	0.80	5.50
$[Au\{(\pm)\text{-ampp}\}]PF_6$	40.00	2.50	8.00
$[Au\{(\pm)\text{-ampp}\}_2]I$	9.25	2.60	5.80
$[Au\{(\pm)\text{-ampp}\}_2]PF_6$	7.80	15.00	9.50
(±)-$[Ag(adpp)_2]NO_3$	4.25	1.75	3.90
$[Ag(adpp)_3]NO_3$	4.00	1.35	3.20
(±)-$[Ag(adpp)_2]PF_6$	3.40	1.48	5.00
$[Ag(adpp)_3]PF_6$	2.25	1.54	3.20
$[Ag\{(\pm)\text{-ampp}\}_3]PF_6$	9.50	5.00	4.40
(±)-$[Cu(adpp)_2]PF_6$	4.20	2.22	11.00
$[Cu(adpp)_3]PF_6$	2.50	2.18	6.00
$[Cu\{(\pm)\text{-ampp}\}_2]PF_6$	49.00	25.00	17.90
$[Cu\{(\pm)\text{-ampp}\}_3]PF_6$	6.00	5.00	9.00
$[Au(dppe)_2]I$	0.22	5.20	0.10
cis-$[PtCl_2(NH_3)_2]$	14.50	0.90*	5.00
adpp	19.50	—	—
dppe	1.75	—	—

* Data taken from ref. 9.

the complexes in the absence of free phosphine. Clearly intermolecular ligand exchange was taking place for all three complexes in the presence of free phosphine.

Variable-temperature ^1H NMR spectra were also recorded for the complexes $[M\{(\pm)\text{-ampp}\}_3]PF_6$ ($M = Ag^I$ or Cu^I) and $[Au\{(\pm)\text{-ampp}\}_2]PF_6$ in CD_2Cl_2 over the temperature range 183–298 K. The low-temperature (183 K) spectra contained poorly resolved multiplets for the PMe and NH_2 resonances of the copper(I) and silver(I) complexes. Separate PMe and NH_2 resonances similarly could not be discerned for the racemic and *meso* diastereomers of $[Au\{(\pm)\text{-ampp}\}_2]PF_6$ in CD_2Cl_2 at 213 K.

Preliminary biological studies

The *in vitro* cytotoxic properties of gold(I), silver(I) and copper(I) complexes have been assessed by measuring the effect on proliferation of three mouse tumour cell lines, P815 mastocytoma, B16 melanoma and P388 leukaemia. The IC_{50} values (concentrations resulting in 50% inhibition of labelled thymidine) for these complexes and for the reference compounds cisplatin and $[Au(dppe)_2]I$ are given in Table 3. Several trends are evident from these results.

(*i*) The nature of the metal ion made very little difference to the cytotoxicity of the complexes, although it was generally seen that silver(I) compounds may be marginally more potent than gold(I) and copper(I) complexes. This trend is illustrated for complexes of the type $[M(adpp)_2]PF_6$ in Fig. 6(*a*).

(*ii*) As the number of ligands co-ordinated to the metal ion increased the cytotoxicity of the complex also increased as reflected in the decrease in IC_{50} value. This trend was seen when the number of ligands co-ordinated was increased from one to two [for gold(I)] and similarly from two to three [for silver(I) and copper(I)]. Fig. 6(*b*) shows this trend for the complexes $[CuL_n]PF_6$.

(*iii*) Complexes containing adpp generally had lower IC_{50} values, and hence were more active, than their (±)-ampp analogues. Fig. 6(*b*) also illustrates this trend.

(*iv*) Toxicity was independent of the counter anion. This is shown for the complexes $[Ag(adpp)_2]X$ in Fig. 6(*c*).

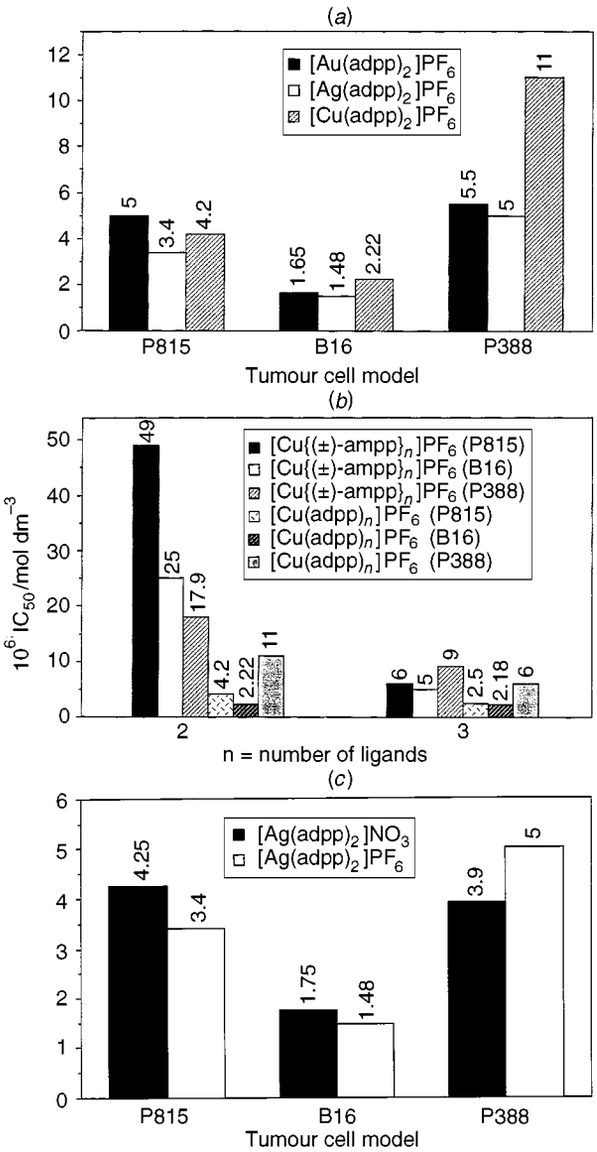


Fig. 6 Graphical representation of IC_{50} values for the complexes (a) $[M(adpp)_2]PF_6$ (M = Cu^I, Ag^I or Au^I), (b) $[CuL_n]PF_6$ [L = adpp or (±)-ampp] and (c) (±)-$[Ag(adpp)_2]X$ ($X^- = NO_3^-$ or PF_6^-) against P815 mastocytoma, B16 melanoma and P388 leukaemia cells

(*v*) The cytotoxicities of the gold(I), silver(I) and copper(I) complexes containing the ligands adpp and (±)-ampp were generally comparable to those of the two reference compounds cisplatin and $[Au(dppe)_2]I$. The relative cytotoxicities were dependent on the tumour cell line being tested.

Points (*i*), (*ii*) and (*iii*) are consistent with the proposition that it is the phosphine ligands which are responsible for the observed cytotoxicity and that the role of the metal ion is possibly to transport them inside cells. This mode of action has previously been proposed for $[Au(dppe)_2]Cl$.[5,30] Ditertiary phosphines are known to exhibit cytotoxic properties but are generally less active than their gold(I), silver(I) and copper(I) complexes.[31,32] The IC_{50} values for addp and dppe against P815 mastocytoma have been included in Table 3. Ligands with phenyl- rather than alkyl-substituted phosphorus donor atoms are more cytotoxic. This trend has previously been observed for a number of tetrahedral bis(bidentate)gold(I) complexes containing a variety of ditertiary phosphine ligands.[33] Point (*iv*) has similarly been reported for these bis(ditertiary phosphine)-gold(I) complexes, and their silver(I) and copper(I) analogues, and suggests that the compounds enter the cell as cationic species.[30,34] This is consistent with the finding that ditertiary phosphine complexes of gold(I) accumulate in the mitochondria of cells.[11,12] The latter possess an electric field gradient across their membrane thereby having a high affinity for positively charged species. It is the accumulation of such species in the mitochondria of cells, and in particular of hepatocytes, which may be responsible for the cytotoxicity of these compounds.

Conclusion

A number of gold(I), silver(I) and copper(I) complexes have been prepared containing the substituted (2-aminophenyl)-phosphines adpp and (±)-ampp. These ligands were chosen for study as completely chemoselective cleavage of the phenyl group(s) from adpp and (±)-ampp is readily achieved and thus the ligands are readily derivatised.[15] This may be important in modifying the solubility, toxicity and anticancer activity of these complexes. Furthermore, chiral ligands of this type are readily resolved and will thereby allow the synthesis of enantiomerically pure copper(I), silver(I) and gold(I) complexes. Since the biological targets of such complexes will invariably be chiral, an enhanced spectrum of activity may result from the use of optically pure compounds.

A preliminary study on the *in vitro* cytotoxic properties of these complexes against three mouse cell lines has shown them, in general, to have comparable activities to those of cisplatin and $[Au(dppe)_2]I$. This augurs well for the role of related complexes containing optically active ligands of this type with stereogenic phosphorus donor atoms as potential anticancer agents. Future work will also involve an investigation into the relationship between the antiproliferative properties of these complexes and their effects on mitochondria.

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