DALTON

Synthesis of platinum(II) and palladium(II) complexes containing substituted (2-aminophenyl)phosphines. Molecular structure of *cis*-[PtMe(2-$HNC_6H_4PPh_2$)(2-$H_2NC_6H_4PPh_2$)]

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Bis(unidentate ligand)platinum(II) complexes of the type *cis*-[$PtMe_2L_2$] (where L = 2-$H_2NC_6H_4PPhR$ and R = H, Me or Ph) were readily formed upon reaction of [$PtMe_2$(cod)] (cod = cycloocta-1,5-diene) with L in *n*-pentane. The neutral ligand L is co-ordinated *via* the phosphorus donor atom. The complex *cis*-[$PtMe_2$(2-$H_2NC_6H_4PPh_2$)$_2$] underwent a novel, facile rearrangement in benzene to give *cis*-[PtMe(2-$HNC_6H_4PPh_2$)(2-$H_2NC_6H_4PPh_2$)] with concomitant loss of methane. The molecular structure of the demethylated complex has been confirmed by an X-ray analysis. Mono(bidentate ligand)platinum(II) complexes of the type [PtCl(Me)L] (where L = 2-$H_2NC_6H_4$-PPhR and R = Me or Ph) have been prepared by treating the appropriate ligand with [PtCl(Me)(cod)] in dichloromethane. Further reaction with HCl gave the dichloroplatinum(II) complexes [$PtCl_2L$]. Substitution of the chloro groups in [MCl_2L] (where M = Pd^{II} or Pt^{II}, L = 2-$H_2NC_6H_4PPhR$ and R = Me or Ph) can be achieved by reaction with silver nitrate in acetonitrile followed by the addition of sodium oxalate to give the complexes [$M(C_2O_4)L$]. These mono(bidentate ligand) complexes are seen as potential anticancer agents. Preliminary biological studies have shown them to be active against the mouse tumour model P815 *in vitro* with cytotoxicities of certain of these complexes being comparable to that of cisplatin, *cis*-[$PtCl_2(NH_3)_2$].

A number of square-planar bis(bidentate ligand) complexes of palladium(II) and platinum(II) containing ligands with tertiary phosphine and primary amine donor groups have been synthesized in which the donor atoms have adopted a *cis* arrangement,[1–3] in keeping with Pearson's symbiosis.[4] By comparison, relatively few examples of mono(bidentate ligand) complexes of palladium(II) and, in particular, of platinum(II) with this type of ligand have been reported. Mono(bidentate ligand) palladium(II) complexes were prepared by treating the appropriate ligand with the chloro-bridged dimer di-μ-chloro-bis[2-(dimethylaminomethyl)phenyl-C^1,*N*]dipalladium(II). Subsequent treatment of the reaction mixture with concentrated hydrochloric acid gave dichloropalladium(II) complexes, for example, [$PdCl_2L$] [where L = (*R*)-, (*S*)-, or (±)-2-$H_2NC_6H_4PPhMe$].[1] Synthetic routes to the analogous platinum(II) complexes have proven to be more elusive. For example, reaction of (±)-2-$H_2NC_6H_4PMePh$ with the dimer di-μ-chloro-bis(2-methoxycycloocta-5-enyl)diplatinum(II), generated *in situ* from [$PtCl_2$(cod)] (cod = cycloocta-1,5-diene) and anhydrous K_2CO_3 in methanol, gave, upon acidification with concentrated hydrochloric acid the dichloroplatinum(II) complex in only *ca.* 30% yield due to competitive protonation of the primary amine group.[1] The analogous complex containing the ligand 2-$H_2NC_6H_4PPh_2$ was prepared in high yield by heating stoichiometric amounts of the ligand and $PtCl_2$ in dimethylformamide at 130 °C.[3] Clearly neither of these routes is suitable for the preparation of related complexes containing optically active ligands of this type with stereogenic phosphorus donor atoms. Our interest in finding a viable synthetic route to such optically active complexes is that they are seen as potential anticancer agents.

This paper describes the high-yield synthesis of mono(bidentate ligand)platinum(II) complexes of the type [PtX_2L] (where X = Cl or $X_2 = C_2O_4$; and L = 2-$H_2NC_6H_4PPhR$ and R = Me or Ph) and of their palladium(II) analogues. The synthesis of bis(unidentate ligand)platinum(II) complexes of the type *cis*-[$PtMe_2L_2$] (where L = 2-$H_2NC_6H_4PPhR$ and R = H, Me or Ph) is also described. Furthermore, preliminary biological results concerning the *in vitro* cytotoxicities of certain of these complexes against the mouse tumour model P815 are 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 values relative to $SiMe_4$ (^{1}H) or 85% H_3PO_4 (^{31}P-{^{1}H}). Infrared spectra were recorded using KBr discs in the range 4000–400 cm^{-1} on a Perkin-Elmer 1600 series FTIR spectrophotometer. Elemental analyses were performed by staff within the Research School of Chemistry.

The compounds (2-aminophenyl)diphenylphosphine, adpp,[5] (±)-(2-aminophenyl)phenylphosphine, app,[1] (±)-(2-aminophenyl)methylphenylphosphine, ampp,[1] [*SP*-4-2]-(cycloocta-1,5-diene)dimethylplatinum(II),[6] [*SP*-4-2]-chloro(cycloocta-1,5-diene)methylplatinum(II),[7] di-μ-chloro-bis[2-(dimethylaminomethyl)phenyl-C^1,*N*]dipalladium(II)[8] and [*SP*-4-2]-[(±)-(2-aminophenyl)methylphenylphosphine]dichloropalladium(II)[1] were prepared by literature procedures.

[*SP*-4-2]-Bis[(2-aminophenyl)diphenylphosphine-*P*]dimethylplatinum(II), *cis*-[$PtMe_2$(adpp)$_2$]. The compound adpp (0.84 g, 3.03 mmol) was dissolved in *n*-pentane (5 cm^3) and added dropwise to a solution of (cycloocta-1,5-diene)dimethylplatinum(II) (0.5 g, 1.50 mmol) in *n*-pentane (10 cm^3). The product was filtered off, washed with *n*-pentane and dried

in vacuo (1.04 g, 89%), m.p. 200 °C (Found: C, 58.7; H, 5.3; N, 3.4. Calc. for $C_{38}H_{38}N_2P_2Pt$: C, 58.5; H, 4.9; N, 3.6%). $\tilde{\nu}_{max}/cm^{-1}$ 3404 (br)s (NH). ^1H NMR (C_6D_6): δ 1.29 (m, 6 H, $^2J_{PtH}$ 69 Hz, PtMe), 4.89 (s, 4 H, NH_2) and 6.50–7.25 (m, 28 H, aromatics). ^{31}P-{^1H} NMR (C_6D_6): δ 19.41 (s, 2 P, $^1J_{PtP}$ 1802 Hz).

[*SP*-4-2]-Bis[(±)-(2-aminophenyl)methylphenylphosphine-*P*]-dimethylplatinum(II), *cis*-[PtMe$_2$(ampp)$_2$]. To a solution of (cycloocta-1,5-diene)dimethylplatinum(II) (0.25 g, 0.75 mmol) in *n*-pentane (5 cm^3) was added a suspension of racemic ampp (0.32 g, 1.49 mmol) in *n*-pentane (5 cm^3). The mixture was stirred for 2 h, the resulting pale yellow crystalline product was filtered off, washed with *n*-pentane and dried *in vacuo* (0.32 g, 63%), m.p. 102 °C (Found: C, 51.0; H, 5.0; N, 4.3. Calc. for $C_{28}H_{34}N_2P_2Pt$: C, 51.3; H, 5.2; N, 4.3%). $\tilde{\nu}_{max}/cm^{-1}$ 3412 (br)s (NH). ^1H NMR (C_6D_6): δ 1.18 (m, 6 H, $^2J_{PtH}$ 67, PtMe), 1.60 (dd, 6 H, $^2J_{PH}$ 7, $^4J_{P'H}$ 4, $^3J_{PtH}$ 41 Hz, PMe), 4.80 (s, 4 H, NH_2) and 6.20–7.60 (m, 18 H, aromatics). ^{31}P-{^1H} NMR (C_6D_6): δ −3.21 (s, 1 P, $^1J_{PtP}$ 1651) and −3.61 (s, 1 P, $^1J_{PtP}$ 1642 Hz).

[*SP*-4-2]-Bis[(±)-(2-aminophenyl)phenylphosphine-*P*]-dimethylplatinum(II), *cis*-[PtMe$_2$(app)$_2$]. To a solution of (cycloocta-1,5-diene)dimethylplatinum(II) (0.25 g, 0.75 mmol) in *n*-pentane (5 cm^3) was added a suspension of racemic app (0.30 g, 1.50 mmol) in *n*-pentane (5 cm^3). The mixture was stirred for 2 h, the resulting product was filtered off, washed with *n*-pentane and dried *in vacuo* (0.33 g, 70%), m.p. 98–100 °C (Found: C, 50.3; H, 4.8; N, 4.8. Calc. for $C_{26}H_{30}N_2P_2Pt$: C, 49.8; H, 4.8; N, 4.5%). $\tilde{\nu}_{max}/cm^{-1}$ 3422 (br)s (NH) and 2300w (PH). ^1H NMR (C_6D_6): δ 1.37 (m, 6 H, $^2J_{PtH}$ 67 Hz, PtMe) and 5.10–7.40 (m, 26 H, aromatics, NH_2 and PH). ^{31}P-{^1H} NMR (C_6D_6): δ −7.77 (d, 1 P, $^1J_{PtP}$ 1590) and −7.96 (d, 1 P, $^1J_{PtP}$ 1590 Hz).

[*SP*-4-3]-[(2-Aminophenyl)phenylphosphine-*P*][2-(diphenylphosphine)phenylamido-*N*,*P*]methylplatinum(II)-benzene, *cis*-[PtMe(2-HNC$_6$H$_4$PPh$_2$)(adpp)]. To a solution of adpp (0.042 g, 0.15 mmol) in benzene (0.5 cm^3) was added a solution of (cycloocta-1,5-diene)dimethylplatinum(II) (0.05 g, 0.15 mmol) in benzene (0.5 cm^3) and the mixture allowed to stand for 3 d. The resulting yellow crystalline product was filtered off, washed with *n*-pentane and dried *in vacuo* (0.068 g, 59%), m.p. 240–246 °C (Found: C, 61.6; H, 5.3; N, 3.3. Calc. for $C_{43}H_{40}N_2P_2Pt$: C, 61.3; H, 4.8; N, 3.3%). $\tilde{\nu}_{max}/cm^{-1}$ 3390 (br)s (NH). ^1H NMR (CD_2Cl_2): δ 0.43 (dd, 3 H, $^2J_{PtH}$ 60 Hz, PtMe), 4.60 (s, 2 H, NH_2) and 6.30–7.45 (m, 29 H, aromatics and NH). ^{31}P-{^1H} NMR (CD_2Cl_2): δ 9.70 (s, 1 P, $^1J_{PtP}$ 3168) and 36.07 (s, 1 P, $^1J_{PtP}$ 1839 Hz).

[*SP*-4-2]-[(2-Aminophenyl)diphenylphosphine]chloro(methyl)-platinum(II), [PtCl(Me)(adpp)]. The compound adpp (0.31 g, 1.10 mmol) was dissolved in tetrahydrofuran (thf) (5 cm^3) and added dropwise to a solution of chloro(cycloocta-1,5-diene)-methylplatinum(II) (0.39 g, 1.10 mmol) in thf (15 cm^3). *n*-Pentane (20 cm^3) was added dropwise and the resulting white crystalline product was filtered off, washed with *n*-pentane and dried *in vacuo* (0.52 g, 91%), m.p. 187 °C (decomp.) (Found: C, 46.4; H, 3.4; N, 2.6. Calc. for $C_{19}H_{19}ClNPPt$: C, 46.3; H, 3.7; N, 2.7%). $\tilde{\nu}_{max}/cm^{-1}$ 3411 (br)s (NH). ^1H NMR ($CDCl_3$): δ 0.66 (d, 3 H, $^3J_{PH}$ 3, $^2J_{PtH}$ 71 Hz, PtMe), 5.64 (s, 2 H, NH_2) and 7.26–7.62 (m, 14 H, aromatics). ^{31}P-{^1H} NMR ($CDCl_3$): δ 21.32 (s, 1 P, $^1J_{PtP}$ 4743 Hz).

[*SP*-4-2]-[(±)-(2-Aminophenyl)methylphenylphosphine]-chloro(methyl)platinum(II), (±)-[PtCl(Me)(ampp)]. To a solution of chloro(cycloocta-1,5-diene)methylplatinum(II) (0.60 g, 1.70 mmol) in thf (10 cm^3) was added a solution of racemic ampp (0.37 g, 1.70 mmol) in thf (5 cm^3). *n*-Pentane (20 cm^3) was added dropwise and the resulting white crystalline product was filtered off, washed with *n*-pentane and dried *in vacuo* (0.66 g, 82%), m.p. 155 °C (decomp.) (Found: C, 36.7; H, 3.3; N, 3.0. Calc. for $C_{14}H_{17}ClNPPt$: C, 36.5; H, 3.3; N, 3.0%). $\tilde{\nu}_{max}/cm^{-1}$ 3422 (br)s (NH). ^1H NMR ($CDCl_3$): δ 0.51 (d, 3 H, $^3J_{PH}$ 3, $^2J_{PtH}$ 78, PtMe), 2.15 (d, 3 H, $^2J_{PH}$ 11, $^3J_{PtH}$ 66 Hz, PMe) and 7.40–7.90 (m, 11 H, aromatics and NH_2). ^{31}P-{^1H} NMR ($CDCl_3$): δ 9.02 (s, 1 P, $^1J_{PtP}$ 4536 Hz).

[*SP*-4-2]-[(2-Aminophenyl)diphenylphosphine]dichloro-platinum(II), [PtCl$_2$(adpp)]. An excess of hydrochloric acid (10 mol dm^{-3}, 0.1 cm^3) was added to a solution of [PtCl(Me)-(adpp)] (0.15 g, 0.29 mmol) in thf (15 cm^3). The reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure and the residue recrystallised from methanol by the addition of diethyl ether. The product was filtered off, washed with diethyl ether and dried *in vacuo* (0.12 g, 76%), m.p. 250 °C (decomp.). $\tilde{\nu}_{max}/cm^{-1}$ 3408 (br)s (NH). ^1H NMR [(CD_3)$_2$SO]: δ 7.50–7.80 (m, 11 H, aromatics and NH_2). ^{31}P-{^1H} NMR [(CD_3)$_2$SO]: δ 18.95 (s, 1 P, $^1J_{PtP}$ 3920 Hz) (identical to that previously reported by Cooper and Downes[3]).

[*SP*-4-2]-[(±)-(2-Aminophenyl)methylphenylphosphine]-dichloroplatinum(II), (±)-[PtCl$_2$(ampp)]. This complex was prepared in the same manner as for [PtCl$_2$(adpp)] except using (±)-[PtCl(Me)(ampp)] (0.15 g, 0.33 mmol). Yield 0.15 g (73%). M.p. 245 °C (decomp.). $\tilde{\nu}_{max}/cm^{-1}$ 3500 (br)s (NH). ^1H NMR [(CD_3)$_2$SO]: δ 2.19 (d, 3 H, $^2J_{PH}$ 12, $^3J_{PtH}$ 65 Hz, PMe) and 7.60–8.20 (m, 11 H, aromatics and NH_2). ^{31}P-{^1H} NMR [(CD_3)$_2$SO]: δ 11.15 (s, 1 P, $^1J_{PtP}$ 3831 Hz). The product was identical to that previously reported.[1]

[*SP*-4-2]-[(2-Aminophenyl)diphenylphosphine]dichloro-palladium(II), [PdCl$_2$(adpp)]. The compound adpp (2.00 g, 7.24 mmol) and the chloro-bridged dimer di-μ-chloro-bis[2-(dimethylaminomethyl)phenyl-*C*^{1},*N*]dipalladium(II) (2.00 g, 3.62 mmol) were suspended in methanol (65 cm^3). Upon dissolution, the solution was filtered and an excess of aqueous NH_4PF_6 (2.36 g) was added followed by water (10 cm^3). The resulting white precipitate was filtered off, dried *in vacuo* and redissolved in acetone (20 cm^3). An excess of hydrochloric acid (10 mol dm^{-3}, 10 cm^3) was added and the volume of the solution reduced to *ca.* 10 cm^3. The bright yellow crystalline product was collected, washed with water, methanol–diethyl ether (1 : 9) and diethyl ether, and dried *in vacuo* (2.38 g, 72%), m.p. 205–210 °C (decomp.) (Found: C, 47.6; H, 3.5; N, 3.0. Calc. for $C_{18}H_{16}Cl_2NPPd$: C, 47.6; H, 3.6; N, 3.1%). $\tilde{\nu}_{max}/cm^{-1}$ 3624 (br)s (NH). ^1H NMR [(CD_3)$_2$SO]: δ 7.50–7.80 (m, 11 H, aromatics and NH_2). ^{31}P-{^1H} NMR [(CD_3)$_2$SO]: δ 46.43 (s, 1 P).

[*SP*-4-2]-[(2-Aminophenyl)diphenylphosphine]oxalato-platinum(II), [Pt(C$_2$O$_4$)(adpp)]. A solution of silver nitrate (0.1362 g, 0.8021 mmol) in water (5 cm^3) was added to a suspension of [PtCl$_2$(adpp)] (0.2179 g, 0.4011 mmol) in acetonitrile (10 cm^3) and the mixture stirred overnight in the absence of light. The silver chloride precipitate was filtered off, a solution of sodium oxalate (0.0550 g, 0.4011 mmol) in water (5 cm^3) added and the mixture stirred for 3 h. The volume of the solution was reduced to *ca.* 5 cm^3. The resulting yellow crystalline product was filtered off, washed with water, methanol–diethyl ether (1 : 9) and diethyl ether, and dried *in vacuo* (0.14 g, 64%), m.p. 178–180 °C (Found: C, 42.4; H, 2.7; N, 3.0. Calc. for $C_{20}H_{16}NO_4PPt$: C, 42.9; H, 2.9; N, 2.5%). $\tilde{\nu}_{max}/cm^{-1}$ 3438 (br) (NH); 1640s, 1384m, 1242w, 880w (C_2O_4). ^1H NMR [(CD_3)$_2$SO]: δ 7.54–7.77 (m, 16 H, aromatics and NH_2). ^{31}P-{^1H} NMR [(CD_3)$_2$SO]: δ 31.81 (s, 1 P, $^1J_{PtP}$ 3884 Hz).

[*SP*-4-2]-[(±)-(2-Aminophenyl)methylphenylphosphine]-oxalatoplatinum(II), (±)-[Pt(C$_2$O$_4$)(ampp)]. This compound was prepared in the same manner as for [Pt(C$_2$O$_4$)(adpp)] except using (±)-[PtCl$_2$(ampp)] (0.1604 g, 0.3340 mmol). Yield 0.07 g (42%). M.p. 220 °C (decomp.) (Found: C, 35.9; H, 2.4; N, 3.2.

Calc. for $C_{15}H_{14}NO_4PPt$: C, 36.2; H, 2.8; N, 2.8%). $\tilde{\nu}_{max}/cm^{-1}$ 3415 (br)s (NH); 1639s, 1384m, 1230w, 886w (C_2O_4). ^1H NMR [$(CD_3)_2SO$]: δ 2.34 (d, 3 H, $^2J_{PH}$ 13, $^3J_{PtH}$ 54 Hz, PMe) and 6.20–7.77 (m, 11 H, aromatics and NH_2). ^{31}P-{^1H} NMR [$(CD_3)_2SO$]: δ 22.77 (s, 1 P, $^1J_{PtP}$ 3776 Hz).

[*SP*-4-2]-[(2-Aminophenyl)diphenylphosphine]oxalatopalladium(II) hemihydrate, [Pd(C_2O_4)(adpp)]. This compound was prepared in a similar manner as for [Pt(C_2O_4)(adpp)] except using [$PdCl_2$(adpp)] (1.00 g, 2.20 mmol). Yield 0.76 g (72%). M.p. 210–212 °C (Found: C, 49.7; H, 3.6; N, 3.2. Calc. for $C_{20}H_{17}NO_{4.5}PPt$: C, 49.9; H, 3.6; N, 2.9%). $\tilde{\nu}_{max}/cm^{-1}$ 3484 (br)s (NH); 1660s, 1385m, 1246w, 884w (C_2O_4). ^1H NMR [$(CD_3)_2SO$]: δ 7.50–8.30 (m, 16 H, aromatics and NH_2). ^{31}P-{^1H} NMR [$(CD_3)_2SO$]: δ 41.66 (s, 1 P).

[*SP*-4-2]-[(±)-(2-Aminophenyl)methylphenylphosphine]-oxalatopalladium(II), (±)-[Pd(C_2O_4)(ampp)]. This compound was prepared in the same manner as for [Pt(C_2O_4)(adpp)] except using (±)-[$PdCl_2$(ampp)] (0.49 g, 1.25 mmol). Yield 0.32 g (63%). M.p. 170 °C (decomp.) (Found: C, 43.5; H, 3.3; N, 3.6. Calc. for $C_{15}H_{14}NO_4PPd$: C, 44.0; H, 3.4; N, 3.4%). $\tilde{\nu}_{max}/cm^{-1}$ 3422 (br)s (NH); 1644s, 1383m, 1233w, 893w (C_2O_4). ^1H NMR [$(CD_3)_2SO$]: δ 2.27 (d, 3 H, $^2J_{PH}$ 13, PMe) and 7.44–7.90 (m, 11 H, aromatics and NH_2). ^{31}P-{^1H} NMR [$(CD_3)_2SO$]: δ 36.18 (s, 1 P).

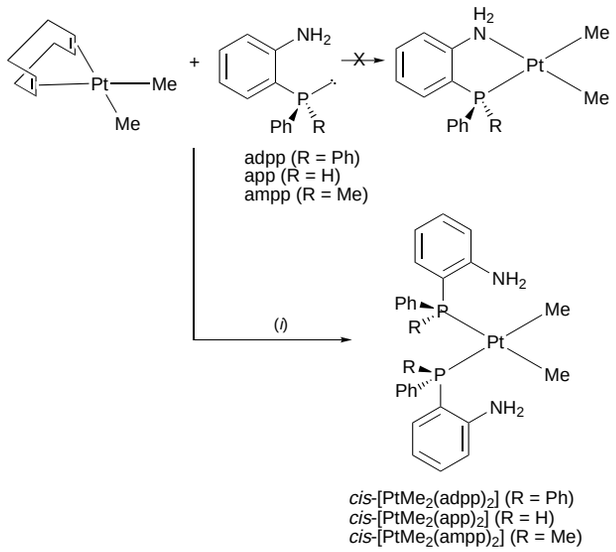
Biological procedures and materials

The P815 mastocytoma cells were cultured in Eagle's Minimum Essential Medium F15 with 10% foetal calf serum (herein EC10) and were maintained in DBA/2 mice. All cells were cultured and incubated in a Froma 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,[9] the compounds tested being 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 EC10.

X-Ray crystallography

Crystal data for *cis*-[PtMe(2-HNC$_6$H$_4$PPh$_2$)(adpp)]·C$_6$H$_6$. $C_{43}H_{40}N_2P_2Pt$, $M = 841.84$, triclinic, space group $P\bar{1}$ (no. 2), $a = 10.1237(9)$, $b = 11.371(1)$, $c = 18.138(2)$ Å, $\alpha = 80.178(9)$, $\beta = 79.089(9)$, $\gamma = 64.522(8)°$, $U = 1841.4(3)$ Å^3 (by least-squares analysis of the setting angles of 24 reflections, $95.44 < 2\theta < 99.65°$), Cu-Kα radiation $\lambda = 1.541\,78$ Å with a graphite monochromator, $Z = 2$, $D_c = 1.52$ g cm^{-3}, $F(000) = 840.00$, specimen $0.20 \times 0.12 \times 0.08$ mm, μ(Cu-Kα) = 79.18 cm^{-1}.

Data collection and processing. A unique data set was measured at 293(1) K using the ω–2θ scan technique to a maximum 2θ value of 120.1° on a Rigaku AFC6R diffractometer. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.29° with a take-off angle of 6.0°. Scans of (0.90 + 0.30 tan θ)° were made at a speed of 16.0° min^{-1} (in ω). The weak reflections [$I < 10.0\sigma(I)$] were rescanned (maximum of four scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The number of unique reflections was 5486. The intensities of three representative reflections were measured after every 150 but showed no significant decrease in intensity during data collection so no decay correction was applied. A semi-empirical absorption correction was applied which resulted in transmission factors ranging from 0.70 to 1.00. The data were corrected for Lorentz-polarisation effects.



Scheme 1 (*i*) *n*-Pentane. Only one stereoisomer of each diastereomeric species is shown

Structure analysis and refinement. The structure was solved by direct methods and expanded using Fourier techniques.[10,11] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included at calculated positions but not refined. The final cycle of full-matrix least-squares refinement was based on 5020 observed reflections [$I > 3.00\sigma(I)$] and 434 variable parameters and converged (largest shift was 0.00 times its e.s.d.) with final R and R' values being 0.025 and 0.025, respectively. The maximum and minimum peaks on the final Fourier-difference map corresponded to 0.96 and −0.68 e Å^{-3}, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[12] Anomalous dispersion effects were included in F_c;[13] the values of $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[14] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[15] All calculations were performed using TEXSAN crystallographic software.[16]

CCDC reference number 186/670.

Results and Discussion

Synthesis of bis(unidentate ligand)platinum(II) complexes

Reaction of [$PtMe_2$(cod)] with 2 equivalents of L [(2-aminophenyl)diphenylphosphine, (±)-(2-aminophenyl)phenylphosphine or (±)-(2-aminophenyl)methylphenylphosphine] in *n*-pentane gave the bis(unidentate)platinum(II) complexes *cis*-[$PtMe_2L_2$] in high yield (Scheme 1). When less than 2 equivalents of L were used in the reaction the only platinum(II)-based products identified by NMR spectroscopy were the bis(unidentate ligand)platinum(II) complexes *cis*-[$PtMe_2L_2$] (where L = adpp, app or ampp) and unreacted [$PtMe_2$(cod)]. No evidence was found for the formation of the mono(bidentate ligand)-platinum(II) complexes [$PtMe_2L$] (where L = adpp, app or ampp).

The neutral ligands L in *cis*-[$PtMe_2L_2$] (where L = adpp, app or ampp) were found to be co-ordinated *via* the phosphorus donor atoms. The ^{31}P-{^1H} NMR spectra of the complexes in C_6D_6 exhibited singlet ^{31}P resonances, a doublet was observed for *cis*-[$PtMe_2$(app)$_2$], flanked by satellites due to ^{195}Pt–^{31}P coupling (Table 1). The $^1J_{PtP}$ values were consistent with the proposed *cis* stereochemistry in which the phosphorus donor atoms were *trans* to methyl groups.[17] Two sets of resonances in the ratio of *ca.* 1:1 were observed for *cis*-[$PtMe_2L_2$] (where

Table 1 Selected NMR data for complexes of the type *cis*-[$PtMe_2L_2$], *cis*-[PtMe(2-HNC_6H_4PPhR)L], [PtCl(Me)L], [MCl_2L] and [$M(C_2O_4)L$]

Compound	^{31}P-{^1H} δ(P)[a]	^1H δ(PtMe)[b]	^1H δ(PMe)[b]	^1H δ(NH_2)
cis-[$PtMe_2$(adpp)$_2$][c]	19.41 (s) (1802)	1.29 (m) (69)	—	4.89 (s)
cis-[$PtMe_2$(app)$_2$][c]	−7.96 (d) (1590) −7.77 (d) (1590)	1.37 (m) (67)[d]	—	*e*
cis-[$PtMe_2$(ampp)$_2$][c]	−3.21 (s) (1651) −3.61 (s) (1642)	1.18 (m) (67)[d]	1.60 (dd) (41)[d]	4.80 (s)[d]
cis-[PtMe(2-$HNC_6H_4PPh_2$)(adpp)][f]	9.70 (s) (3168) 36.07 (s) (1839)	0.43 (dd) (60)	—	4.60 (s)
cis-[PtMe(2-HNC_6H_4PMePh)(ampp)][f,g]	−13.17 (d) (3130) −12.90 (d) (3130) 18.15 (d) (1750) 18.45 (d) (1750)			
[PtCl(Me)(adpp)][h]	21.32 (s) (4743)	0.66 (d) (71)	—	5.64 (s)
(±)-[PtCl(Me)(ampp)][h]	9.02 (s) (4536)	0.51 (d) (78)	2.15 (d) (66)	*e*
[$PtCl_2$(adpp)][i]	18.95 (s) (3920)	—	—	*e*
(±)-[$PtCl_2$(ampp)][i]	11.15 (s) (3831)	—	2.19 (d) (65)	*e*
[$PdCl_2$(adpp)][i]	46.43 (s)	—	—	*e*
(±)-[$PdCl_2$(ampp)][i]	41.05 (s)	—	2.26 (d)	*e*
[$Pt(C_2O_4)$(adpp)][i]	31.81 (s) (3884)	—	—	*e*
(±)-[$Pt(C_2O_4)$(ampp)][i]	22.77 (s) (3776)	—	2.34 (d) (54)	*e*
[$Pd(C_2O_4)$(adpp)][i]	41.66 (s)	—	—	*e*
(±)-[$Pd(C_2O_4)$(ampp)][i]	36.18 (s)	—	2.27 (d)	*e*

[a] Coupling constant $^1J_{PtP}$ in Hertz in parentheses. [b] Coupling constant $^2J_{PtH}$ in Hertz in parentheses. [c] In C_6D_6. [d] Separate resonances from the two diastereomers could not be discerned. [e] Obscured by the aromatic protons. [f] In CD_2Cl_2. [g] Not isolated. Present as a *ca.* 4:1 mixture of *cis*-[$PtMe_2$(ampp)$_2$] and *cis*-[PtMe(2-HNC_6H_4PMePh)(ampp)]. [h] In $CDCl_3$. [i] In $(CD_3)_2SO$.

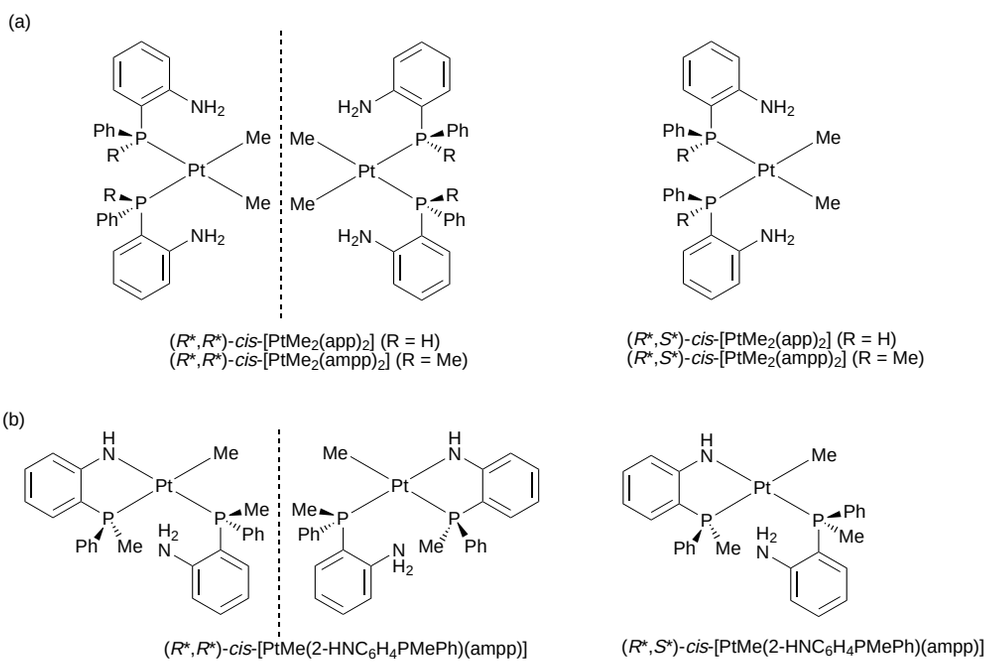


Fig. 1 Diastereomerism in (a) *cis*-[$PtMe_2L_2$] (where L = app or ampp) and (b) *cis*-[PtMe(2-HNC_6H_4PMePh)(ampp)]

L = app or ampp) due to the presence of (*R**,*R**) and (*R**,*S**) diastereomers (Fig. 1). A single methyl resonance with accompanying ^{195}Pt satellites for the equivalent PtMe groups and a singlet resonance for the unco-ordinated NH_2 moieties were observed for each of the complexes in the ^1H NMR spectrum, in keeping with the proposed structure. The PtMe resonances appeared as multiplets and were not susceptible to first-order analysis. They are examples of $AA'MX_3X_3'$ splitting patterns and have previously been noted for related square-planar complexes of the type *cis*-[$PtMe_2(PR_3)_2$].[18]

Rearrangement of *cis*-[$PtMe_2$(adpp)$_2$]

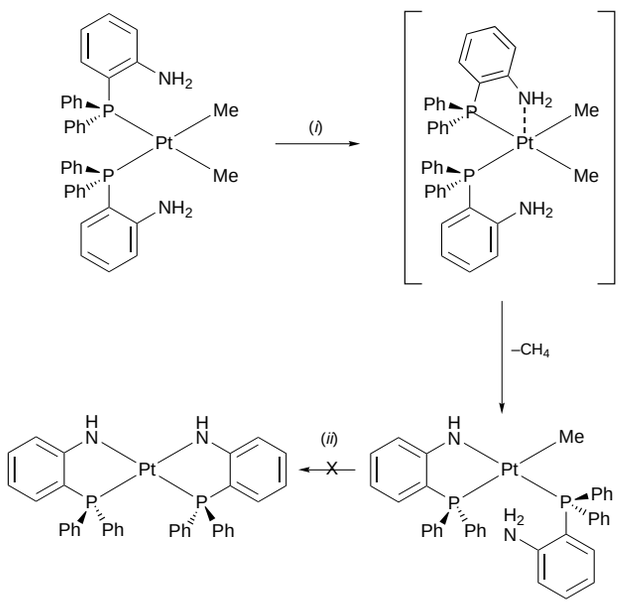
Reaction of [$PtMe_2$(cod)] with 2 equivalents of the unsymmetrical bidentate ligand adpp in benzene gave, after 3 d of standing, a quantitative yield of the complex *cis*-[PtMe-(2-$HNC_6H_4PPh_2$)(adpp)] (Scheme 2). The same product was obtained when a solution of the bis(unidentate)platinum(II) complex *cis*-[$PtMe_2$(adpp)$_2$] in benzene was allowed to stand for the same period of time.

The ^{31}P-{^1H} NMR spectrum of the complex *cis*-[PtMe-(2-$HNC_6H_4PPh_2$)(adpp)] in CD_2Cl_2 contained two singlet ^{31}P resonances, with accompanying ^{195}Pt satellites, at δ 9.70 ($^1J_{PtP}$ 3168) and 36.07 ($^1J_{PtP}$ 1839 Hz), consistent with phosphorus *trans* to nitrogen and carbon, respectively.[17] The ^1H NMR spectrum of the complex in the same solvent contained a doublet of doublets resonance for the PtMe moiety, flanked by ^{195}Pt satellites, and a singlet resonance for the unco-ordinated NH_2 group (Table 1). The NH signal was obscured by the aromatic proton resonances.

Table 2 Selected non-hydrogen interatomic distances (Å) and interatomic angles (°) for *cis*-[PtMe(2-$HNC_6H_4PPh_2$)(addp)]

Pt–P(1)	2.298(1)	Pt–P(2)	2.243(1)
Pt–C(1)	2.097(5)	Pt–N(1)	2.028(4)
Pt · · · N(2)*	3.559(8)		
P(1)–Pt–P(2)	102.98(4)	P(2)–Pt–C(1)	88.9(1)
P(1)–Pt–N(1)	82.0(1)	P(2)–Pt–N(1)	175.0(1)
P(1)–Pt–C(1)	167.5(1)	N(1)–Pt–C(1)	86.2(2)

* Non-bonded contact.



Scheme 2 (*i*) C_6H_6; (*ii*) thf, reflux, 7 d

The mechanism of the facile rearrangement of *cis*-[$PtMe_2$(adpp)$_2$] to form *cis*-[PtMe(2-$HNC_6H_4PPh_2$)(adpp)] is not known but presumably proceeds with concomitant loss of methane and hence involves cleavage of a platinum–carbon bond. The latter is known to occur readily in the presence of mineral acids and is believed to proceed either *via* oxidative addition of HX to the platinum(II) centre followed by reductive elimination of methane,[19–21] *via* three-centre transition states[19,22,23] or *via* rapid formation of a five-co-ordinate intermediate, involving the interaction of the conjugate base of the acid with the square-planar substrate, combined with slow, parallel protonation of both the substrate and the intermediate.[24,25] Recently, cleavage of a platinum–carbon bond has also been demonstrated in the presence of the strong Lewis acid $B(C_6F_5)_3$.[26] In the present case, the Pt–C bond cleavage is believed to proceed *via* a five-co-ordinate intermediate in which the NH_2 group of one of the adpp ligands of *cis*-[$PtMe_2$(adpp)$_2$] interacts with the platinum(II) centre. This interaction presumably increases the acidity of the NH_2 protons to such an extent as to allow the demethylation step to proceed (Scheme 2). No evidence for the further demethylation of *cis*-[PtMe(2-$HNC_6H_4PPh_2$)(adpp)], to give the bis(bidentate ligand)-platinum(II) complex *cis*-[Pt(2-$HNC_6H_4PPh_2$)$_2$], has been found in this work. The latter complex has previously been prepared by treatment of a solution of *cis*-[Pt(adpp)$_2$][$PtCl_4$] or *cis*-[Pt(adpp)$_2$]Cl_2 with an excess of base.[27]

Rearrangement of the analogous bis(unidentate ligand)-platinum(II) complex *cis*-[$PtMe_2$(ampp)$_2$] was found to be markedly less favourable and was only observed after a sample of the complex in thf had been heated under reflux for 1 week. The related secondary phosphine complex *cis*-[$PtMe_2$(app)$_2$] decomposed under similar reaction conditions. The ^{31}P-{^1H} NMR spectrum of the crude product from the former experiment indicated a *ca.* 20% conversion of *cis*-[$PtMe_2$(ampp)$_2$] into *cis*-[PtMe(2-HNC_6H_4PMePh)(ampp)]. Two sets of doublet ^{31}P resonances were observed for the latter complex consistent with the presence of (*R**,*R**) and (*R**,*S**) diastereomers (Fig. 1). Selected NMR data are given in Table 1.

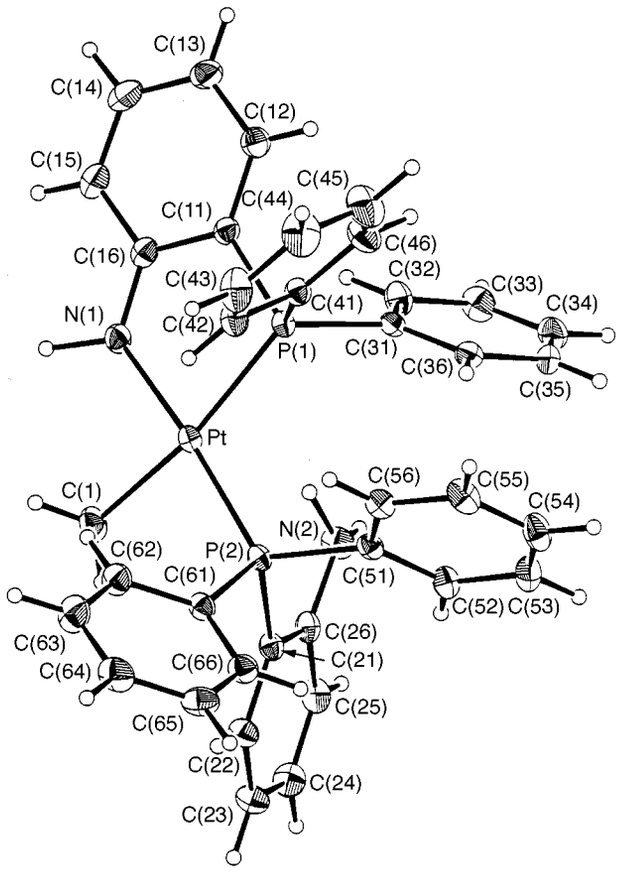


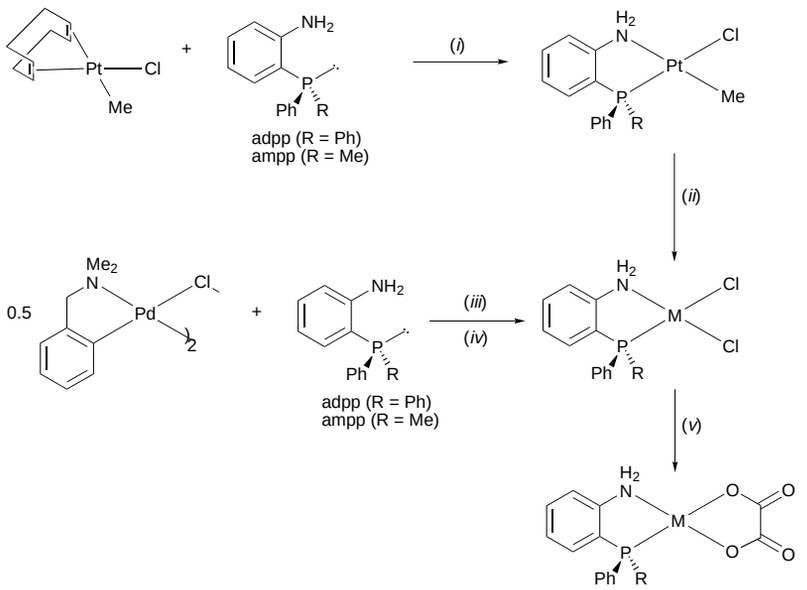
Fig. 2 Molecular structure of *cis*-[PtMe(2-$HNC_6H_4PPh_2$)(adpp)]

Crystal structure of *cis*-[PtMe(2-$HNC_6H_4PPh_2$)(adpp)]·C_6H_6

The molecular structure of the complex *cis*-[PtMe(2-$HNC_6H_4PPh_2$)(adpp)] has been confirmed by an X-ray analysis. The stereochemistry of the complex is depicted in Fig. 2. Selected bond lengths and angles are given in Table 2. The platinum atom has a distorted square-planar co-ordination geometry with angles about the metal centre of P(1)–Pt–N(1) 82.0(1), N(1)–Pt–C(1) 86.2(2), P(2)–Pt–C(1) 88.9(1) and P(1)–Pt–P(2) 102.98(4)°. The structure clearly showed the presence of a single methyl group co-ordinated to the platinum(II) centre and arranged *cis* to a unidentate adpp ligand attached to the metal centre *via* the phosphorus donor atom. The remaining two co-ordination sites were occupied by a deprotonated adpp ligand in which both the nitrogen atom of the amido group and the phosphorus donor atom were attached to the platinum(II) centre. Furthermore, the two phosphorus donor atoms had adopted a *cis* arrangement in the complex.

Synthesis of mono(bidentate ligand)-platinum(II) and -palladium(II) complexes

Mono(bidentate ligand)platinum(II) complexes of the type [PtCl(Me)L] (where L = adpp or ampp) were successfully prepared *via* the reaction of [PtCl(Me)(cod)] with 1 equivalent of L in thf (Scheme 3). The ^{31}P-{^1H} NMR spectra of the complexes in $CDCl_3$ exhibited singlet ^{31}P resonances with ^{195}Pt satellites at δ 21.32 ($^1J_{PtP}$ 4743) and 9.02 ($^1J_{PtP}$ 4536 Hz) for [PtCl(Me)-(adpp)] and (±)-[PtCl(Me)(ampp)], respectively; consistent with the phosphorus donor atom being *trans* to the chloro group.[17] A significant downfield shift of *ca.* 2 ppm was also observed for



Scheme 3 (*i*) thf; (*ii*) thf, concentrated HCl; (*iii*) MeOH, NH_4PF_6 in water; (*iv*) acetone, concentrated HCl; (*v*) MeCN, $AgNO_3$ in water, $Na_2C_2O_4$ in water. Only one stereoisomer of each diastereomeric species is shown

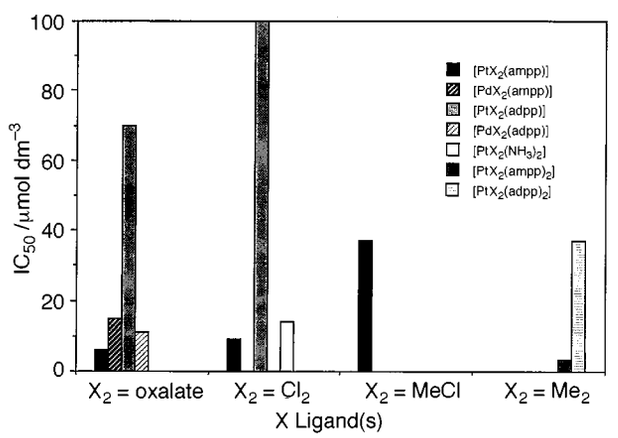


Fig. 3 Graphical representation of IC_{50} values for the complexes *cis*-[$PtMe_2L_2$], [$M(C_2O_4)L$], [$PtCl_2L$] and [PtCl(Me)(ampp)] (where L = adpp or ampp and M = Pd^{II} or Pt^{II}), and cisplatin. Note: the IC_{50} of [$PtCl_2$(adpp)] was >100 μmol dm^{-3} and hence could not be determined from the concentration range used in the assay

the NH_2 resonance in the ^1H NMR spectra of these complexes in $CDCl_3$ compared to that of free adpp and ampp, consistent with co-ordination of the NH_2 group to the platinum(II) centre (Table 1).

Subsequent reaction of the mono(bidentate ligand)-platinum(II) complexes [PtCl(Me)L] (where L = adpp or ampp) with concentrated hydrochloric acid in thf gave the dichloro-platinum(II) complexes [$PtCl_2$(adpp)] and (±)-[$PtCl_2$-(ampp)]. The analogous dichloropalladium(II) complexes [$PdCl_2$(adpp)] and (±)-[$PdCl_2$(ampp)] were prepared *via* a standard route which involved a bridge-splitting reaction between the dimer di-μ-chloro-bis[2-(dimethylaminomethyl)-phenyl-C^1,N]dipalladium(II) and the appropriate ligand in methanol followed by treatment with concentrated hydrochloric acid in acetone.[1]

Oxalato complexes of the type [$M(C_2O_4)L$] (where L = adpp or ampp and M = Pd^{II} or Pt^{II}) were prepared by treating the appropriate dichloro complex with 2 equivalents of silver nitrate in acetonitrile followed by the addition of sodium oxalate. Selected NMR data for all of the mono(bidentate ligand) complexes is summarised in Table 1.

Preliminary biological studies

The *in vitro* cytotoxic properties of the bis(unidentate ligand)-platinum(II) complexes *cis*-[$PtMe_2L_2$] and the mono(bidentate ligand) complexes [$M(C_2O_4)L$], [$PtCl_2L$] and (±)-[PtCl(Me)-(ampp)] (where L = adpp or ampp and M = Pd^{II} or Pt^{II}) have been assessed against the mouse P815 mastocytoma tumour cell line by determining the concentration of the respective compound which inhibited 50% [^3H]-thymidine incorporation. This concentration is known as the inhibitory concentration for 50% of the group, or the IC_{50}. The IC_{50} values for these complexes and for the reference compound *cis*-diamminedichloro-platinum(II), cisplatin, are summarised in Fig. 3. These results indicate that complexes containing ampp generally had lower IC_{50} values, and hence were more active, than their adpp analogues. The relatively high values obtained for [$PtCl_2$(adpp)] and its oxalato counterpart may be due to the low solubilities of these complexes. Furthermore, all of the complexes containing ampp had activities comparable to those of cisplatin, except for the mono(bidentate ligand) complex (±)-[PtCl(Me)(ampp)]. This is in keeping with the structure–activity relationships reported for platinum(II)-based anticancer agents which suggest that complexes containing at least one neutral am(m)ine ligand and having two labile co-ordination sites are the most active.[28] This suggests that the mechanism of action of the mono(bidentate ligand) complexes is similar to that of cisplatin.

The most active compound in this preliminary study was the bis(unidentate ligand)platinum(II) complex *cis*-[$PtMe_2$(ampp)$_2$] which was somewhat unexpected as tertiary phosphine complexes of platinum(II) have previously been shown to be inactive as a result of their kinetic inertness in biological systems.[29]

Conclusion

A general synthetic route to mono(bidentate ligand)-platinum(II) complexes containing unsymmetrical bidentate ligands with tertiary phosphine and primary amine donor groups has been devised which can be used to synthesize related complexes containing optically active ligands of this type with stereogenic phosphorus donor atoms. Furthermore, a preliminary study on the *in vitro* cytotoxicities of several optically inactive complexes of this type against the mouse P815 mastocytoma tumour cell line has shown those containing the ligand (±)-(2-aminophenyl)methylphenylphosphine, ampp, to have comparable activities to those of cisplatin. 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.

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