Correspondence to:

Associate Professor W. Henderson,

Department of Chemistry,

University of Waikato,

Private Bag 3105,

Hamilton,

New Zealand

e-mail: w.henderson@waikato.ac.nz

FAX: 0064-7-838-4219

Platinum(II) complexes containing ferrocene-derived phosphonate ligands; synthesis, structural characterisation and antitumour activity

William Henderson* and Steven R. Alley

Department of Chemistry, University of Waikato, Private Bag 3105, Hamilton, New Zealand.

Synopsis and graphical abstract

Platinum ferrocenyl-phosphonate complexes [Fc$(CH_2)_n PO_3 Pt(PPh_3)_2$] [**5**, n = 0; **6**, n = 1; **7**, n = 2; Fc = (η^5-C_5H_4)Fe(η^5-C_5H_5)] and the dinuclear phosphonate-bridged complex [1,1'-Fc'$\{PO_3Pt(PPh_3)_2\}_2$] **9** [Fc' = Fe(η^5-$C_5H_4)_2$] have been synthesised, and complexes **6**, **7** and **9** have been characterized by X-ray structure determinations; moderate activity against P388 leukaemia cells is exhibited by **6** and **7**, but the parent phosphonic acids are inactive.

Abstract

Platinum ferrocenyl-phosphonate complexes, containing four-membered Pt-O-P(O)-O rings, have been synthesised by the reactions of *cis*-[$PtCl_2(PPh_3)_2$] with the ferrocene-derived phosphonic acids $Fc(CH_2)_nP(O)(OH)_2$ (n = 0-2) [Fc = (η^5-C_5H_4)Fe(η^5-C_5H_5)] and 1,1'-Fc'[$P(O)(OH)_2$]$_2$ [Fc' = Fe(η^5-C_5H_4)$_2$] in the presence of Ag_2O. The complexes have been characterised by NMR spectroscopy, together with crystal structure determinations on [$Fc(CH_2)_nPO_3Pt(PPh_3)_2$] (n = 1,2) and [1,1'-Fc'{$PO_3Pt(PPh_3)_2$}$_2$]. The complexes [$Fc(CH_2)_nPO_3Pt(PPh_3)_2$] (n = 1,2) show moderate activity against P388 leukaemia cells, whereas the parent phosphonic acids are inactive.

Keywords: Platinum complexes; Phosphonate complexes; Antitumour activity; Crystal structures

1. Introduction

Due to the efficacy of various platinum complexes as antitumour agents a wide variety of platinum complexes have been screened for antitumour activity. Among these are complexes containing phosphonate ligands, [1] which include, for example, complexes effective against osteosarcoma, a specificity believed to be due to the affinity of the phosphonate groups for calcified tissue.[2] A wide range of platinum complexes containing aminophosphonate [3] and other phosphonate [4] ligands have been described in the literature, many of which have antitumour activity. Relevant to the studies described in this paper, complexes of the type **1** were synthesised by Kemmitt and co-workers by the reaction of *cis*-[$PtCl_2L_2$] (L= ancillary donor ligand, e.g. PPh_3) with the phosphonic acid or phosphoric acid monoester and excess Ag_2O (as a halide abstracting agent and base).[5] In this paper we extend this methodology to the synthesis of platinum phosphonate complexes using ferrocene-derived phosphonic acids which we have recently reported.[6]

2. Results and discussion

2.1 Synthesis and characterisation

Reactions of the ferrocenyl monophosphonic acids **2-4** with *cis*-[$PtCl_2(PPh_3)_2$] and excess Ag_2O in refluxing dichloromethane gives the platinum phosphonate complexes **5-7** respectively in high yield, Scheme 1, while the corresponding reaction with the bis(phosphonic acid) **8** gives the binuclear complex **9**, Scheme 2. The products are air-stable pale yellow solids which crystallise with dichloromethane of crystallisation, and decompose when heated. Complexes **5-7** are soluble in organic solvents such as dichloromethane and chloroform, while **9** is soluble in more polar solvents such as dimethylsulfoxide and methanol. In the case of **9**, satisfactory elemental analyses could not be obtained, but confirmation of the product was achieved by NMR spectroscopy and an X-ray structure determination.

The $^{31}P-\{^{1}H\}$ NMR spectra of the platinum phosphonate complexes are very distinctive, due to coupling between the phosphine and phosphonate P atoms, and coupling of these P nuclei to the ^{195}Pt nucleus. ^{31}P NMR data are summarised in Table 1. Values of

$^{1}J(PtP)$ are consistent with PPh_3 ligands *trans* to an oxygen donor, and data for the new complexes compare very favourably with those of the known complexes $[Pt(O_3PR)(PPh_3)_2]$ (R = Me, Ph, OPh); data for R = Me are included in Table 1 for comparison. [5] The positive ion electrospray mass spectra of **5-7** in dichloromethane showed a single low intensity $[M + H]^+$ ion at the expected *m/z* value (e.g. for **7** at *m/z* 1012). Interestingly, spectra in methanol-water gave a low intensity $[M + H]^+$ ion, with ions containing a cyclometallated PPh_3 ligand observed in positive ion mode, and the parent phosphonic acid monoanion observed in negative ion mode, indicating dissociation of the platinum-phosphonate complex.

The structures of **6**, **7** and **9** were determined by single-crystal X-ray diffraction studies, in order to confirm the bonding mode of the phosphonate ligand, and to provide a comparison between three closely related complexes. Selected bond lengths and angles for the three structures are given in Tables 2 (**6**), 3 (**7**) and 4 (**9**), while the molecular structures and atom numbering schemes are given in Figures 1-3 respectively. Overall, the structure determinations were routine, and bond lengths and angles of the platinum-phosphonate moiety were consistent with those of $[Pt(O_3PPh)(PMePh_2)_2]$.[5]

The structure of **6**, when compared to that of the free acid [6] shows only minor changes in bond angles and lengths upon coordination to platinum. Most notable are the reduction in the P=O bond length (1.566 Å in the free acid *vs*. 1.476 Å in **6**), as the opportunity for hydrogen-bonding is removed, and the decrease in the O-P-O bond angle (108° in free acid *vs*. 101° in **12**) due to the constrained nature of the four-membered Pt-O-P-O ring. The P=O bond lengths in all three structures are shorter than those of the metallacyclic P-O bonds. The cyclopentadienyl rings of the ferrocene group adopt an eclipsed conformation and the C(1)-C(11) bond lies in the plane of the cyclopentadienyl ring.

The principal difference in the structures of **6** and **7** lies in the orientation of the ferrocenyl unit with respect to the platinum coordination plane, as shown in Figure 4. In **6**, the ferrocenyl axis perpendicular to the cyclopentadienyl planes is almost parallel with the Pt…P(1) axis. This minimises steric interactions between the ferrocenyl group and the phenyl rings of the PPh_3 ligands. In contrast, for **7** the corresponding ferrocenyl axis lies at an angle of *ca*. 60° to the Pt….P(1) axis. The additional CH_2 spacer in **7** reduces steric congestion between the ferrocenyl and PPh_3 groups, and the ferrocenyl group is subsequently able to adopt an orientation more strongly influenced by crystal packing forces than internal steric demands.

The cyclopentadienyl rings of **9** adopt a staggered conformation with the two PO_3 units in an *anti* configuration to minimise steric interactions (Figure 5); the same configuration is also seen in the free acid. [6] The core of this complex is very nearly centrosymmetric about the Fe atom; bond lengths are essentially identical for the two halves of the molecule. The coordination planes of the platinum atoms are almost perpendicular to the plane of the ferrocenyl cyclopentadienyl rings.

All of the complexes possess a distorted platinum square plane. Table 5 lists the twist and fold angles across the platinum square plane for compounds **6**, **7** and **9** and $[Pt(O_3PPh)(PMePh_2)_2]$ for comparison. The twist angle is a measure of the distortion about the platinum centre, while the fold angle is a measure of the coplanarity of the platinum and phosphonate centres. The twist angle is larger in complexes **6** and **7** than in $[Pt(O_3PPh)(PMePh_2)_2]$ presumably due to the steric bulk of the ferrocenylphosphonate groups and PPh_3 ligands compared to the phenylphosphonate and $PMePh_2$ groups of $[Pt(O_3PPh)(PMePh_2)_2]$. However, the twist angles in **9** are similar to that reported for $[Pt(O_3PPh)(PMePh_2)_2]$ but the fold angles are significantly larger.

2.2 Antitumour activity

Given the interest in biological activity of platinum complexes [7], phosphonate complexes [1], and ferrocene-based complexes [8], the antitumour activity of the platinum phosphonate complexes described herein was considered worthy of preliminary investigation. Samples of **6** and **7** were assayed for activity against P388 leukaemia cells, with the activity of the parent phosphonic acids $FcCH_2PO_3H_2$ and $FcCH_2CH_2PO_3H_2$ also undertaken for comparison. IC_{50} data are listed in Table 6; the phosphonic acids are essentially inactive, whereas the platinum complexes **6** and **7** show moderate activity.

3. Experimental

General experimental procedures were as described previously [6]; reactions were carried out in solvents which were not deoxygenated. IR spectra were recorded as KBr disks. NMR spectra were recorded in $CDCl_3$ solution unless otherwise stated. The compounds *cis*-$[PtCl_2(PPh_3)_2]$ [9], silver(I) oxide [10], and the phosphonic acids [6] were prepared as described previously. The atom numbering schemes of the ferrocenyl groups is as previously reported. [6]

Antitumour assays were carried out by the Marine Chemistry Group, University of Canterbury, NZ. The samples were dissolved in 1:3 dichloromethane-methanol (typically 5 mg mL^{-1}; 2.5 mg mL^{-1} for **6**), and a two-fold series of dilutions incubated for 72 hours with P388 (Murine Leukaemia) cells. The IC_{50} value was determined by reduction of the yellow dye MTT tetrazolium by healthy cells to the purple dye MTT formazan. Mitomycin C was used as a positive control.

Synthesis of platinum ferrocenylphosphonate complexes

The general method used was that described by Kemmitt *et al.*[5] A mixture of the phosphonic acid, *cis*-[$PtCl_2(PPh_3)_2$] and excess silver(I) oxide was refluxed in dry dichloromethane. The mixture was filtered to remove insoluble silver salts, the resulting yellow solution concentrated to *ca*. 2 mL and petroleum spirits added to precipitate the product as a pale yellow powder.

[$FcPO_3Pt(PPh_3)_2$] **5**

$FcP(O)(OH)_2$ **2** (0.017 g, 0.063 mmol), *cis*-[$PtCl_2(PPh_3)_2$] (0.05 g, 0.063 mmol) and Ag_2O (0.03 g, excess) in CH_2Cl_2 (5 mL) were refluxed for 1.5 h. Workup gave 0.042 g (68%) of **5** as a yellow powder. M.p. decomp. 138-142 °C. Found: C, 53.9; H, 4.2. $C_{46}H_{39}FeO_3P_3Pt.CH_2Cl_2$ requires C, 52.8; H, 3.9%. $^{13}C-\{^1H\}$ NMR, δ 69.47 (s, C4), 69.62 [d, $^3J(PC)$ 12, C3], 71.95 [d, $^2J(PC)$ 14, C2], 128.32-134.51 (m, PPh_3). ^1H NMR, δ 4.06 (5H, s, H4), 4.23 [2H, d, $^3J(PH)$ 0.4, H2], 4.54 (2H, s, H3), 7.18-7.45 (30H, m, PPh_3). IR (cm^{-1}): 1882(w), 1211(w), 1174(w), 1098(m), 1027(w), 999(w), 927(m), 879(w), 610(m), 555(s), 529(s).

[$FcCH_2PO_3Pt(PPh_3)_2$] **6**

$FcCH_2P(O)(OH)_2$ **3** (0.019 g, 0.07 mmol), *cis*-[$PtCl_2(PPh_3)_2$] (0.053 g, 0.07 mmol) and Ag_2O (0.03 g, excess) in CH_2Cl_2 (10 mL) were refluxed for 1 h. Workup gave 0.057 g (86%) of **6** as a pale yellow powder. Single crystals of the bis(dichloromethane) solvate were obtained by vapour diffusion of diethyl ether into a dichloromethane solution of the complex at 4 °C. Crystals visibly lose solvent on air-drying. M.p. decomp. 165-168 °C. Found: C, 53.0; H, 4.2. $C_{47}H_{41}FeO_3P_3Pt.CH_2Cl_2$ requires C, 53.2; H, 4.0 %. $^{13}C-\{^1H\}$ NMR, δ 32.53 [d, $^1J(PC)$ 117, CH_2P], 66.74 (s, C3), 68.82 (s, C4), 70.28 (s, C2), 127.75-134.55 (m, PPh_3). ^1H NMR, δ 2.72 [2H, d, $^2J(PH)$ 18.7, CH_2P], 4.02 (5H, s, H4), 4.04 (2H, s, H3), 4.10 (2H, s, H2), 7.13-7.31 (30H, m, PPh_3). IR (cm^{-1}): 1217(w), 1182(m), 1098(m), 999(w), 924(m), 612(w), 584(w), 554(s), 530(s).

$[FcCH_2CH_2PO_3Pt(PPh_3)_2]$ **7**

$FcCH_2CH_2P(O)(OH)_2$ **4** (0.040 g, 0.13 mmol), *cis*-$[PtCl_2(PPh_3)_2]$ (0.107 g, 0.13 mmol) and Ag_2O (0.05 g, excess) in CH_2Cl_2 (10 mL) were refluxed for 1 h. Workup gave 0.13 g (94%) of **7** as a pale yellow powder. Single crystals were obtained by vapour diffusion of diethyl ether into a dichloromethane solution of the complex at 4 °C. M.p. 209-212 °C (decomp.). Found: C, 50.7; H, 4.1. $C_{48}H_{43}FeO_3P_3Pt.2CH_2Cl_2$ requires C, 50.85; H, 4.0%. $^{13}C-\{^1H\}$ NMR (d^6-DMSO), δ 25.09 (s, **C**H_2CH_2P), 32.70 [d, $^1J(PC)$ 120, **C**H_2P], 67.49 (s, C3), 68.07 (s, C2), 68.75 (s, C4), 127.7-134.5 (m, PPh_3). ^1H NMR (d^6-DMSO), δ 1.93 (2H, m, C**H**$_2$P), 2.68 (2H, m, C**H**$_2CH_2P$), 4.05 (2H, s, H3), 4.09 (5H, s, H4), 4.13 (2H, s, H2), 7.2-7.5 (m, 30H, PPh_3). IR (cm^{-1}): 1482(w), 1437(w), 1196(m), 1098(m), 999(w), 918(m), 595(m), 555(s), 529(s), 512(m).

$[1,1'\text{-Fc}'\{PO_3Pt(PPh_3)_2\}_2]$ **9**

1,1'-Fc'$[P(O)(OH)_2]_2$ **8** (0.023 g, 0.067 mmol), *cis*-$[PtCl_2(PPh_3)_2]$ (0.106 g, 0.134 mmol) and Ag_2O (0.10 g, excess) in CH_2Cl_2 (5 mL) were refluxed for 2 h. Workup gave 0.088 g (74%) of **9** as a pale yellow powder. Single crystals of the complex suitable for an X-ray structure determination were obtained by vapour diffusion of diethyl ether into a dichloromethane-methanol (9:1) solution of the complex at -20 °C. M.p. 218-226 °C (decomp.). Satisfactory microanalytical data could not be obtained. ^{1}H NMR (d^6-DMSO), δ 4.08 (4H, s, H3), 4.31 (2H, s, H2), 7.25-7.65 (60H, m, PPh_3).

Crystal structure determinations

Data for **6** were collected on a Nicolet R3 diffractometer at the University of Canterbury, while data for **7** and **9** were collected on a Siemens Smart CCD diffractometer at the University of Auckland, and corrected for absorption using SADABS. [11] The structures were solved by Patterson methods for platinum and iron and developed routinely using the SHELX-97 program [12] with full-matrix least-squares refinement based on F_o^2. The structures of **6** and **7** each include two independent dichloromethane molecules of crystallisation. Complete refinement of **9** was hampered by the presence of disordered solvent molecules. A single methanol of crystallisation was successfully modelled but the final difference map contained several large peaks of electron density, some of which were able to be successfully modelled as carbon or oxygen atoms, but were unable to be refined in chemically sensible solvent molecules. Despite this, an acceptable R_1 of 0.0473 was achieved and the structure of the platinum complex was refined without ambiguity. All non-hydrogen atoms were refined using anisotropic temperature factors, while hydrogen atoms were placed in calculated positions. Crystallographic data and analysis parameters for the three structures are given in Table 7.

Crystallographic data (excluding structure factors) for the three structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-###### (**6**), ###### (**7**) and ###### (**9**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank the University of Waikato for financial support (including a scholarship to S.R.A.), the New Zealand Lottery Grants Board for a grant-in-aid for the mass spectrometer purchase, and Gill Ellis (University of Canterbury) for antitumour assay data. Prof. Ward Robinson (University of Canterbury) and Associate Professor Cliff Rickard (University of Auckland) are thanked for collection of the X-ray data sets, and Professor B. K. Nicholson provided guidance in the X-ray crystallography. The generous loan of platinum from Johnson Matthey plc is acknowledged.

References

[1] (a) T. Klenner, P. Valenzuela-Paz, F. Amelung, H. Muench, H. Zahn, B.K. Keppler and H. Blum, *Metal complexes in cancer chemotherapy*, B. K. Keppler (Ed), VCH, Weinheim, Germany, 1993, pp. 84-127; (b) T. Klenner, P. Valenzuela-Paz, B. K. Keppler, G. Angres, H. R. Scherf, F. Wingen, F. Amelung and D. Schmaehl, *Cancer Treat. Rev.*, 1990, **17**, 253.

[2] (a) S. Slaby, M. Galanski, S. W. Metzger and B. K. Keppler, *Contrib. Oncol.,* 1999, **54**, 201; (b) M. Galanski, S. Slaby, and B. K. Keppler, *Contrib. Oncol*., 1999, **54**, 435.

[3] Selected refs: (a) T. G. Appleton, K. A. Byriel, J. R. Hall, C. H. L. Kennard, D. E. Lynch, J. A. Sinkinson and G. Smith, *Inorg. Chem*., 1994, **33**, 444; (b) M. J. Bloemink, J. P. Dorenbos, R. J. Heetebrij, B. K. Keppler, J. Reedijk, and H. Zahn, *Inorg. Chem.*, 1994, **33**, 1127; (c) L. Bláha, I. Lukeš, J. Rohovec and P. Hermann, *J. Chem. Soc., Dalton Trans*., 1997, 2621; (d) I. Lukeš, L. Bláha, F. Kesner, J. Rohovec and P. Hermann*, J. Chem. Soc., Dalton Trans*., 1997, 2629.

[4] (a) R. Bau, S. K. S. Huang, J.-A. Feng and C. E. McKenna*, J. Am. Chem. Soc*., 1988, **110**, 7546; (b) L. S. Hollis, A. V. Miller, A. R. Amundsen, J. E. Schurig and E. W. Stern, *J. Med. Chem*., 1990, **33**, 105.

[5] R. D. W. Kemmitt, S. Mason, J. Fawcett and D. R. Russell, *J. Chem. Soc., Dalton Trans*., 1992, 851.

[6] S. R. Alley and W. Henderson*, J. Organomet. Chem*., accepted.

[7] C. A. McAuliffe, H. I. Sharma and N. D. Tinker in *Chemistry of the Platinum Group Metals, Recent Developments*, Ed. F. R. Hartley, Elsevier, Amsterdam, 1991, chapter 16.

[8] (a) E. W. Neuse, M. G. Meirim and N. F. Blom, *Organometallics*, 1988, **7**, 2562; (b) R. W. Mason, K. .McGrouther, P. R. R. Ranatunge-Bandarage, B. H. Robinson, and J. Simpson, *Appl. Organomet. Chem*., 1999, **13**, 163.

[9] C. Decker, W. Henderson and B. K. Nicholson, *J. Chem. Soc., Dalton Trans*., 1999, 3507.

[10] H. L. Riley and H. B. Baker, *J. Chem. Soc.,* 1926, 2510.

[11] R. H. Blessing, *Acta Crystallogr.,* 1995, **A51**, 33.

[12] G. M. Sheldrick, SHELX-97 programs for solution and refinement of crystal structures, University of Göttingen, 1997.

Table 1. ^{31}P NMR data† for the platinum ferrocenylphosphonate complexes

Complex	$\delta(^{31}PPh_3)$	$^{1}J(PtP)$	$\delta(^{31}PO_3)$	$^{2}J(PtP)$	$^{3}J(PP)$
5	8.2	3850	43.4	125	5.8
6	7.2	3895	50.5	116	6.0
7	7.9	3845	49.8	113	6.0
9	8.1	3844	41.9	122	5.7
$[Pt(O_3PMe)(PPh_3)_2]$ ¶	7.25	3848	46.8	122	10

¶ Data from ref. [5]

† Recorded in $CDCl_3$ solution, except for **9** in CH_2Cl_2 with an external D_2O lock

Table 2. Selected bond lengths (Å) and angles (°) for [$FcCH_2PO_3Pt(PPh_3)_2$] **6**.

O(1)-Pt	2.081(3)	O(2)-Pt	2.075(3)
Pt-P(2)	2.2253(10)	Pt-P(3)	2.2378(10)
C(1)-C(11)	1.502(6)	C(1)-P(1)	1.807(5)
P(1)-O(1)	1.563(3)	P(1)-O(2)	1.566(3)
P(1)-O(3)	1.476(3)		
Cp Fe-C	average 2.032	range 2.014-2.042	
Cp C-C	average 1.413	range 1.364-1.439	

O(1)-Pt-P(3)	93.18(8)	O(1)-P(1)-C(1)	110.41(19)
O(2)-Pt-P(2)	99.01(8)	O(2)-P(1)-O(3)	116.42(17)
P(2)-Pt-P(3)	97.31(4)	O(2)-P(1)-C(1)	105.69(19)
O(1)-Pt-O(2)	71.14(11)	O(3)-P(1)-C(1)	107.41(19)
Pt-O(1)-P(1)	93.21(13)	C(11)-C(1)-P(1)	116.8(3)
Pt-O(2)-P(1)	93.34(13)	C(1)-C(11)-C(12)	127.0(4)
O(1)-P(1)-O(2)	101.17(15)	C(1)-C(11)-C(15)	126.0(4)
O(1)-P(1)-O(3)	115.29(18)		

Table 3. Selected bond lengths (Å) and angles (°) for [$FcCH_2CH_2PO_3Pt(PPh_3)_2$] **7**.

O(1)-Pt	2.077(3)	O(2)-Pt	2.066(3)
Pt-P(2)	2.2330(13)	Pt-P(3)	2.2656(11)
C(1)-C(11)	1.505(8)	C(1)-C(2)	1.512(9)
C(2)-P(1)	1.812(5)	P(1)-O(1)	1.571(3)
P(1)-O(2)	1.577(3)	P(1)-O(3)	1.481(4)
Cp Fe-C	average 2.041	range 2.028-2.063	
Cp C-C	average 1.415	range 1.387-1.436	

O(1)-Pt-P(3)	96.51(9)	O(1)-P(1)-C(1)	109.4(4)
O(2)-Pt-P(2)	94.32(10)	O(2)-P(1)-O(3)	115.6(2)
P(2)-Pt-P(3)	98.45(5)	O(2)-P(1)-C(1)	105.3(2)
O(1)-Pt-O(2)	71.00(0)	O(3)-P(1)-C(1)	110.2(2)
Pt-O(1)-P(1)	93.8(2)	C(1)-C(2)-P(1)	115.3(4)
Pt-O(2)-P(1)	93.99(14)	C(11)-C(1)-C(2)	115.9(5)
O(1)-P(1)-O(2)	99.7(2)	C(1)-C(11)-C(12)	125.8(5)
O(1)-P(1)-O(3)	115.9(2)	C(1)-C(11)-C(15)	126.9(6)

Table 4. Selected bond lengths (Å) and angles (°) for [1,1'-Fc'{$PO_3Pt(PPh_3)_2$}$_2$] **9**.

Pt(1)-P(11)	2.258(2)	Pt(1)-P(12)	2.255(2)
Pt(2)-P(21)	2.255(2)	Pt(2)-P(22)	2.242(2)
P(1)-C(11)	1.801(7)	P(2)-C(21)	1.795(7)
P(1)-O(11)	1.565(5)	P(1)-O(12)	1.576(5)
P(1)-O(13)	1.501(5)	P(2)-O(21)	1.565(4)
P(2)-O(22)	1.567(5)	P(2)-O(23)	1.505(5)
O(11)-Pt(1)	2.097(4)	O(12)-Pt(1)	2.092(4)
O(21)-Pt(2)	2.094(4)	O(22)-Pt(2)	2.086(4)
Cp Fe-C	average 2.048	range 2.040-2.059	
Cp C-C	average 1.425	range 1.413-1.436	

P(11)-Pt(1)-P(12)	99.91(6)	O(11)-P(1)-O(13)	115.1(2)
P(21)-Pt(2)-P(22)	100.35(6)	O(21)-P(2)-O(23)	114.8(3)
P(11)-Pt(1)-O(11)	98.06(13)	O(11)-P(1)-C(11)	109.1(3)
P(21)-Pt(2)-O(21)	93.73(12)	O(21)-P(2)-C(21)	105.9(3)
O(11)-Pt(1)-O(12)	70.62(17)	O(12)-P(1)-O(13)	114.2(3)
O(21)-Pt(2)-O(22)	70.86(17)	O(22)-P(2)-O(23)	115.7(3)
O(12)-Pt(1)-P(12)	91.33(13)	O(12)-P(1)-C(11)	107.9(3)
O(22)-Pt(2)-P(22)	94.77(13)	O(22)-P(2)-C(21)	107.3(3)
Pt(1)-O(11)-P(1)	93.4(2)	O(13)-P(1)-C(11)	109.0(3)
Pt(2)-O(21)-P(2)	92.5(2)	O(23)-P(2)-C(21)	110.9(3)

Pt(1)-O(12)-P(1)	93.3(2)	P(1)-C(11)-C(12)	124.9(6)
Pt(2)-O(22)-P(2)	92.7 (2)	P(2)-C(21)-C(22)	126.5(5)
O(11)-P(1)-O(12)	100.8 (2)	P(1)-C(11)-C(15)	127.6(5)
O(21)-P(2)-O(22)	101.3(2)	P(2)-C(21)-C(25)	125.9(6)

Table 5. Twist and fold angles (°) about the platinum centres for platinum phosphonate complexes.

Compound		Twist angle†	Fold angle‡
6		9.2	11.3
7		10.7	13.1
9	Pt(1)	3.0	14.3
	Pt(2)	5.5	17.0
$[Pt(O_3PPh)(PMePh_2)_2]$ ¶		2.2	12.9

†Angle between P-Pt-P and O-Pt-O planes

‡Angle between O-Pt-O and O-P-O planes

¶ Data from ref. [5]

Table 6. Antitumour (P388 leukaemia) assay data

Compound	IC_{50} ¶	
	ng mL^{-1}	mM
$FcCH_2PO_3H_2$ **3**	538115	1915
$FcCH_2CH_2PO_3H_2$ **4**	>62500	>219
6	5838	5.8
7	5046	5.0

¶ Concentration of sample required to reduce the cell growth of the P388 leukaemia cell line by 50%.

Table 7. Crystal data and refinement details for $[FcCH_2PO_3Pt(PPh_3)_2]$ **6**, $[FcCH_2CH_2PO_3Pt(PPh_3)_2]$ **7** and $[1,1'\text{-}Fc'\{PO_3Pt(PPh_3)_2\}_2]$ **9**.

Compound	**6**	**7**	**9**
Empirical formula	$C_{47}H_{41}FeO_3P_3Pt.$ $2CH_2Cl_2$	$C_{48}H_{43}FeO_3P_3Pt.$ $2CH_2Cl_2$	$C_{82}H_{68}FeO_6P_6Pt_2.$ CH_3OH
Crystal size (mm)	0.65x0.55x0.32	0.45x0.13x0.06	0.37x0.33x0.23
Formula weight	1167.5	1181.53	1863.12
Crystal system	Orthorhombic	Triclinic	Triclinic
Space group	Pbca	$P\bar{1}$	$P\bar{1}$
a (Å)	20.4241(9)	13.3696(2)	12.5981(1)
b (Å)	18.4116(9)	14.3472(3)	16.3884(2)
c (Å)	25.0622(13)	14.6522(2)	23.0691(2)
α (°)	90	74.144(1)	93.815(1)
β (°)	90	83.00(0)	104.156(1)
γ (°)	90	62.248(1)	111.58
V (Å^3)	9424.4(8)	2392.56(7)	4229.22(7)
Z	8	2	2
D_{calc} (g cm^{-3})	1.646	1.64	1.463
F(000)	4640	1176	1944
μ(Mo-Kα) (mm^{-1})	3.64	3.36	3.63
Temperature (K)	158(2)	200(2)	200(2)

2θ range for data collection	$6 < 2\theta < 53°$	$3 < 2\theta < 55°$	$2 < 2\theta < 54°$
Total reflections	24352	8329	17728
Unique reflections	8654	7064	15684
T_{min}	0.6584	0.6386	0.4504
T_{max}	1.0000	0.8608	0.5494
R_1 [$I > 2\sigma(I)$]	0.0318	0.0283	0.0473
wR_2	0.0797¶	0.808§	0.1379 ☻
GOF	1.037	1.058	1.138
Residual electron density (e $Å^{-3}$)			
Max.	1.227	0.741	3.462
Min.	-1.205	-0.853	-0.775

¶ $w = [\sigma^2(F_o)^2 + (0.0262P)^2 + 37.6334P]^{-1}$

§ $w = [\sigma^2(F_o)^2 + (0.0406P)^2 + 2.5846P]^{-1}$

☻ $w = [\sigma^2(F_o)^2 + (0.0673P)^2 + 24.25P]^{-1}$

where $P = (F_o^2 + 2F_c^2)/3$

Captions for Figures

Fig. 1. Molecular structure of [$FcCH_2PO_3Pt(PPh_3)_2$] **6**. Hydrogen atoms and the two CH_2Cl_2 molecules of crystallization are omitted. Ellipsoids are at the 50% probability level.

Fig. 2. Molecular structure of [$FcCH_2CH_2PO_3Pt(PPh_3)_2$] **7**. Hydrogen atoms and the two CH_2Cl_2 molecules of crystallization are omitted. Ellipsoids are at the 50% probability level.

Fig. 3. Molecular structure of [1,1'-Fc'$\{PO_3Pt(PPh_3)_2\}_2$] **9** with hydrogen atoms and solvent molecules of crystallization omitted. Ellipsoids are shown at the 50% probability level.

Fig 4. Orientation of the ferrocenyl groups with respect to the platinum coordination planes in complexes **6** and **7**, with all H atoms and phenyl rings omitted for clarity.

Fig. 3. Molecular structure of [1,1'-Fc'$\{PO_3Pt(PPh_3)_2\}_2$] **9** viwed down the C_5H_4-Fe-C_5H_4 axis showing the *trans* arrangement. Phenyl rings and H atoms are omitted.