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FULL PAPER

Control of aminophosphine chelate ring-opening in Pt(II) and Pd(II) complexes: potential dual-mode anticancer agents

Abraha Habtemariam,[a] Beth Watchman,[a] Brian S. Potter,[b] Rex Palmer,[b] Simon Parsons,[a] Andrew Parkin[a] and Peter J. Sadler *[a]

[a] *Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh, UK EH9 3JJ. E-mail: P.J.Sadler@ed.ac.uk*

[b] *Department of Crystallography, Birkbeck College, University of London, Malet Street, London, UK WC1E 7HX*

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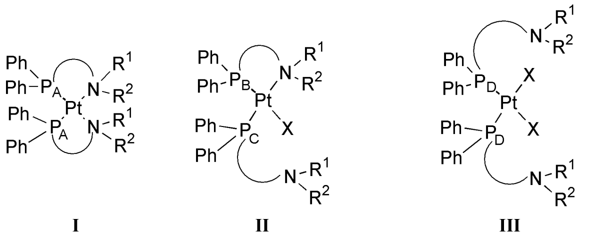
We show that bis(aminophosphine) complexes of the type $[M(R^1R^2N(CH_2)_nPPh_2)_2]^{2+}$, M = Pt(II) or Pd(II), can exist in chelate ring-closed and ring-opened forms both in the solid state and in aqueous solution. The equilibrium between them in solution can be controlled by the nature of the groups R^1 and R^2 (H, Me, Bz, cyclohexyl), by the bridge length *n*, and by the pH and Cl^- concentration. X-Ray crystal structures are reported for the ring-closed complexes *cis*-$[Pt(H_2N(CH_2)_2PPh_2\text{-}P,N)_2]Cl_2$, *cis*-$[Pt(H_2N(CH_2)_3PPh_2\text{-}P,N)_2]Cl_2$, and *cis*-$[Pt(Me(H)N(CH_2)_2PPh_2\text{-}P,N)_2][HCl_2]_2$, the mono-ring-opened complex *cis*-$[Pd(Me_2N(CH_2)_2PPh_2\text{-}N,P)Cl(Me_2NH(CH_2)_2PPh_2\text{-}P)](NO_3)_2$, the di-ring-opened complex *cis*-$[Pt(Me_2N(CH_2)_3PPh_2\text{-}P)_2Cl_2]$, and, for comparison, the monochelate *cis*-$[Pd(Me_2N(CH_2)_3PPh_2\text{-}N,P)Cl_2]$. These square-planar complexes exhibit varying degrees of distortion and variable M–N bond lengths dependent not only on the *trans* influence of P but also on steric effects within the complex. pH-induced chelate ring-opening of *cis*-$[Pt(Me_2N(CH_2)_2PPh_2\text{-}P,N)_2]Cl_2$ had an associated p*K* value of 6.9. In contrast, complexes with R^1 and R^2 = H, *n* = 2 or 3 or R^1 = H and R^2 = Me, *n* = 2, are more difficult to ring-open. Thus the complexes *cis*-$[Pt(Me(H)N(CH_2)_2PPh_2\text{-}P,N)_2]Cl_2$ and *cis*-$[Pt(H_2N(CH_2)_3PPh_2\text{-}P,N)_2]Cl_2$, had associated p*K* values of 2.1 and 2.9, respectively. These aminophosphine complexes may exhibit anticancer activity by two mechanisms: by disrupting mitochondrial membrane potentials as bis-chelated (ring-closed) lipophilic cations, or by direct binding to DNA bases as ring-opened complexes.

Introduction

Aminophosphine complexes contain mixed donor ligands: one soft phosphorus donor and one relatively hard nitrogen donor, and can act as bridging ligands or as chelating agents thereby conferring enhanced stability to the complex. In Pt(II) complexes, the nitrogen atom binds more weakly than phosphorus, especially when N is *trans* to P, which exerts a high *trans* influence.[1] Furthermore, the strength of M–N bonds is affected much more by steric factors than for the corresponding M–P bonds.[2] Thus with the appropriate choice of nucleophiles, and under a given set of conditions such as pH, and chloride concentration, equilibria involving the dissociation of the amino group can be established resulting in ring-opened complexes with a potential binding site on the metal centre. Consequently, P,N chelated Pt(II) complexes are known to display a considerably higher reactivity than the bis(phosphine) complexes.[3] Depending on the steric demands of the substituents on N and the length of the N–P linker in the aminophosphine ligand, bis-chelate, mono-chelate ring-opened, or non-chelate complexes can be formed (Scheme 1).



I II III

Scheme 1 Ring-closed (**I**), mono-ring-opened (**II**) and di-ring-opened (**III**) aminophosphine complexes. X = Cl, OH_2.

There are many previous reports relating to the potential use of aminophosphine Pt(II) complexes in catalysis.[4–7] However, very few[8] of these studies have explored the potential biological activities of these complexes, even though they contain *cis* amine ligands, a feature found in many active platinum anticancer agents,[9] together with *cis* phosphine ligands. Certain diphosphines have also previously been shown to exhibit anticancer activity, especially 1,2-diphosphinoethane (dppe) complexes of Cu(I), Ag(I) and Au(I).[10] In addition a range of monophosphine complexes of Au(I) exhibit antiarthritic activity and one of these, the PEt_3 complex auranofin, is now in clinical use as an antiarthitic drug.[10] In addition, they offer potential as anticancer agents *via* disruption of mitochondrial function due to their lipophilic cationic character.[11]

Recently we have established that the chelate ring-opening reactions of Pt(II) aminophosphine complexes can be controlled under conditions of biological relevance, and that they bind reversibly to the DNA base guanine.[12,13] We have also shown that chelate ring-opened Pt(II) aminophosphine complexes can bind rapidly and strongly to the DNA base thymine as well as to the RNA base uracil under physiological conditions, in contrast to platinum(II) am(m)ine anticancer complexes.[14] Some aminophosphine complexes are cytotoxic to cancer cells including cisplatin-resistant cells, but the potency depends on the cell type. Different complexes may act *via* different mechanisms in different kinds of cells.[12] The biological activity may arise from a combination of antimitochondrial activity due to the ring-closed forms and attack on DNA by the chelate ring-opened complexes.

In the present work, we have prepared and characterised both chelate ring-closed and ring-opened aminophosphine complexes of Pt(II) and Pd(II) and investigated the effect of pH and

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chloride on chelate ring-opening in aqueous solution. Our aim is to develop a rational approach towards the design and synthesis of new Pt and Pd drugs with improved therapeutic properties, in particular overcoming factors which limit the use of current Pt anticancer drugs: resistance, toxicity, and narrow spectrum of treatable cancers.

Experimental

Reagents

$H_2N(CH_2)_2Cl\cdot HCl$, $H_2N(CH_2)_3Cl\cdot HCl$, $Me_2N(CH_2)_2Cl\cdot HCl$, $Bz_2N(CH_2)_2Cl\cdot HCl$, BzN(H)Me, 5%Pd/C and ethylene oxide were purchased from Aldrich, $C_6H_{11}(H)N(CH_2)_2OH$ and $Bz(H)N(CH_2)_2OH$ from Lancaster Synthesis. $(COD)PtCl_2$ (COD = cycloocta-1,5-diene) and $(COD)PdCl_2$ were purchased from Aldrich or prepared by literature methods.[15,16] Solvents were generally dried and purified by standard methods, and freshly distilled before use.

NMR spectroscopy

Spectra were recorded on JEOL GSX270 (67.80 MHz for ^{13}C, 109.25 MHz for ^{31}P and at 57.94 MHz for ^{195}Pt) and DMX 500 spectrometers (202 MHz for ^{31}P). Chemical shifts (δ) are reported in ppm relative to internal TMS ($CDCl_3$) or TSP (D_2O) for ^1H and ^{13}C, and to external 85% H_3PO_4 for ^{31}P, and 1 M Na_2PtCl_6 for ^{195}Pt. Coupling constants (J) are given in Hz and NMR signals are described as singlets (s), doublets (d), triplets (t), multiplets (m) and quintets (q).

Microanalyses and mass spectrometry

Microanalyses were obtained from the Department of Chemistry, University College, London, and the University of Edinburgh. Fast atom bombardment (FAB) mass spectra were obtained at the School of Pharmacy, University of London on a VG Analytical ZAB-SE instrument.

pH Measurements

These were made using a Corning 145 pH meter equipped with an Aldrich micro combination electrode calibrated with standard buffer solutions at pH 4 and 7. Readings of the pH meter for D_2O solutions were not corrected for deuterium isotope effects and are designated as pH* values.

p*K* Determinations

The relative concentrations of species were determined from ^{31}P peak integrals and fitted to the Henderson–Hasselbalch equation using the program KALEIDAGRAPH.[17]

Crystallography

Table 1 summarises the crystal data, data collection, structure solutions and refinement parameters for complexes **1**, **2**, **8**, **9**, **14b** and **18**. The X-ray data for complexes **1**, **14b** and **18** were collected on a Nonius CAD4 diffractometer. The structures were solved by heavy atom methods using SHELXS-97[18] and SHELXL-93.[19] Subsequent refinements were made by the full-matrix least-squares technique on $|F^2|$. Anisotropic displacement parameters were used for non-H-atoms, isotropic for H-atoms in geometrically fixed, riding mode.

X-Ray data for **8** were collected on a Bruker SMART APEX CCD diffractometer. The structure was solved by the Patterson method and refined against F^2 (SHELXTL).[20] Hydrogen atoms attached to O1W were placed using the difference map and refined freely. Other H-atoms were placed in calculated positions and treated using a riding model.

X-Ray data for **2** and **9** were collected on a Stoe Stadi-4 diffractometer. The structures were solved by the Patterson method; structure **2** was refined against F^2 (SHELXTL),[20] and structure **9** was refined against F (CRYSTALS).[21] In structure **2**, one of the two phenyl rings exhibited 50/50 rotational disorder about a common pivot atom (C11). The disorder components were restrained to be similar and have a C_2 axis of symmetry running through the ordered atoms. Partial weight C-atoms were refined with common isotopic thermal parameters for C21/C21′, C31/C31′ *etc*. The assignment of the anion as $[Cl–H–Cl]^-$ was made on the basis of the $Cl\cdots Cl$ distance and the suggestion of a hydrogen position in a ΔF map, this H-atom being subsequently refined freely. Other H-atoms were placed in calculated positions and treated using a riding model. H-atoms on partially occupied H_2O molecules were placed to form favourable H-bonds. In **9** the ligands were restrained to be geometrically similar.

CCDC reference numbers 152973–152978.

See http://www.rsc.org/suppdata/dt/b0/b009117k/ for crystallographic data in CIF or other electronic format.

Preparation of ligands

$H_2NCH_2CH_2PPh_2$. The preparation was based on a literature method.[22] To a suspension of Bu^tOK (8.5 g, 76 mmol) in dry and freshly distilled THF (100 ml), PPh_2H (5 ml, 5.35 g, 28.76 mmol) was added under Ar, and stirred at ambient temperature for 40 min. Then crystalline $H_2NCH_2CH_2Cl\cdot HCl$ (3.24 g, 28.2 mmol) was added and the reaction mixture was heated under reflux for 20 h. During that time the deep-red solution became almost colourless. The solvent was then removed *in vacuo* and 10% HCl solution was added. The solution was then washed with benzene and made alkaline with 10% NaOH solution. The product was then extracted into benzene (3 × 50 ml), washed with brine, and dried over Na_2SO_4. After filtration and rotary evaporation, a colourless viscous liquid was obtained, which was dissolved in ether and purified by passage through a short alumina column. Yield 46%, ^1H NMR ($CDCl_3$): δ 1.51 (2 H, br, s, H_2N), 2.26 (2 H, m, P–CH_2), 2.86 (2 H, m, N–CH_2), 7.1–7.4 (10 H, m, Ph); ^{31}P-{^1H} NMR ($CDCl_3$): δ −21.5. The following compounds were prepared by analogous methods.

$H_2NCH_2CH_2CH_2PPh_2$. Yield 40%, ^1H NMR ($CDCl_3$): δ 1.32 (2 H, br, s, H_2N), 1.43–1.49 (2 H, q, CH_2), 1.91–1.97 (2 H, t, CH_2), 2.62–2.67 (2 H, t, CH_2) 7.17–7.33 (10 H, m, Ph); ^{31}P-{^1H} NMR ($CDCl_3$): δ −21.5.

$Me_2NCH_2CH_2PPh_2$. Yield 40%, ^1H NMR ($CDCl_3$): δ 2.24 (6 H, s, N–CH_2), 2.26–2.28 (2 H, m, P–CH_2), 2.38–2.44 (2 H, m, N–CH_2), 7.31–7.34 (10 H, m, Ph); ^{31}P-{^1H} NMR ($CDCl_3$): δ −19.07.

(c-C_6H_{11})$HNCH_2CH_2PPh_2$. To a cooled solution (0 °C) of (c-C_6H_{11})$HNCH_2CH_2OH$ (14.32 g, 0.1 mol) in $CHCl_3$ (200 ml) thionyl chloride (90.44 g, 60 ml, 0.76 mol) was added dropwise under Ar. The reaction mixture was then heated under reflux for 3 h. The solvent and excess thionyl chloride were removed *in vacuo* to leave a dark-brown oily solid. This was washed with ether and dried over P_2O_5. The product was recrystallised from ethanol–ether to give a shiny whitish crystalline solid of (c-C_6H_{11})$HNCH_2CH_2Cl\cdot HCl$. Yield 70%, (Found: C, 48.76; H, 8.64; N, 6.99. Calc. for $C_8H_{16}Cl_2N$: C, 48.48; H, 8.58; N, 7.07%).

The above compound was then used to prepare (c-C_6H_{11})-$HNCH_2CH_2PPh_2$ in a similar way to that described for the above ligand. Yield 50%, ^1H NMR ($CDCl_3$): δ 1.18–1.26, 1.69–1.86 (11 H, br), 2.26–2.29 (4 H, m), 7.36–7.48 (10 H, m, Ph); ^{31}P-{^1H} NMR ($CDCl_3$): δ −19.92.

(Me)$HNCH_2CH_2PPh_2$. In the first instance (Me)$BzNCH_2$-CH_2OH was prepared as described below. THF (200 ml) was added to ethylene oxide (100 ml, 2.38 mol), obtained by condensation of the gas from a lecture bottle into a 500 ml 3-neck round-bottom flask fitted with a dry ice–acetone condenser,

Table 1 Details of X-ray data collection and refinements for compounds **1**, **2**, **8**, **9**, **14b**, and **18**

Compound	**1**	**2**	**8**	**9**	**14b**	**18**
Empirical formula	$C_{28}H_{38}Cl_2N_2O_3P_2Pt$	$C_{30}H_{40}Cl_4N_2OP_2Pt$	$C_{32}H_{44}Cl_2N_4O_5P_2Pt$	$C_{35}H_{46}Cl_4P_2N_2Pt$	$C_{32}H_{45}ClN_4O_8P_2Pd$	$C_{17}H_{22}Cl_2NPPd$
M	778.49	843.47	892.64	893.61	817.54	448.48
Temperature/K	291(2)	220(2)	150(2)	220(2)	291(2)	293(2)
Space group	$P2_1/n$	$P2_1/n$	$P\bar{1}$	$P2_1/c$	$P2_1/n$	$P2_1/n$
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic
λ/Å	1.54180	0.71073	0.71073	0.71073	1.54180	1.54180
a/Å	9.1827(4)	8.938(4)	9.4849(8)	10.141(1)	12.120(2)	10.128(4)
b/Å	25.826(5)	12.149(4)	11.3914(9)	18.817(2)	12.4800(10)	11.527(4)
c/Å	13.384(3)	15.7788(5)	17.8243(15)	20.230(2)	24.400(2)	15.795(6)
α/°			95.7700(10)			
β/°	92.25(1)	99.35(3)	96.9850(10)	101.25(1)	91.838(9)	102.42
γ/°			109.0030(10)			
U/Å^3	3171.6(9)	1691.6(11)	1787.1(3)	3786.31	3688.8(7)	1800.8(12)
Z	4	2	2	4	4	4
D_c/g cm^{-3}	1.618	1.656	1.659	1.57	1.380	1.485
μ/mm^{-1}	11.027 (Cu-Kα)	4.584 (Mo-Kα)	4.209 (Mo-Kα)	4.14 (Mo-Kα)	5.904(Cu-Kα)	12.593(Cu-Kα)
F(000)	1520	836	892	1777.39	1576	796
Scan mode	ω–2θ	ω–θ	ψ and ω scans	ω–θ	ω–2θ	ω–2θ
Crystal size/mm	0.42 × 0.25 × 0.18	0.27 × 0.16 × 0.12	0.38 × 0.10 × 0.05	0.16 × 0.16 × 0.04	0.2 × 0.3 × 0.4	0.3 × 0.3 × 0.4
Colour, habit	White, needles	Colourless, block	Colourless, lath	Colourless, tablet	White, needles	Colourless, needles
θ range/°	3.42–71.82	2.61–25.01	1.91–26.38	2.50–25.00	3.62–73.91	4.76–73.89
h, k, l ranges	−11–0, 0–31, −16–16	−10–10, 0–14, 0–18	−11–11, −14–14, −22–22	−12–11, 0–22, 0–24	−15–15, 0–15, 0–30	0–12, −14–0, −19–19
Reflections collected	6631	3783	12153	11044	7648	3873
Independent reflections (R_{int})	6239 (0.0564)	2980 (0.0445)	7160 (0.0261)	6096 (0.05)	7473 (0.0633)	3663 (0.0312)
Data/restraints/parameters	6236/0/308	2970/32/180	7160/0/423	4543/0/398	7424/0/468	3663/0/225
Goodness of fit on F^2	1.089	1.087	0.940	1.0742	0.921	1.010
Final R indices $R1$, $wR2$	0.0535, 0.1546	0.0528, 0.1475	0.0296, 0.0669	0.0530, 0.0547	0.0751, 0.2114	0.0443, 0.1208
Maximum Δ/σ	0.0	0.1	0.001	0.078326	0.001(1)	0.001(1)

and the reaction mixture was kept at 0 °C. To this cold mixture, $PhCH_2NH(Me)$ (15 ml, 0.12 mol) was added dropwise. The reaction was then initiated by the addition of $ZnBr_2$ (1 g) and was left stirring overnight at ambient temperature. The solvent was removed *in vacuo* and the residual oil distilled (100–107 °C, 2 mm Hg) to give $(Me)BzNCH_2CH_2OH$. Yield 55%, ^1H NMR ($CDCl_3$): δ 2.18, (3 H, s, CH_3), 3.43 (2 H, t, O–CH_2), 3.58 (2 H, t, N–CH_2) 7.18–7.25 (5 H, m, Ph); ^{13}C-{^1H} NMR ($CDCl_3$): δ 41.57 (CH_3), 58.49 (N–CH_2), 62.29 (O–CH_2), 127.13 (*para*), 128.6 (*ortho*), 128.93 (*meta*), 138.54.

A solution of $(Me)BzNCH_2CH_2OH$ (10 g, 0.06 mol) in 98% ethanol (20 ml) was placed in a bomb at ambient temperature and 2–3 atm in a standard hydrogenation set-up, in the presence of 2 g of 5% palladium on carbon. The hydrogenolysis was complete in about 2 h. The catalyst was then removed by filtration and the solvent removed on a rotary evaporator to leave a slightly yellowish oil. This was distilled (30–32 °C, 1 mm Hg) to give $(Me)HNCH_2CH_2OH$ as a colourless oil. Yield 67%, ^1H NMR ($CDCl_3$): δ 2.48, (3 H, s, N–CH_3), 2.69 (2 H, t, CH_2), 3.42 (br, NH) 3.61 (2 H, t, CH_2); ^{13}C-{^1H} NMR ($CDCl_3$): δ 35.97, 53.95, 60.44. ν_{max}/cm^{-1} 3641, 1060 (OH), 3294, 1688, 1656 (NH).

It was then chlorinated in the usual manner to give $(Me)HNCH_2CH_2Cl{\cdot}HCl$ in 95% yield. (Found: C, 27.56; H, 7.01; N, 10.57. Calc. for $C_3H_9Cl_2N$: C, 27.69; H, 6.92; N, 10.77%). The above salt was then used to prepare $(Me)HNCH_2CH_2PPh_2$ using a similar procedure to that described earlier. Yield 30%, ^1H NMR ($CDCl_3$): δ 2.34 (2 H, m, CH_2) 2.81 (6 H, s, N–CH_3), 3.12 (2 H, m, CH_2) 3.6 (2 H, t, CH_2), 7.36–7.48 (10 H, m, Ph); ^{31}P-{^1H} NMR ($CDCl_3$): δ −19.97.

$(Bz)HNCH_2CH_2PPh_2$. The hydrochloride salt $(Bz)HNCH_2CH_2Cl{\cdot}HCl$ was prepared from $(Bz)HNCH_2CH_2OH$ in the usual manner. Yield 81%, mp 197 °C (dec.) (Found: C, 52.53; H, 6.40; N, 6.79. Calc. for $C_9H_{13}Cl_2N$: C, 52.42; H, 6.31; N, 6.79%). ^1H NMR ($CDCl_3$): δ 3.46 (2 H, m) 3.84 (2 H, m), 4.25 (2 H, s) 7.46 (6 H, s).

The preparation of $(Bz)HNCH_2CH_2PPh_2$ was carried out in the usual fashion, but the work-up was modified as follows. After the THF was removed *in vacuo*, addition of 20% HCl solution gave rise to a whitish solid that was filtered off, redissolved in $CHCl_3$ and filtered to remove the insoluble impurities. The solvent was removed on a rotary evaporator to leave a whitish powder, which was recrystallised from methanol–ether to give shiny white crystals. Yield 84%, (Found: C, 70.41; H, 6.44; N, 4.14. Calc. for $C_{21}H_{23}ClNP$: C 70.88; H, 6.46; N, 3.93%). ^1H NMR ($CDCl_3$): δ 2.59 (m) 2.82 (s, br) 3.8 (s, br) 7.4–7.62 (Ph) 10.09 (NH); ^{31}P-{^1H} NMR ($CDCl_3$): δ −20.33.

The following were also prepared analogously.

$(Bz)MeNCH_2CH_2PPh_2$. $(Bz)MeNCH_2CH_2OH$ was chlorinated to give $(Bz)MeNCH_2CH_2Cl{\cdot}HCl$ as a whitish solid in 95% yield. mp 144 °C. (Found: C, 54.85; H, 7.04; N, 5.97. Calc. for $C_{10}H_{15}Cl_2N$: C, 54.54; H, 6.81; N, 6.36%). This was then used to prepare $(Bz)MeNCH_2CH_2PPh_2$ with a yield of 45%. ^1H NMR ($CDCl_3$): δ 2.5 (s, br) 3.2–3.50 (m, br) 3.9–4.4 (m, br) 7.1–7.92 (Ph); ^{31}P-{^1H} NMR ($CDCl_3$): δ −19.00.

$(Bz)_2NCH_2CH_2PPh_2$. This was prepared as above in 66% yield. mp 105 °C. (Found: C, 72.25; H, 6.84; N, 3.34. Calc. for $C_{28}H_{28}NP{\cdot}3H_2O$: C, 72.41; H, 7.32; N, 3.03%). ^1H NMR ($CDCl_3$): δ 2.59 (m) 2.87 (m) 4.06, 4.27 (m) 7.19–7.77 (Ph); ^{31}P-{^1H} NMR ($CDCl_3$): δ −19.59.

$Me_2NCH_2CH_2CH_2PPh_2$. To a mixture of 37% HCOH (37 g, 0.46 mol) and 98% HCOOH (27 g, 22 ml, 0.57 mol), $H_2NCH_2CH_2CH_2Cl{\cdot}HCl$ (10 g, 0.076 mol) was added and the reaction mixture heated under reflux for 30 h. The light brown solution was made alkaline with 10% NaOH, extracted with CH_2Cl_2 (3 × 50 ml) and dried over Na_2SO_4. The solvent was then removed *in vacuo* to leave a brownish liquid, to which ethanolic hydrogen chloride (20 ml) was added. The solvent was then removed *in vacuo* to leave a brownish oil which was dissolved in hot propan-2-ol. The precipitate obtained after addition of ether was filtered, and washed with ether to give a whitish highly hygroscopic solid ($Me_2NCH_2CH_2CH_2Cl{\cdot}HCl$). Yield 30%, ^1H NMR ($CDCl_3$): δ 2.81 (6 H, s, N–CH_2) 3.6 (2 H, t, CH_3), 2.34 (2 H, m, CH_2) 3.12 (2 H, m, CH_2).

$Me_2NCH_2CH_2CH_2Cl{\cdot}HCl$ was then used to prepare the above ligand as described earlier. Yield 38%, ^1H NMR ($CDCl_3$): δ 1.44–1.53 (2 H, m) 1.93–1.99 (2 H, m, CH_2), 2.05 (6 H, N–CH_3) 2.21–2.26 (2 H, t, CH_2) 7.17–7.21, 7.24–7.35 (10 H, m, Ph); ^{31}P-{^1H} NMR ($CDCl_3$): δ −19.33.

Preparation of platinum complexes

$[Pt(H_2NCH_2CH_2PPh_2)_2]Cl_2{\cdot}3H_2O$ 1. A solution of $H_2NCH_2CH_2PPh_2$ (0.2 g, 0.26 mmol) in CH_2Cl_2 (2 ml) was added dropwise to a clear solution of $(COD)PtCl_2$ (0.093 g, 0.26 mmol) in CH_2Cl_2 (25 ml) and the reaction mixture was stirred at ambient temperature for 1 h. The volume was then reduced to *ca.* 7 ml and diethyl ether was added to precipitate a whitish powder which was then filtered off and washed with diethyl ether and recrystallised from acetone–dichloromethane.

Yield 86%, mp 235 °C (dec.) (Found: C, 43.33; H, 4.80; N, 3.44; Cl, 9.62. Calc. for $C_{28}H_{32}Cl_2N_2P_2Pt{\cdot}3H_2O$: C, 43.18; H, 4.88; N, 3.59; Cl, 9.12%). *m*/*z* (FAB MS): 652 (100%, $M^+ - 2Cl$). ^1H NMR ($CDCl_3$) δ 2.71–2.77 (2 H, m, N–CH_2), 3.02–3.07 (2 H, m, P–CH_2), 7.25 (H_2N, br, s, ^2J(PtH) 42 Hz), 7.25–7.53 (10 H, Ph); ^{31}P-{^1H} NMR ($CDCl_3$): δ 33.70 ^1J(PtP) 3300 Hz; ^{195}Pt-{^1H} NMR ($CDCl_3$): δ −4589 ^1J(PtP) 3344 Hz.

The following complexes were also prepared in a similar manner.

$[Pt(H(Me)NCH_2CH_2PPh_2)_2][Cl–H–Cl]_2{\cdot}H_2O$ 2. Yield 71% (Found: C, 43.80; H, 4.82; N, 3.30. Calc. for $C_{30}H_{38}Cl_6N_2P_2Pt{\cdot}H_2O$: C, 42.70; H, 4.74; N, 3.32%).^1H NMR ($CDCl_3$) δ 2.78 (2H, br), 3.05 (N–Me), 3.35 (2H, br), 6.5 (NH) 7.3–7.6 (10 H, Ph); ^{31}P-{^1H} NMR (D_2O, pH* 3.85): δ 28.9 ^1J(PtP) 3300 Hz, ^{195}Pt-{^1H} NMR ($CDCl_3$): δ −4575 ^1J(PtP) 3330 Hz. Crystals suitable for X-ray structure determination were obtained by recrystallisation from H_2O–EtOH (1 : 1).

$[PtCl((c\text{-}C_6H_{11})HNCH_2CH_2PPh_2)_2]Cl{\cdot}4H_2O$ 3. Yield 81% (Found: C, 49.56; H, 6.15; N, 2.87. Calc. for $C_{40}H_{52}Cl_2N_2P_2Pt{\cdot}4H_2O$: C, 49.94; H, 6.25; N, 2.91%). ^{31}P-{^1H} NMR ($CDCl_3$): δ 36.45, ^1J(PtP) 3294; ^{195}Pt-{^1H} NMR ($CDCl_3$): δ −4538 (t) ^1J(PtP) 3233 Hz. A $CHCl_3$ solution of the crude product of the above compound was left at 4 °C for about 10 h after which time crystals formed. These were filtered off and dried to give the monochelate complex $[Pt((c\text{-}C_6H_{11})HNCH_2CH_2PPh_2)Cl_2]$ as a minor product (*ca.* 5%). (Found: C, 41.10; H, 4.49; N, 2.22. Calc. for $C_{20}H_{26}Cl_2NPPt$: C, 41.59; H, 4.50; N, 2.42%). ^{31}P-{^1H} NMR ($CDCl_3$): δ 24.81 ^1J(PtP) 4064 Hz.

$[Pt(H(Bz)NCH_2CH_2PPh_2)_2]Cl_2$ 4. Yield 46% (Found: C, 51.74; H, 5.08; N, 2.81. Calc. for $C_{42}H_{44}Cl_2N_2P_2Pt$: C, 51.60; H, 4.74; N, 2.87%). ^1H NMR ($CDCl_3$) δ 2.55, 2.88, 3.1, 3.9, 3.5, 7.0–7.60, (15 H, Ph); 10.09 (NH) ^{31}P-{^1H} NMR ($CDCl_3$): δ 30.3 ^1J(PtP) 3420 Hz, 40.0 ^1J(PtP) 3800 Hz, 5.0 ^1J(PtP) 3348 Hz.

$[PtCl(Me_2NCH_2CH_2PPh_2)_2]Cl{\cdot}HCl$ 5b. Yield 90%, mp 194 °C (dec.) (Found: C, 47.63; H, 4.99; N, 3.26; Cl, 12.75; P, 8.1. Calc. for $C_{32}H_{40}Cl_2N_2P_2Pt{\cdot}HCl$: C, 47.03; H, 5.02; N, 3.42; Cl, 13.04; P, 7.59%). *m*/*z* (FAB MS): 745 (100%, $M^+ - Cl$). ^1H NMR ($CDCl_3$) δ 2.15 (s), 2.17–2.20 (s, br), 2.70–2.79 (s, br), 3.01–3.15 (s, br), 7.16–7.49 (10 H, Ph); ^{31}P-{^1H} NMR ($CDCl_3$): δ 36.52 ^1J(PtP) 3691 Hz, −0.46 ^1J(PtP) 3187 Hz; ^{195}Pt-{^1H} NMR ($CDCl_3$): δ −4505 (dd).

$[Pt(Me(Bz)NCH_2CH_2PPh_2)_2]Cl_2$ 6. Yield 83% (Found: C, 56.98; H, 5.13; N, 2.91. Calc. for $C_{44}H_{48}Cl_2N_2P_2Pt$: C, 56.65; H, 5.15; N, 3.00%). ^1H NMR ($CDCl_3$) δ 1.8 (s, br), 2.16 (m, br), 2.46 (s, br), 3.44 (s, br) 7.1–7.9 (15 H, Ph); $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 30.69 $^1J(PtP)$ 3754 Hz, −0.06 $^1J(PtP)$ 3184 Hz, $^2J(P_BP_C)$ 17 Hz.

$[Pt((Bz)_2NCH_2CH_2PPh_2)_2]Cl_2$ 7. Yield 81% (Found: C, 61.54; H, 5.15; N, 2.40. Calc. for $C_{56}H_{56}Cl_2N_2P_2Pt$: C, 61.99; H, 5.16; N, 2.58%). ^1H NMR ($CDCl_3$) δ 1.18 (s, br), 2.16 (s, br), 2.46 (s, br), 3.44 (s, br) 7.1–7.9 (20 H, Ph); $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 4.5 $^1J(PtP)$ 3635 Hz.

$[Pt(H_2NCH_2CH_2CH_2PPh_2)_2]Cl_2$ 8. Yield 50%, mp 235 °C (dec.) (Found: C, 43.24; H, 5.52; N, 2.93. Calc. for $C_{30}H_{36}Cl_2N_2P_2Pt\cdot 4H_2O$: C, 43.68; H, 5.33; N, 3.39%). *m*/*z* (FAB MS): 680 (100%, $M^+ - 2Cl$). ^1H NMR ($CDCl_3$) δ 1.84–1.99 (2 H, m), 2.60–2.69 (2 H, m), 3.18–3.20 (2H, m), 6.06–6.21 (br, H_2N, $^2J(PtH) = 44.7$ Hz), 7.20–7.53 (10 H, Ph); $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ −3.77 $^1J(PtP)$ 3287 Hz. $^{195}Pt\text{-}\{^1H\}$ NMR ($CDCl_3$): δ −4455 (t). Crystals suitable for X-ray structure determination were obtained by recrystallisation from CH_3NO_2 solution as **8**$\cdot H_2O\cdot 2CH_3NO_2$.

$[PtCl_2(Me_2NCH_2CH_2CH_2PPh_2\text{-}P)_2]$ 9. Yield 55%, mp 235 °C (dec.) (Found: C, 49.59; H, 5.27; N, 3.37. Calc. for $C_{34}H_{44}Cl_2N_2P_2Pt$: C, 49.39; H, 5.56; N, 3.38%). *m*/*z* (FAB MS): 773 (100%, $M^+ - Cl$). ^1H NMR ($CDCl_3$) δ 1.71–1.73 (2 H, m), 2.11 (6 H, s), 2.16–2.11 (2 H, m) 2.26–2.32 (2 H, m), 7.25–7.53 (10 H, Ph); $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 8.18 $^1J(PtP)$ 3640 Hz. $^{195}Pt\text{-}\{^1H\}$ NMR ($CDCl_3$): δ −4408 (t) $^1J(PtP)$ 3642 Hz. Crystals suitable for X-ray structure determination were obtained by recrystallisation from a CH_2Cl_2–Et_2O mixture as **9**$\cdot CH_2Cl_2$.

$[PtCl(Me_2NCH_2CH_2CH_2PPh_2)_2]Cl$ 9b. To a solution of $[PtCl_2(Me_2NCH_2CH_2CH_2PPh_2)_2]$ (0.1 g, 0.12 mmol) in $CHCl_3$ (20 ml) $AgBF_4$ (0.024 g, 0.12 mmol) was added and the reaction mixture stirred at room temperature for 10 minutes in the dark. The milky suspension was then filtered. To this solution Et_2O was added to initiate recrystallisation. Storage of the solution at 4 °C resulted in the formation of yellowish crystals of $[PtCl(Me_2NCH_2CH_2CH_2PPh_2)_2]BF_4$ in 95% yield. $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 7.95 $^1J(PtP)$ 3761 Hz, 4.85 $^1J(PtP)$ 3199 Hz.

The preparation of palladium complexes

The palladium complexes were prepared in an analogous way to the platinum complexes.

$[Pd(H_2NCH_2CH_2PPh_2)_2]Cl_2$ 10. Yield 95%. Recrystallised from acetone–dichloromethane (Found: C, 49.05; H, 5.22; N, 4.07. Calc. for $C_{28}H_{32}Cl_2N_2P_2Pd\cdot 3H_2O$: C, 48.76; H, 5.51; N, 4.06%). *m*/*z* (FAB MS): 599 (20% $M^+ - 2Cl$), 563 (100% $M^+ - Cl$). ^1H NMR ($CDCl_3$) δ $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 55.80.

$[Pd(H(Me)NCH_2CH_2PPh_2)_2]Cl_2\cdot 6H_2O$ 11. Yield 71%. (Found: C, 46.80; H, 5.20; N, 4.00. Calc. for $C_{30}H_{36}Cl_2N_2P_2Pd\cdot 6H_2O$: C, 46.69; H, 5.96; N, 3.63%). $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 52.55.

$[Pd((c\text{-}C_6H_{11})HNCH_2CH_2PPh_2)_2]Cl_2\cdot H_2O$ 12. Yield 78%. Recrystallised from ether–dichloromethane (Found: C, 57.65; H, 6.68; N, 3.35. Calc. For $C_{40}H_{52}Cl_2N_2P_2Pd\cdot H_2O$: C, 57.48; H, 6.46; N, 3.35%). $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 54.4 (br).

$[Pd(H(Bz)NCH_2CH_2PPh_2)_2]Cl_2\cdot HCl\cdot 2H_2O$ 13. Yield 46% (Found: C, 56.91; H, 5.62; N, 2.87. Calc. for $C_{42}H_{44}Cl_2N_2P_2Pd\cdot HCl\cdot 2H_2O$: C, 56.78; H, 5.52; N, 3.15%). $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 60.5, 22.5, $^2J(PP)$ 13 Hz.

$[Pd(Me_2NCH_2CH_2PPh_2)_2]Cl_2$ 14a. Yield 90%. Recrystallised from acetone–dichloromethane (Found: C, 53.76; H, 5.60; N, 4.04. Calc. For $C_{32}H_{40}Cl_3N_2P_2Pd\cdot H_2O$: C, 54.16; H, 5.92; N, 3.94%). ^1H NMR ($CDCl_3$) δ 1.71–1.73 (2 H, m), 2.11 (6 H, s), 2.16–2.11 (2 H, m) 2.26–2.32 (2 H, m), 7.25–7.53 (10 H, Ph); $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 50.0 (broad, $\Delta\nu_{1/2}$ 186 Hz).

$[PdCl(Me_2NCH_2CH_2PPh_2)_2]Cl$ 14b. To a solution of $[Pd(Me_2NCH_2CH_2PPh_2)_2]Cl_2$ (30 mmol), was added HNO_3 to lower the pH to *ca.* 2. After a few hours at ambient temperature, crystals of *cis*-$[Pd(Me_2N(CH_2)_2PPh_2\text{-}N,P)Cl(Me_2NH(CH_2)_2PPh_2\text{-}P](NO_3)_2\cdot 2H_2O$ formed which were suitable for X-ray structure determination. $^{31}P\text{-}\{^1H\}$ NMR (D_2O, pH* 4.5): δ 58.90, 23.55.

$[Pd(Me(Bz)NCH_2CH_2PPh_2)_2]Cl_2\cdot 2HCl$ 15. Yield 83%. (Found: C, 53.07; H, 5.41; N, 3.00. Calc. for $C_{44}H_{48}Cl_2N_2P_2Pd\cdot 2HCl$: C, 53.47; H, 5.06; N, 2.83%). $^{31}P\text{-}\{^1H\}$ NMR (D_2O–EtOD-d_6): δ 14.60.

$[Pd((Bz)_2NCH_2CH_2PPh_2)_2]Cl_2\cdot 2HCl$ 16. Yield 81% (Found: C, 62.02; H, 5.44; N, 2.44. Calc. for $C_{56}H_{56}Cl_2N_2P_2Pd\cdot 2HCl$: C, 62.80; H, 5.42; N, 2.61%). $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 13.5.

$[Pd(H_2NCH_2CH_2CH_2PPh_2)_2]Cl_2$ 17. Yield 70%. Recrystallised from acetone–dichloromethane (Found: C, 50.32; H, 5.77; N, 3.82. Calc. for $C_{30}H_{36}Cl_2N_2P_2Pd\cdot 3H_2O$: C, 50.20; H, 5.85; N, 3.90%). *m*/*z* (FAB MS): 628 (28% $M^+ - Cl$), 591 (62% $M^+ - 2Cl$). ^1H NMR ($CDCl_3$) δ 1.7–1.8 (2 H, br, m), 2.5–2.66 (2 H, br, m) 3.14–3.16 (m, br), 5.62 (NH_2, br), 7.20–7.57 (10 H, m, Ph); $^{31}P\text{-}\{^1H\}$ NMR ($CDCl_3$): δ 20.0.

$[PdCl_2(Me_2NCH_2CH_2CH_2PPh_2)]$ 18. Yield 88%. Recrystallised from acetone–dichloromethane (Found: C, 45.62; H, 4.94; N, 3.02. Calc. For $C_{17}H_{22}Cl_2NPPd$: C, 45.63; H, 4.91; N, 3.13%). *m*/*z* (FAB MS): 450 (10% M^+), 414 (21% $M^+ - Cl$) 376 (30% $M^+ - 2Cl$). ^1H NMR (CD_2Cl_2–DMF-d_7) δ 2.08 (2 H, m), 2.53 (2 H, m) 2.98 (2H, s), 3.43 (6 H, s), 7.52–7.63 (10 H, m, Ph); $^{31}P\text{-}\{^1H\}$ NMR (CD_2Cl_2–DMF-d_7): δ 16.76.

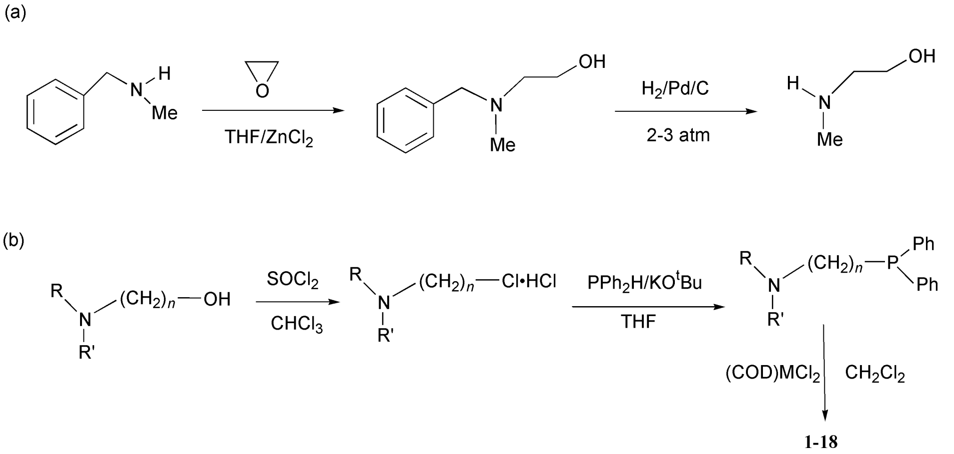
Results and discussion

Preparation and properties of ligands

A number of methods have been reported for the preparation of aminophosphine ligands.[4–7,22] In the present work, the most convenient starting materials were aminoalcohols, a large number of which are either available commercially or can be prepared by the reduction of amino acids.[22–28] The aminoalcohol, $H(Me)NCH_2CH_2OH$ was prepared as shown in Scheme 2a. Chlorination of the aminoalcohol followed by reaction with the diphenylphosphine anion afforded the required ligand (Scheme 2b). The ligands were obtained as viscous oils except for $Bz(R)NCH_2CH_2PPh_2$ (R = H, Me or Bz), which were obtained as the hydrochloride salts. The oily ligands were readily purified by passing solutions in ether through a short alumina column and the salts were recrystallised from methanol–ether. The ^1H NMR spectra of the ligands in $CDCl_3$ showed the expected peaks with the backbone CH_2 appearing as triplets and the NH_2 as broad peaks in the region of 1–2 ppm. The ^{31}P NMR spectra showed single resonances in the region of −19 to −21 ppm.

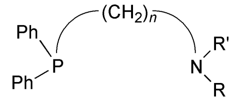
Synthesis and characterisation of Pt(II) and Pd(II) complexes

The Pt(II) and Pd(II) complexes were characterised by FAB mass spectrometry, ^1H, ^{31}P, ^{195}Pt, ^{13}C NMR and IR spectroscopies, and elemental analysis. X-Ray crystal structures were obtained for complexes **1**, **2**, **8**, **9**, **14b** and **18** (see Table 2 for definitions of complexes). The ^{31}P NMR spectra showed coordination shifts ranging from 65 ppm to 18 ppm downfield for



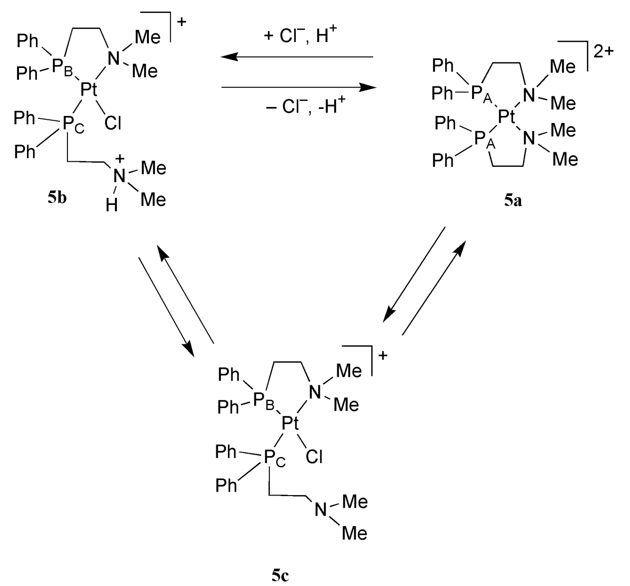
Scheme 2 Preparation of (a) $H(Me)NCH_2CH_2OH$ and (b) aminophosphines and complexes.

Table 2 Complexes prepared in this work. All have a 2 : 1 ligand-to-metal ratio except **18** (1 : 1). See Scheme 1 for different coordination modes adopted by the complexes



Complex number		Substituents		
M = Pt	M = Pd	R	R′	Linker *n*
1[a]	**10**	H	H	2
2[a]	**11**	H	Me	2
3	**12**	H	c-C_6H_{11}	2
4	**13**	H	Bz	2
5a[b]	**14a**	Me	Me	2
5b	**14b**[a,c]			
6	**15**	Me	Bz	2
7	**16**	Bz	Bz	3
8[a]	**17**	H	H	3
9[a]	**18**[a]	Me	Me	3
9b[b]				

[a] X-Ray structure determined. [b] Prepared by reacting **5b** with $AgNO_3$ or **9** with $AgBF_4$ and subsequent removal of AgCl. [c] Prepared by lowering the pH to <4.



Scheme 3 The effect of pH and chloride on chelate ring-opening and closure in **5**.

^{31}P in 5- and 6-membered chelate rings, respectively. Such low-field shifts upon chelation are common for complexes of Pt(II) and Pd(II) phosphines.[29] In the FAB MS spectra, the base peaks were usually [molecular ion − Cl] which has also been found to be the case for similar complexes.[30] The expected isotopic patterns for platinum were also found. The ^{13}C NMR spectra were generally very broad and peaks in the aromatic region were difficult to assign. Remarkably, most of the complexes were generally soluble in water as well as in common organic solvents.

Complex **1**, *cis*-$[Pt(H_2N(CH_2)_2PPh_2\text{-}P,N)_2]Cl_2$, is a water-soluble white solid which decomposes upon heating at about 250 °C. The FAB MS spectrum had a base peak of 652 ($M^+ - 2Cl$) with the expected isotopic pattern for platinum. The ^1H NMR spectrum in $CDCl_3$ indicated that the resonances of the CH_2 groups were broad multiplets and the NH_2 peak was at δ 7.25 with a ^2J(PtH) of 42 Hz. This is a large downfield shift from the free ligand at δ 1.51 indicative of N coordination and the formation of 5-membered chelate rings. The ^{31}P NMR spectrum (Table 3) showed a single peak at δ 33.7 (P_A, for atom labelling see Scheme 3) with a co-ordination shift of 55 ppm, consistent with the formation of a bis-chelated complex.[29] The coupling constant $^1J(PtP_A)$, of 3300 Hz is typical of ^{31}P *trans* to nitrogen.[31–33] The ^{195}Pt NMR spectrum also showed a triplet at δ −4589 confirming the bis-chelated nature of the complex. The ^1H and ^{31}P NMR spectra in D_2O were similar to those from $CDCl_3$ solutions. The Pd analogue, **10**, *cis*-$[Pd(H_2NCH_2CH_2PPh_2\text{-}P,N)_2]Cl_2$, was also shown by ^{31}P NMR to exist in a ring-closed form in both $CDCl_3$ and D_2O, and, as for the Pt analogue, it remained ring-closed even under highly acidic conditions (pH < 2).

The FAB MS spectrum of **5b** had a base peak at 745 ($M^+ - Cl$). The elemental analysis showed that the complex was isolated as the hydrochloride salt suggesting that one of the amino groups is protonated and thus the complex exists in a ring-opened form (*cis*-$[Pt(Me_2N(CH_2)_2PPh_2\text{-}N,P)Cl(Me_2NH(CH_2)_2PPh_2\text{-}P)]Cl_2$) in the solid state. The ^{31}P NMR spectrum in $CDCl_3$ (Table 3) showed two resonances: a peak at δ 36.5 assignable to P in a P,N chelate ring (P_B) and at δ −0.46 assignable to P in a P-bound ring-opened ligand (P_C) (for atom labelling see Scheme 1). The respective ^1J(PtP) couplings were 3691 and 3187 Hz, which are values typical of P *trans* to Cl and N, respectively.[31–33] The corresponding co-ordination shifts were 55 ppm for P_B and 19 ppm for P_C. The peaks were relatively broad and did not show any doublet splitting due to $^2J(P_BP_C)$. The ^{31}P NMR data thus show that the ring-opened species is also the preferred form of the complex in solution ($CDCl_3$). The inequivalence of the two phosphorus atoms was also confirmed from the ^{195}Pt NMR spectrum, which showed a doublet of doublets centred at δ −4505. The ^1H NMR spectrum in $CDCl_3$ showed the expected peaks, albeit very broad ones. The broadening may arise from an exchange process involving chelate ring-closing and opening. This was even more

Table 3 ^{31}P NMR data for complexes **1–18** and p*K* values for ring-opening determined from pH* titrations

	Chemical shifts[a] (^1J(PtP)/Hz)					
Complex	δ(P$_A$)	δ(P$_B$)	δ(P$_C$)	δ(P$_D$)	pH*	p*K*
1[c]	33.7(3300)	—	—	—	—	<1
2[c]	28.9(3300)	—	—	—	3.85	2.1
	—	41.1(3770)	1.9(3300)	—	<2	
3[d]	—	38.89(3783)	0.5(3239)	—	4	6.3
3	36.45(3294)	—	—	—	—	—
4	30.3(3420)	40.0(3880)	5.0(3348)	—	—	—
5b	—	36.5(3691)	−0.46(3187)	—	—	—
5b[c]	25.25(3294)	36. 5(3792)	−0.06(3128)	—	8.6	6.9
	—	36.5(3792)	−0.06(3128)	—	5.0	
5a[c]	25.5(3225)	—	—	—	8.6	*ca.* 2
	—	25.3(4008)[b]	−1.96(3298)	—	2.0	
6	—	30.7(3754)	−0.06(3184)	—	—	—
7	—	—	—	4.50(3635)	—	—
8[c]	−1.88(3199)	—	—	—	6.5	2.9
	—	0.55(3625)	4.24(3272)	—	1	
8	−3.77(3287)	—	—	—	—	—
9	—	—	—	8.18(3640)	—	—
9b	—	7.95(3761)	4.85(3199)	—	—	—
10	55.50	—	—	—	—	—
11	52.55	—	—	—	—	—
12	54.44	—	—	—	—	—
13	—	60.5	22.5	—	—	—
14a	50.0	—	—	—	—	—
14b[c]	50.48	—	—	—	8.6	6.0
	—	58.9	23.55	—	4.5	
15[d]	—	—	—	14.6	—	—
16	—	—	—	13.5	—	—
17	20.0	—	—	—	—	—
18[e]	16.76	—	—	—	—	—

[a] See Scheme 1 for atom labelling. (P$_A$ = P in bis chelate, *trans* to N; P$_B$ = P in P,N chelate-ring, *trans* to Cl; P$_C$ = P in P-bound, ring-opened ligand, *trans* to N; P$_D$ = P in P-bound ring-opened ligand, *trans* to Cl). Solvent CDCl$_3$ unless otherwise stated. [b] *trans* to OH$_2$. [c] D$_2$O. [d] D$_2$O–EtOD-d$_6$. [e] CD$_2$Cl$_2$–DMF-d$_7$.

evident in the ^{13}C NMR spectrum, in which the ethylene carbons were so broad that they were difficult to observe.

The ^{31}P NMR spectrum of **6** in CDCl$_3$ showed that it exists exclusively as a mono-ring-opened species, *cis*-[Pt(Bz(Me)N-(CH$_2$)$_2$PPh$_2$-*N*,*P*)Cl(Bz(Me)N(CH$_2$)$_2$PPh$_2$-*P*)]Cl. In contrast to **5b**, the peaks were sharp doublets: doublets at δ 30.7 (P$_B$) and −0.06 (P$_C$) with the corresponding ^1J(PtP) values of 3754 and 3184 Hz, respectively. The doublet splitting can be assigned to a ^2J(P$_B$P$_C$) coupling of 17 Hz. The sharpening of the peaks suggest the absence of an exchange process involving chelate ring-closing and -opening under these conditions.

Complex **5b** dissolves readily in water. The ^{31}P NMR spectrum of the solution in D$_2$O (Fig. 1a, pH* 8.56), in contrast to the spectrum recorded in CDCl$_3$, showed two sets of peaks. There was a broad singlet at δ 25.25 (P$_A$) with a ^1J(PtP$_A$) value of 3294 Hz, assignable to a bis-chelated (ring-closed) form of the complex, and singlets at δ 36.5 (P$_B$) and −0.06 (P$_C$) with ^1J(PtP) couplings of 3792 and 3128 Hz, respectively, assignable to the ring-opened form. The ratio of ring-closed to ring-opened species was 2:1. The ^{195}Pt NMR spectrum showed a doublet of doublets centred at δ −4505 for the ring-opened species, with splitting due to two inequivalent P atoms, and a triplet centred at δ −4653 corresponding to the bis-chelated species. Thus in aqueous solution the two forms of the complex exist in equilibrium. The position of the equilibrium was found to be dependent upon pH and chloride concentration, and is further discussed in the next section.

The ^{31}P NMR spectrum of the palladium analogue, **14a**, *cis*-[Pd(Me$_2$N(CH$_2$)$_2$Ph$_2$-*P*,*N*)$_2$]Cl$_2$, in CDCl$_3$ showed a single peak at δ 50.0 (P$_A$) with a co-ordination shift of 70 ppm. The peak was broad with a width at half height ($\Delta\nu_{1/2}$) of 186 Hz. The spectrum of **14a** recorded in D$_2$O (pH, 8.6), showed a very broad single peak at δ 50.5 ($\Delta\nu_{1/2}$ 1656 Hz). The broadening suggested that exchange between the ring-opened and ring-closed species was occurring. It was, however, possible to isolate the ring-opened form of the complex (**14b**) at low pH (*ca.* 4). The X-ray crystal structure of the ring-opened species and the pH dependence of the chelate ring-opening and -closing processes are discussed further below.

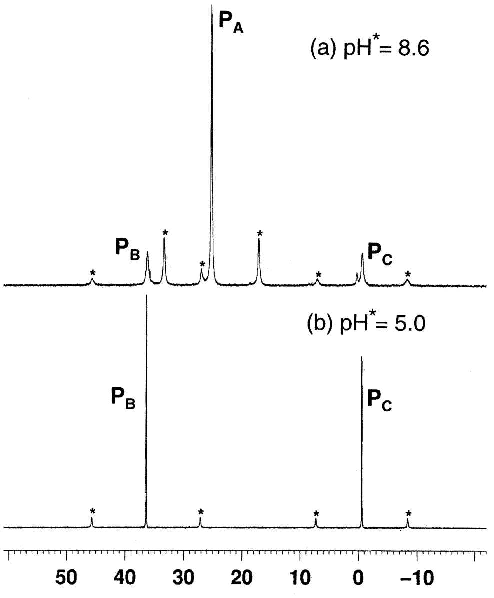


Fig. 1 ^{31}P-{H} NMR spectra of **5b** in D$_2$O (a) pH* 8.6, (b) pH* 5.0. Assignments: P$_A$ = P in bis-chelate; P$_B$ = P in P,N chelate-ring, P$_C$ = P in P-bound, ring-opened ligand (see Scheme 3). * = ^{195}Pt satellites.

Complex **2** was prepared as shown in Scheme 1 and was isolated as the hydrogen dichloride salt: *cis*-[Pt(Me(H)N-(CH$_2$)$_2$PPh$_2$-*P*,*N*)$_2$]·[HCl$_2$]$_2$. The ^{31}P NMR spectrum in D$_2$O (pH* 3.85) showed a peak at δ 28.9 (P$_A$) with ^1J(PtP$_A$) couplings of 3300 Hz. Complex **2** exists as a ring-closed, bis-chelated complex above pH* 3. The ^{31}P NMR spectrum of **3**, [PtCl((c-C_6H_{11})HN$(CH_2)_2PPh_2)_2$]Cl, in $CDCl_3$ showed a broad single peak at δ 36.45 (P_A) with the $^1J(PtP_A)$ value of 3294 Hz. The ^{195}Pt NMR spectrum showed a triplet centred at δ −4538. There was also a minor product (*ca.* 5%) which was isolated by fractional recrystallization from chloroform and shown to be the mono-chelate complex, *cis*-[Pt(c-C_6H_{11})HN$(CH_2)_2PPh_2$-*N*,*P*)Cl_2], by elemental analysis. The ^{31}P NMR spectrum showed a peak at δ 24.8 with a ^1J(PtP) value of 4064 Hz, consistent with the formation of a monochelate. The ^{31}P NMR spectrum of the palladium analogue, [Pd(c-C_6H_{11})HN$(CH_2)_2$-$PPh_2)_2Cl_2$], **12**, was recorded in different solvents. In D_2O–ethanol the singlet peak was sharp at δ 52.7 (P_A) accompanied by two minor broad peaks at δ 63.0 (P_B) and 22.0 (P_C), whereas in $CDCl_3$ the peak at δ 54.4 (P_A) was very broad, and, in addition, there were two minor peaks at δ 57.6 (P_B) and 33.7(P_C). In both cases the ring-closed form is the major species and the minor peaks correspond to the ring-opened form. Similarly, in CD_2Cl_2, the broad peak at δ 57.9 (P_A) was accompanied by two broad minor peaks centred at δ 63.5 (P_B) and 22.8 (P_C) possibly as a result of traces of HCl in the solvent.

The ^{31}P NMR spectrum of **4** in $CDCl_3$, showed that there were two sets of peaks assignable to the chelate ring-opened complex *cis*-[Pt(BzHN$(CH_2)_2PPh_2$-*N*,*P*)Cl(BzHN$(CH_2)_2$-PPh_2-*P*)]Cl and ring closed complex *cis*-[Pt(BzHN$(CH_2)_2$-PPh_2-*N*,*P*$)_2$]Cl_2. In contrast, the ^{31}P NMR spectrum of **7**, *cis*-[Pt($Bz_2N(CH_2)_2PPh_2)_2$-*P*$)_2Cl_2$], showed a single peak at δ 4.5 (P_D) with $^1J(PtP_D)$ value of 3635 Hz, suggesting that it exists as a di-ring-opened complex co-ordinated through phosphorus only.

The ^{1}H NMR spectrum of *cis*-[Pt($H_2N(CH_2)_3PPh_2$-*P*,*N*$)_2$]-Cl_2, **8**, in $CDCl_3$ showed that the NH_2 peaks had shifted from δ 1.38 for the free ligand to δ 6.14 ($^2J(PtH) = 44.7$ Hz), a shift of 4.72 ppm downfield upon coordination. The ^{31}P NMR spectrum also showed a single peak at δ −3.77 (P_A), with a $^1J(PtP_A)$ value of 3287 Hz, showing that **8** was isolated as a bis-chelated complex. However the ^{31}P NMR spectrum of a solution in D_2O–ethanol showed the expected peaks at δ −3.8 (P_A) with $^1J(PtP_A)$ value of 3336 Hz, which corresponds to the ring-closed form. The ^{195}Pt NMR spectrum of the same sample showed a triplet centred at δ −4455 (P_A) with $^1J(PtP_A)$ value of 3330 Hz. The FAB MS spectrum for *cis*-[Pt($Me_2N(CH_2)_3PPh_2$-*P*$)_2Cl_2$], **9**, showed a base peak at 773 for [molecular ion − Cl]. The ^{31}P NMR spectrum in $CDCl_3$ showed a single peak at δ 8.18 (P_D) with $^1J(PtP_D)$ value of 3640 Hz. Thus the above data show that **9** exists as a di-ring-opened complex. When the complex was reacted with two molar equivalents of $AgBF_4$, it was possible to isolate the mono-chelated (ring-opened) species (**9b**). The ^{31}P NMR spectrum in $CDCl_3$ showed a singlet at δ 7.95 (P_B) with a $^1J(PtP_B)$ value of 3761 Hz and a singlet at δ 4.85 (P_C), with a $^1J(PtP_C)$ value of 3199 Hz.

When two molar equivalents of $Me_2N(CH_2)_3PPh_2$ were reacted with one molar equivalent of (COD)$PdCl_2$ in the usual manner, the only product which could be isolated was the mono-chelated dichloro complex [Pd($Me_2N(CH_2)_3PPh_2$-*P*,*N*)Cl_2], **18**, even when a large excess of the ligand was used. The structure of the product was confirmed by X-ray analysis and the FAB MS spectrum showed a base peak at *m*/*z* 450 which corresponds to the molecular ion.

This series of complexes clearly demonstrates how the steric nature of the substituents on nitrogen as well as the length of the methylene backbone (P–N linker) can determine whether the complex exists in ring-opened or closed forms. Complexes **1** and **10**, which contain only hydrogen substituents on N, exist as ring-closed forms in both $CDCl_3$ and D_2O. As the hydrogen is replaced progressively by more sterically demanding substituents for example in **5b**, in which H is replaced by CH_3, the mono-chelate ring-opened species is favoured in chloroform and an equilibrium exists between the ring-closed and -opened forms in aqueous solution (Fig. 2). In complex **2**, where the substituent on N has a steric bulk between that of **1** and **5b**, it was possible to open the chelate ring only under acidic conditions. In complex **7**, where N has two benzyl substituents, the ligand was co-ordinated *via* the phosphorus atoms only. When the number of methylene carbon atoms in the backbone of the ligand is increased from two to three, together with an increase in the steric bulk on nitrogen, as in **9**, the di-ring-opened species is formed preferentially, chelation being achieved only in the absence of chloride. This illustrates the relatively weak nature of the platinum–nitrogen interaction within the 6-membered chelate rings.

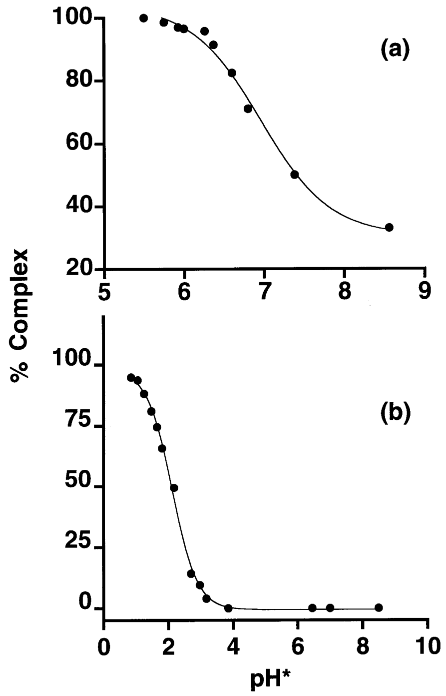


Fig. 2 Plots of the relative amounts of ring-opened complex determined from ^{31}P NMR peak areas *versus* pH*. (a) Complex **5b**. (b) Complex **2**. The curves correspond to computer best fits and p*K* values of 6.9 and 2.1, respectively.

Chelate ring-opening and -closing of complexes in aqueous solution

The equilibrium between the chelate ring-opened and closed forms in aqueous solution as a function of pH and chloride concentration was studied by ^{31}P NMR spectroscopy. The complexes were titrated over a wide pH* range (*ca.* 3–11). For complexes **2**, **3**, **5b**, **8** and **14a**, the p*K* values were determined from computer best fits of plots of the relative amounts of the ring-opened and ring-closed species, as determined by the integration of ^{31}P NMR peaks, *versus* pH* (see Fig. 2). Chelate ring-opening is induced by protonation of amino groups.

The ^{31}P NMR data for complex **5b** in aqueous solution suggest that an equilibrium exists between the ring-opened, **5b**, and ring-closed, **5a**, complexes which is dependent upon pH* and chloride concentrations (Scheme 3). A solution of **5b** (20 mM) in D_2O was titrated over the pH* range 2–11. Under acidic conditions, the amount of ring-opened species, **5b**, increased such that by *ca.* pH* 5.5 it was the only product present. The ^{31}P NMR spectrum at pH* 5 (Fig. 1b) thus shows only one set of doublets, and the peaks were considerably sharper than at higher pH* due to the absence of exchange. The doublet splitting can be assigned to $^2J(P_AP_C)$ coupling of 18 Hz. The reaction was reversible. When the pH* was reversed, a ^{31}P NMR spectrum identical to the original one was obtained. A plot of the relative amounts of the ring-opened and ring-closed species *versus* pH*, is shown in Fig. 2a, and was fitted to a p*K* value of 6.9. Therefore at neutral pH*, the two species exist in

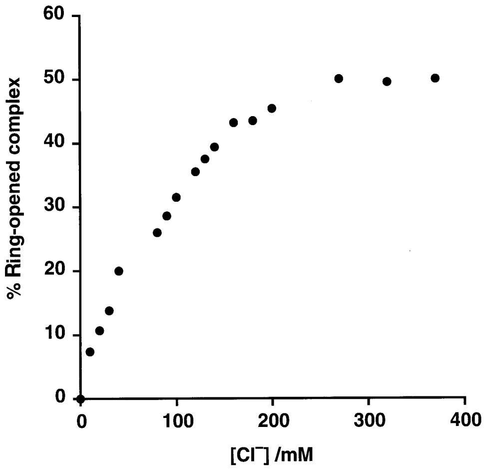


Fig. 3 Dependence of the amount of ring-opened complex **5c** on the concentration of NaCl added to complex **5a**, *cis*-[Pt(Me$_2$N(CH$_2$)$_2$PPh$_2$-*P*,*N*)$_2$](NO$_3$)$_2$ (40 mM, pH* 8.6), as determined from ^{31}P NMR peak areas.

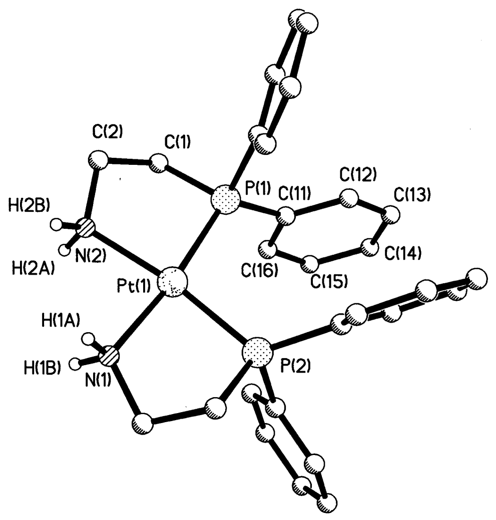


Fig. 4 Crystal structure of the ring-closed complex *cis*-[Pt(H$_2$N(CH$_2$)$_2$PPh$_2$-*P*,*N*)$_2$]$^{2+}$, **1**, and numbering scheme.

almost equal amounts. There was no evidence for the opening of the second chelate ring even at very low pH* (1).

When **5b** was reacted with AgNO$_3$, the isolated product was the ring-closed bis-chelate complex, **5a**. In this case, in the absence of chloride, when the pH* was lowered by the addition of DNO$_3$, it was possible to observe chelate-ring-opening only below pH* 2. The ^{31}P NMR spectrum at pH* 2 showed a singlet at δ 25.5 (P$_A$) with a ^1J(PtP$_A$) coupling of 3225 Hz, corresponding to the ring-closed species **5a** and a set of peaks assignable to the ring-opened species *cis*-[Pt(Me$_2$N(CH$_2$)$_2$PPh$_2$-*N*,*P*)-(OH$_2$)(Me$_2$N(CH$_2$)$_2$PPh$_2$-*P*)]ONO$_2$ (singlet δ 25.3 (P$_B$) and at δ −1.96 (P$_C$), for atom labelling see Scheme 3). The ^1J(PtP) couplings were 4008 and 3298 Hz which are within the range for phosphorus *trans* to O and N, respectively.[31–33]

A titration of **5a** with chloride ions (added as NaCl) was studied at pH* 8.6 (Fig. 3) in order to determine the chloride association constant K_c by measuring the relative intensities of peaks for the ring-opened and ring-closed species in the ^{31}P NMR spectra. A pH* much higher than the p*K* value was chosen so that protonation of the amino group did not influence the position of the equilibrium. The amount of **5c** increased steadily with chloride addition (Fig. 3) and at about 150 mM chloride about 40% of **5c** was present. In a separate experiment, 320 mM chloride was added to a sample containing 20 mM of **5a** which resulted in the formation of a precipitate. The solid and supernatant were separated by centrifugation. The ^{31}P NMR of the supernatant showed that ring-opened and ring-closed species were present in about equal amounts. The ^{31}P NMR spectrum of the precipitate redissolved in D$_2$O was identical to that of **5a**, (see above) with 80% of the amount present corresponding to the ring-closed form. From the data obtained from a titration of 40 mM **5a** with up to 180 mM chloride an association constant of 4.95 M^{-1} was obtained for chloride binding to **5a**, at pH* 8.6 ($K_c = [\mathbf{5c}]/([\mathbf{5a}][\mathrm{Cl}^-]_f)$; $[\mathrm{Cl}^-]_f$ = free chloride.). Thus chelate ring-opening and -closing can be controlled as a function of both pH* and chloride concentration.

When the pH* of **14a** was measured immediately after dissolving the complex in D$_2$O, it was found to be alkaline (pH* 8.6). When the pH* was lowered to 5 one of the chelate rings opened to give *cis*-[Pd(Me$_2$N(CH$_2$)$_2$PPh$_2$-*N*,*P*)Cl(Me$_2$NH-(CH$_2$)$_2$PPh$_2$-*P*)]$^{2+}$, **14b**, as seen by the appearance of two sharp peaks at δ 58.9 (P$_B$) and 23.55 (P$_C$). A solution of **14a** in D$_2$O was titrated over the pH* range of 2–9 and afforded a p*K* value of 6.0.

The ^{31}P NMR spectrum of complex **2** at pH* 1.2 showed doublets at δ 41.1 (P$_A$) and δ 1.9 (P$_C$) with ^1J(PtP) couplings of 3770 and 3300 Hz, respectively. The doublet spitting can be assigned to ^2J(P$_A$P$_C$) coupling of 18 Hz. A pH* titration of the complex (20 mM) showed that the chelate ring is opened below pH* 3 and afforded a p*K* value of 2.1 (Fig. 2b).

Complex **3** was sparingly soluble in water, however the ^{31}P NMR spectrum in D$_2$O–ethanol showed the presence of both the ring-opened and closed forms and a pH* titration of a 20 mM solution of **3** afforded a p*K* value of 6.3 uncorrected for the presence of EtOH. As for complex **14**, the switch from ring-opened to ring-closed forms occurred within a narrow pH* range (*ca.* 1), suggesting that protonation of the amino group and chloride binding are co-operative.

When the pH* of the aqueous solution of **12**, [Pd((c-C$_6$H$_{11}$)-HN(CH$_2$)$_2$PPh$_2$-*N*,*P*)$_2$]Cl$_2$ was lowered, one of the chelate rings opened as seen by the appearance of two ^{31}P NMR doublets at δ 62.9 (P$_B$) and 29.9 (P$_C$). These peaks were relatively sharp with a ^2J(P$_B$P$_C$) coupling of 12 Hz. A pH* titration of the complex (20 mM) afforded a p*K* value of 6.0. Above pH* 7 only the ring-closed form was observed, whereas below pH* 5 only the ring-opened form was present.

A gradual opening of the chelate ring was observed when the pH* of a solution of **8**, [Pt(H$_2$N(CH$_2$)$_3$PPh$_2$-*N*,*P*)$_2$]Cl$_2$ in D$_2$O was lowered, in contrast to the 5-membered ring analogue, **1**, which remained ring-closed. The ^{31}P NMR resonance for **8** (δ 1.88) began to disappear below pH* 6, and was replaced by doublets with δ 0.55 (P$_B$) and 4.24 (P$_C$) and corresponding ^1J(PtP) couplings of 3625 and 3272 Hz, respectively, and ^2J(P$_B$P$_C$) of 17 Hz. A pH* titration of the complex (20 mM) afforded a p*K* value of 2.9.

The above data show that it was not possible to achieve chelate ring-opening for the 5-membered ring complexes **1** and **10** even at very low pH conditions. On the other hand it was possible to ring-open the 6-membered, chelate ring analogue, **8**, at very low pH. The replacement of one of Me substituents on N in **5b** by H as in **2** resulted in a dramatic drop in the p*K* value: from 6.9 for **5b** to 2.12 for **2** (Fig. 2). This highlights the highly acidic conditions required to ring-open complexes with low steric requirements for the substituents on N in these aminophosphine complexes and the greater stability of 5-membered as opposed to a 6-membered chelate rings.

Crystallography

The X-ray crystal structures of **1**, **2**, **8**, **9**, **14b** and **18** were determined and are shown as SHELXTL[20] plots in Figs. 4–9. Data collection and refinement parameters, bond distances and angles are listed in Tables 1 and 4, respectively. The complexes have square-planar co-ordination geometry with varying degrees of distortion. In complexes **1**, **2**, **8**, **9** and **14b**, the two phosphino groups have a *cis* arrangement.

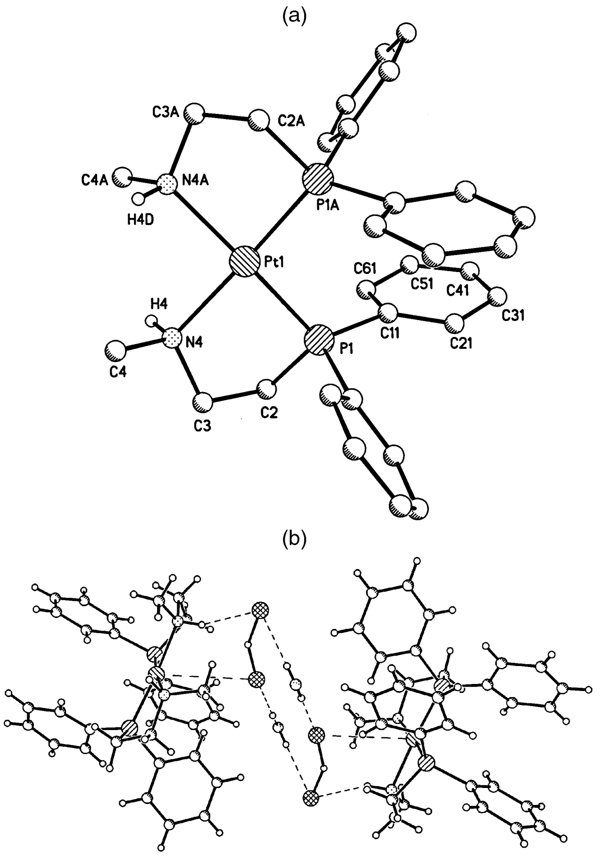


Fig. 5 (a) Crystal structure of the ring-closed complex *cis*-[Pt(Me(H)N(CH$_2$)$_2$PPh$_2$-*P*,*N*)$_2$]$^{2+}$, **2**, with the numbering scheme. (b) In the unit cell one [Cl–H–Cl]$^-$ is associated with each complex ion. The Cl–H and H–Cl distances are 1.631 and 1.610 Å, respectively. The two anions are connected *via* a water molecule with a Cl···H distance of 2.359 Å. One of the *ortho* H atoms of the phenyl rings is also H-bonded (Cl···H = 2.359 Å).

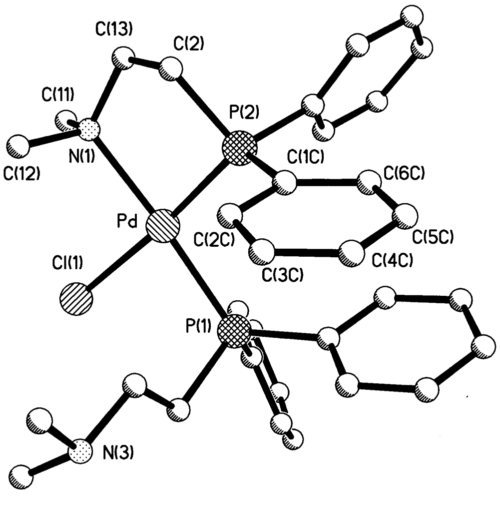


Fig. 6 Crystal structure of the ring-opened complex *cis*-[Pd(Me$_2$N(CH$_2$)$_2$PPh$_2$-*N*,*P*)Cl(Me$_2$NH(CH$_2$)$_2$PPh$_2$-*P*)]$^{2+}$, **14b**, with the numbering scheme.

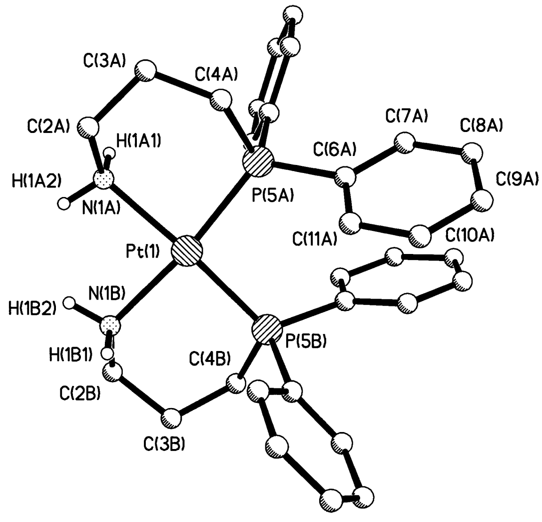


Fig. 7 Crystal structure of the ring-closed complex, *cis*-[Pt(H$_2$N(CH$_2$)$_3$PPh$_2$-*N*,*P*)$_2$]$^{2+}$, **8**, with the numbering scheme.

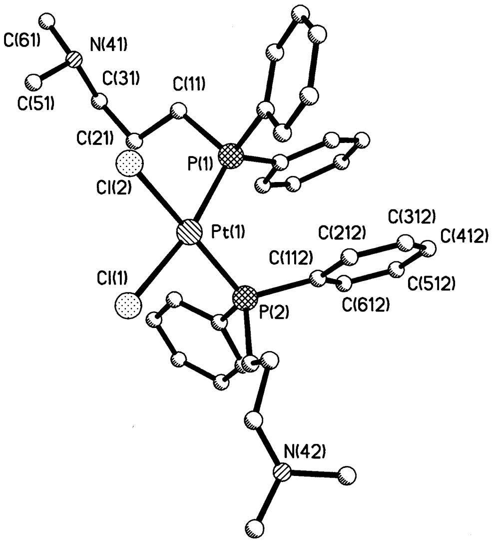


Fig. 8 Crystal structure of the di-ring-opened complex, *cis*-[Pt(Me$_2$N(CH$_2$)$_3$PPh$_2$-*P*)$_2$Cl$_2$], **9**, with the numbering scheme.

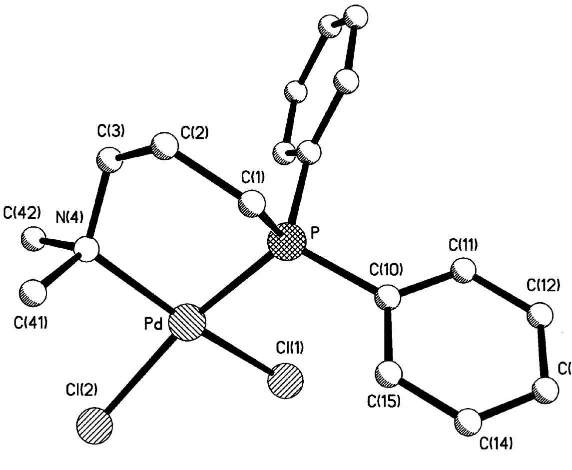


Fig. 9 Crystal structure of the monochelate complex, [Pd(Me$_2$N(CH$_2$)$_3$PPh$_2$-*P*,*N*)Cl$_2$], **18**, with the numbering scheme. The bond angles of the alkyl chain deviate from ideality: (N(4)–C(3)–C(2) = 116.6(4), C(2)–C(1)–P(1) = 114.4(3) and C(3)–C(2)–C(1) = 117.2(4)°.

In **1**, *cis*-[Pt(H$_2$N(CH$_2$)$_2$PPh$_2$-*N*,*P*)$_2$]Cl$_2$, the square-plane formed by N(1), N(2), P(1) and P(2), shows a slight deviation from planarity (Fig. 4). If we consider N(1)–Pt–P(2) be in one plane, then P(1) is out of plane by +0.052 Å and N(2) by −0.054 Å in the opposite direction. The P(1)–Pt–P(2) angle 102.98° is rather large for a square-planar complex. The steric crowding around the phosphorus atoms due to the presence of the phenyl rings, appears to cause the opening up of the angle, which presumably also results in the reduction of the other angles to below 90°, but within the range for five-membered chelate rings.[34] The *trans* angles N(1)–Pt–P(1) and N(2)–Pt–P(2) of 173.1(2) and 172.1(2)°, respectively, also show slight distortions from the ideal value. The Pt–N distances are relatively long (2.090 Å) compared with the literature values,[34]

Table 4 Summary of selected bond lengths [Å] and angles [°] for complexes **1**, **2**, **8**, **9**, **14b** and **18** with estimated standard deviations (e.s.d.s) in parentheses

	1 M = Pt	**2** M = Pt	**8** M = Pt	**9** M = Pt	**14b** M = Pd	**18** M = Pd
Bond lengths						
M–P	2.235(2)	2.34(2)	2.2543(11)	2.247(2)	2.2800(13)[a]	2.224(11)
	2.239(2)	2.34(2)	2.2565(11)	2.251(2)	2.2438(12)[b]	
M–N	2.090(6)	2.148(8)	2.116(3)		2.172(4)	2.1299(3)
	2.111(5)	2.148(8)	2.129(3)			
M–Cl				2.354(3)	2.3721(13)	2.3817(14)[c]
				2.361(2)		2.292(12)[b]
trans angles						
P–M–N	173.1(2)	173.9(2)	171.67(10)			
	172.1(2)	173.9(2)	171.43(10)		176.49(5)	
P–M–Cl				173.61(9)	173.68(5)	167.81(4)
				169.84(9)		
N–M–Cl						170.15(10)
cis angles						
P–M–P	102.98(6)	99.33(13)	98.16(4)	99.76(9)	98.57(11)	
P–M–N	83.8(2)	84.0(2)	89.60(10)		84.63(12)	92.42(10)
	84.8(2)	84.0(2)	86.69(10)			
N–M–N	88.4(2)	93.2(4)	86.04(13)			
P–M–Cl				83.84(9)		87.68(5)
				89.12(9)	85.37(5)	
Cl–M–Cl				87.78(9)		90.66(5)
N–M–Cl					91.32(12)	91.26(10)

[a] *trans* to Cl. [b] *trans* to N. [c] *trans* to P.

Table 5 Comparison of $[Cl–H–Cl]^-$ parameters

Species	Cl · · · Cl/Å	Cl–H–Cl/°	Method	Ref.
$[Cl–H–Cl]^-$	3.100	180	Calcd.	36
$[Cl–H–Cl]^-$	3.147	180	Exptl.	37
cis-$[Pt(Me(H)N(CH_2)_2PPh_2)_2][Cl–H–Cl]_2·0.5H_2O$ (**2**, Fig. 5)	3.2051	152.4	X-ray	[a]
[K(18-crown-6)][Cl–H–Cl]	3.117(1)		X-ray	38
$[Mg(18\text{-crown-}6)][Cl–H–Cl]_2$	3.286(1)	161	X-ray	38
	3.331(1)	173		
$[(4\text{-}MeOC_6H_4)(Me)PCl_2][Cl–H–Cl]$	3.210(3)	172	X-ray	39
$[NMe_4][Cl–H–Cl]$	3.22	180		40
$[H_3O(18\text{-crown-}6)][Cl–H–Cl]$	3.11(1)	168	X-ray	41

[a] This work.

but not unprecedented.[3] These distances provide evidence for weakening of the Pt–N bond, due to the strong *trans* influence of the tertiary phosphine. The P–Pt bond distances of 2.235 and 2.239 Å are within the expected range.[34]

The X-ray analysis of **2**, showed that the complex has crystallographic C_2 symmetry and one of the phenyl rings is disordered (Fig. 5a). It was formulated as *cis*-$[Pt(Me(H)N(CH_2)_2PPh_2)_2][Cl–H–Cl]_2·0.5H_2O$. One $[Cl–H–Cl]^-$ anion is associated with each molecule in the unit cell. The Cl–H and H–Cl distances are 1.630 and 1.610 Å, respectively, with Cl–H–Cl of 152.4°. The $[Cl–H–Cl]^-$ anion appears to be involved in a network of H-bonding with each molecule in the unit cell, and in turn the two anions are connected *via* a water molecule, for which the Cl · · · H distance is 2.359 Å. The $[Cl–H–Cl]^-$ anion is also H-bonded to one of the *ortho* H atoms of one of the phenyl rings. (Cl · · · H = 2.359 Å) (Fig. 5b). The anion $[Cl–H–Cl]^-$ was first observed in 1909 in the reaction $HNR_3Cl + HCl$, which resulted in the formation of $[HNR_3][Cl–H–Cl]$.[35] The structure of $[Cl–H–Cl]^-$ has been determined using semi-empirical and *ab initio* methods[36] as well as experimentally,[37] and its X-ray structure has been determined in several salts.[38–41] The parameters for $[Cl–H–Cl]^-$ are compared with literature values in Table 5. The platinum atom has a slightly distorted square-planar co-ordination. If we consider the N(4A)–Pt–P(1a) to be in one plane, N(4) is out of plane by +0.202 Å and P(1) by −0.197 Å in the opposite direction. The Pt–N bond distances of 2.148(8) Å are also longer than that observed for **1** which can be attributed to an increase in steric hindrance at N in **2** compared to **1**. The Pt–P distances, both 2.34 Å, are again longer than for the other complexes in this series. The P(1)–Pt–P(2) angles of 99.33° are larger and comparable to **1**. The P–Pt–N angles of 84.0° are also low, presumably related to the large angle of P(1)–Pt–P(2). The *trans* angles N(1)–Pt–P(1) and N(2)–Pt–P(2), both 173.9(2)°, also show distortions from the ideal value.

The X-ray crystal structure for complex **8**, *cis*-$[Pt(H_2N(CH_2)_3PPh_2\text{-}N,P)_2]Cl_2·H_2O·2CH_3NO_2$ (Fig. 7) shows many similarities to that of complex **1** (Fig. 4). Again the square-planar geometry shows slight deviations from ideal planarity. The P(5A)–Pt–P(5B) angle is increased to 98.16°, due to the steric bulk of the phenyl groups, with corresponding reduction of the other angles around the platinum. The *trans* angles P(5A)–Pt–N(1B) and P(5B)–Pt–N(1A) are 171.43° and 171.67°, respectively, showing slight distortion. The Pt–N bond lengths are further increased to 2.12 and 2.13 Å due to the *trans* influence of the tertiary phosphines. Again the Pt–P bond lengths, 2.25 and 2.26 Å, are within the expected range. The ligands form 6-membered chelate rings and both adopt the chair conformation, although one ring is oriented above the platinum square-plane and the other below the plane.

Complex **9**, *cis*-[Pt($Me_2N(CH_2)_3PPh_2$-*P*)$_2$Cl$_2$], crystallised in a fully ring-opened form as a CH_2Cl_2 solvate (Fig. 8). The Pt–P bond lengths, 2.25 Å, show little change from the ring-closed structure despite the presence of chloride and not amine ligands in the *trans* position. The Pt–Cl bond lengths, 2.35 Å are longer than expected due to the high *trans* influence of the phosphine ligands. Despite the removal of strain in the complex due to the lack of chelation, the structure shows a similar distortion from square-planar geometry. The P(1)–Pt–P(2) angle is increased to 99.76° and the *trans* angles, P(1)–Pt–Cl(1) and P(2)–Pt–Cl(2), are reduced to 169.84° and 173.61°, respectively.

Crystals suitable for X-ray analysis of the ring-opened form of the Pd(II) complex **14b** were grown under acidic conditions (pH* *ca.* 4) in D_2O (Fig. 6). Even though the opening of one of the chelate rings must have relieved the severe steric strain along the N–Pd bond, the complex still shows distortion from square-planar geometry, and greater than that observed for **1** and **2**. If N(1)–Pd–Cl atoms are used to define the plane, P(1) is out of plane by 0.072 Å and P(2) by 0.195 Å. The P–Pd–P angle is relatively high at 98.57° due to the steric constraint caused by the presence of the phenyl rings. However the *trans* angles, N(1)–Pd–P(2) and P(2)–Pd Cl(1) of 176.49 and 173.68°, respectively, suggest only minor distortions. The Pd–N bond distance of 2.172 Å is relatively long, and is the longest M–N bond observed in this work, indicative of the weakening of the Pd–N bond. The Pd–Cl distance at 2.37 Å is as expected for Cl *trans* to phosphorus.[42] The two Pd–P distances are relatively short[34] comparable with that *trans* to Cl, 2.28 Å, and somewhat longer than that *trans* to N, 2.243 Å, due to the relatively larger *trans* influence of Cl compared to N.

The X-ray analysis of [Pd($Me_2N(CH_2)_3PPh_2$-*P*,*N*)Cl$_2$], **18** (Fig. 9), shows that the 6-membered ring is highly sterically strained. This is indicated by the bond angles of the alkyl chain, which show deviations from ideality (116.6(4), 114.4(3) and 117.2(4)°). This type of ring strain has also been observed for the dppp (1,3-bis(diphenylphosphino)propane) ligand which appears to form a significantly strained complex with palladium as opposed to the dppe (1,2-bis(diphenylphosphino)ethane) ligand which has an ideal square-planar geometry with maximum interaction between the phosphorus and palladium atom.[43] In addition the geometry at palladium in **18** is highly distorted from square-planar. The displacement of the P and N from the $PdCl_2$ plane is +0.465 Å and −0.357 Å for P and N, respectively. Similar geometric features have also been observed in [Pd(dppp)(bipy)]PF$_6$], where the two phosphorus atoms were displaced by −0.33 and +0.50 Å.[44] For [Pd(dppm)Cl$_2$] the displacements are −0.136 and +0.242 Å[43] and for [Pd(dppp)-Cl$_2$], are −0.053 and +0.312 Å. In contrast, the displacements observed for 5-membered chelated complexes are relatively small: −0.072 and + 0.195 Å for **14b**, −0.052 and +0.054 Å for **1**, and −0.072 and +0.087 Å for [Pd(dppe)Cl$_2$][43], confirming the highly sterically strained nature of the 6-membered chelated complex. The two Pd–Cl bond lengths for **18** are different, with that *trans* to P (2.33 Å) being somewhat longer than that *trans* to N (2.22 Å) due to the larger *trans* influence of a tertiary phosphine relative to that of the amine. The Pd–P bond distance is relatively short, at 2.22 Å and the Pd–N bond distance is rather long, at 2.12 Å, a common feature for this type of complex (Table 4). The P–Pd–P angle at 92.42° shows only a minor distortion although, the *trans* angles N(4)–Pd–Cl(1) and P(1)–Pd–Cl(2) of 170.15 and 167.8°, respectively, show a deviation from ideality which can be associated with the steric strain of the 6-membered chelated complex.

The X-ray crystallographic studies show that the metal–nitrogen bond distances for these complexes are relatively long and suggest a weakening of the Pt–N bonds, attributable to the strong *trans* influence of the tertiary phosphine. In addition changing the substituents at nitrogen from hydrogen to the more sterically demanding methyl group, results in the lengthening of the metal nitrogen bond.

Conclusions

The steric bulk of the substituents on nitrogen as well as the length of the $(CH_2)_n$ P–N linker in aminophosphine complexes can determine whether the complexes exist in ring-opened or closed forms. The aminophosphine complex, *cis*-[Pt($Me_2N(CH_2)_2PPh_2$-*N*,*P*)Cl($Me_2NH(CH_2)_2PPh_2$-*P*)]Cl, **5b**, has been shown by ^1H and ^{31}P solution studies to undergo reversible chelate ring-opening reactions in aqueous solution. These processes are dependent upon pH and chloride ion concentration. The equilibrium constant for Cl^- binding to *cis*-[Pt($Me_2N(CH_2)_2PPh_2$-*P*,*N*)$_2$](NO$_3$)$_2$ at pH* 8.6 was determined to be 4.95 M^{-1}, and pH-induced chelate ring-opening of *cis*-[Pt($Me_2N(CH_2)_2PPh_2$-*P*,*N*)$_2$]Cl$_2$ had an associated p*K* of 6.9. In contrast, the complexes with less steric bulk on nitrogen are more difficult to ring-open, and complexes *cis*-[Pt(Me(H)N$(CH_2)_2PPh_2$-*P*,*N*)$_2$]Cl$_2$ and *cis*-[Pt($H_2N(CH_2)_3PPh_2$-*P*,*N*)$_2$]Cl$_2$ had associated p*K* values of 2.1 and 2.9, respectively. X-Ray crystallographic studies show that these aminophosphine complexes exhibit square-planar geometries with varying degrees of distortion and relatively long metal–nitrogen bond distances. Some of the complexes are cytotoxic to cancer cells and may be promising new antitumour agents.[12] In chelate-ring-closed form they can act as antimitochondrial agents and destroy membrane potentials, whereas in the ring-opened form they can bind to nucleobases on DNA.

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