NMR study of mononuclear, binuclear and trinuclear tris(hydroxymethyl)phosphine-platinum(II) complexes with aquo or hydroxo ligands

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Abstract

Treatment of $[PtX_2\{P(CH_2OH)_3\}_2]$ (X = Cl or Br) with AgY (Y = NO_3, BF_4, PF_6 or ClO_4) in water gives three species **A**, **B** and **C**. Addition of HY to this mixture gives **A** exclusively which is identified as the bis(aquo) cation $[Pt(OH_2)_2\{P(CH_2OH)_3\}_2]^{2+}$. The aquo ligands can be substituted by pyridine, 2,2′-bipyridine or 9,10-phenanthroline to give the corresponding $[PtL_2\{P(CH_2OH)_3\}_2]^{2+}$. Treatment of $[Pt(OH_2)_2\{P(CH_2OH)_3\}_2]^{2+}$ with NEt_3 gives **B** which is identified as the binuclear species $[Pt_2(\mu\text{-}OH)_2\{P(CH_2OH)_3\}_4]^{2+}$ After 24 h in acid solution in the presence of Ag^+, the third species **C** is the main product which is trinuclear (as evidenced by ^{31}P and ^{195}Pt NMR spectroscopy) and is assigned the structure $[Pt_3(\mu\text{-}OH)_3\{P(CH_2OH)_3\}_6]^{3+}$. The products are very soluble in water and have been characterised only by ^{31}P and ^{195}Pt NMR spectroscopy. The chemistry of these $P(CH_2OH)_3$ complexes is compared with the chemistry of the analogous PMe_3 complexes.

Introduction

The reported [1] anti-cancer activity of bis(phosphine)platinum(II) analogues of cisplatin makes it important to understand the aqueous chemistry of such systems [2]. Longato and co-workers [3] and Miyamoto *et al.* [4] have recently shown that the aquo species $[Pt(PMe_3)_2(OH_2)_2]^{2+}$ is readily made and that its form in water depends critically on the pH, as summarised in Scheme 1. We have previously shown [5] that the hydrophilic ligand tris(hydroxymethyl)phosphine (**1**) has coordinating properties similar to PMe_3 but with the added dimension of high water solubility of its complexes. In this paper, we report the aquo complex $[Pt(OH_2)_2\{P(CH_2OH)_3\}_2]^{2+}$ and compare its chemistry with the PMe_3 analogue. This work is given added interest by the reported [6] anti-cancer activity of platinum(II) complexes of **1**.

Experimental

The reactions were carried out in H_2O or D_2O in air (no differences were observed if the reactions were carried out under nitrogen). The starting material $[PtCl_2\{P(CH_2OH)_3\}_2]$ was made as previously described [5a]. The products were exceedingly water soluble and our attempts to isolate them as solids for further analysis were unsuccessful. Hence all products were characterised only by NMR (see Table 1).

Preparation of $[Pt(OH_2)_2\{P(CH_2OH)_3\}_2](NO_3)_2$

A solution of $AgNO_3$ (97 mg, 0.57 mmol) in D_2O (0.5 cm^3) was added to a solution of $[PtCl_2\{P(CH_2OH)_3\}_2]$ (124 mg, 0.24 mmol) in D_2O (0.7 cm^3) to give immediately a precipitate of AgCl. After 5 min, this solution was filtered and then concentrated nitric acid (0.030 cm^3) was added. The product was then analysed by NMR spectroscopy. Similar procedures using $AgBF_4/HBF_4$, $AgPF_6/HPF_6$ and $AgClO_4/HClO_4$ gave the corresponding salt in solution. Addition of $AgNO_3/HNO_3$ to $[PtBr_2\{P(CH_2OH)_3\}_2]$ gave the same species.

Preparation of $[PtL_2\{P(CH_2OH)_3\}_2](NO_3)_2$, L = py, bipy or phen

Solutions of $[Pt(OH_2)_2\{P(CH_2OH)_3\}_2](NO_3)_2$ were generated as described above and then pyridine (0.030 cm^3, 0.37 mmol), 2,2′-bipyridine (20 mg, 0.13 mmol) or 9,10-phenanthroline (25 mg, 0.13 mmol) was added and the product identified by ^{31}P NMR spectroscopy.

Preparation of $[Pt_2(\mu\text{-}OH)_2\{P(CH_2OH)_3\}_4](NO_3)_2$

A solution of $AgNO_3$ (97 mg, 0.57 mmol) in D_2O (0.5 cm^3) was added to a solution of $[PtCl_2$-

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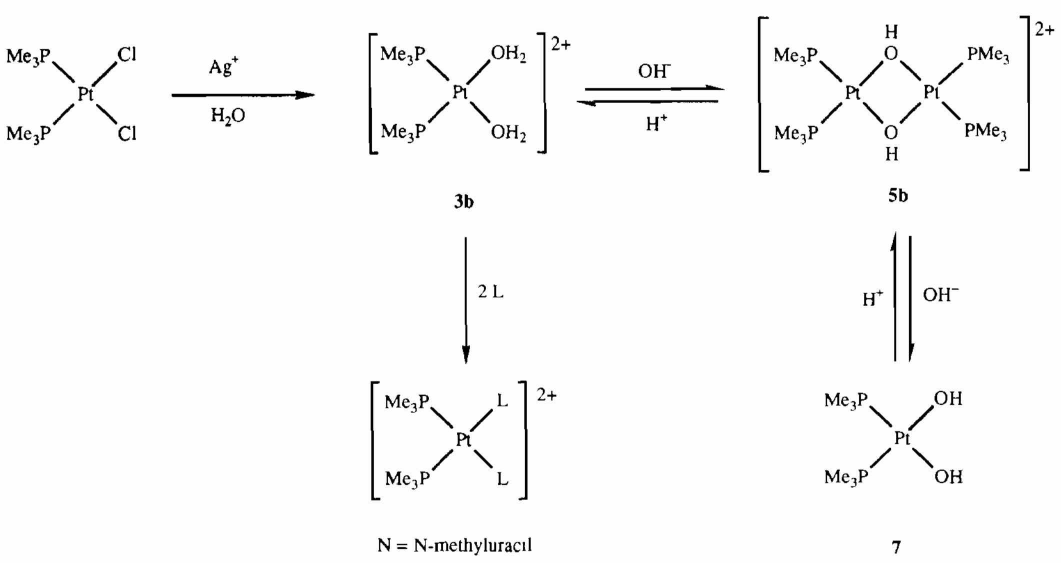


Scheme 1. Aqueous chemistry with Pt–PMe_3 systems.

$\{P(CH_2OH)_3\}_2]$ (124 mg, 0.24 mmol) in D_2O (0.7 cm^3) to give immediately a precipitate of AgCl. After 5 min this solution was filtered and then 0.1 M aqueous NEt_3 was added dropwise until the pH was 7 and the product was characterised by NMR spectroscopy.

Preparation of $[Pt_3(\mu\text{-}OH)_3\{P(CH_2OH)_3\}_6](NO_3)_3$

A solution of $AgNO_3$ (194 mg, 1.14 mmol) in D_2O (0.5 cm^3) was added to a solution of $[PtCl_2\{(CH_2OH)_3\}_2]$ (124 mg, 0.24 mmol) in D_2O (0.7 cm^3) to give immediately a precipitate of AgCl. After 5 min this solution was filtered and then allowed to stand at room temperature for 24 h. The species **C** was then over 90% of the phosphorus-containing product. The same species was obtained using $AgPF_6$ in place of $AgNO_3$.

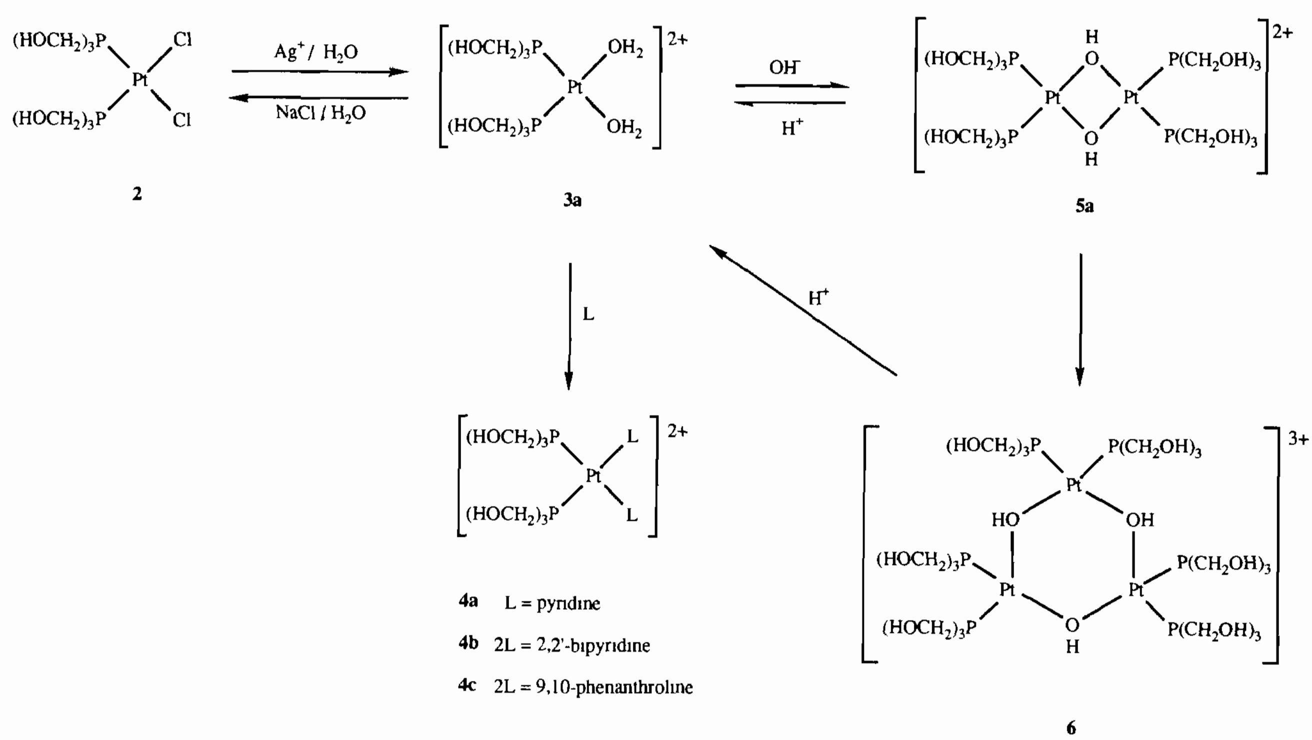
Results and discussion

The aqueous chemistry that we have discovered is summarised in Scheme 2. Treatment of $[PtCl_2\{P(CH_2OH)_3\}_2]$ (**2**) with an excess of $AgNO_3$ gave a strongly acidic (pH *c.* 1) solution which contained a mixture of three phosphorus-containing species **A**, **B** and **C** as shown by ^{31}P NMR spectroscopy. Initially **A** and **B** predominate but after 8 h all three species were clearly present (see Fig. 1). Addition of nitric acid to this mixture gave **A** exclusively to which we assign the structure $[Pt(OH_2)_2\{P(CH_2OH)_3\}_2]^{2+}$ (**3a**) based on the following observations. The ^{31}P and ^{195}Pt NMR data are similar to the analogous PMe_3 (**3b**) and PEt_3(**3c**) species (see Table 1). The product of this reaction is independent of the silver salt ($AgNO_3$, $AgBF_4$, $AgPF_6$ or $AgClO_4$), the acid (HNO_3, HBF_4, HPF_6 or $HClO_4$) and the halide in $[PtX_2\{P(CH_2OH)_3\}_2]$ (X = Cl or Br) showing that neither halide nor nitrate coordination is involved.

The water ligands in **3a** are easily substituted by chloride to regenerate the precursor **2** (see Scheme 2). Treatment of **3a** with pyridine, bipy or phen gave new species to which we assign structures **4a–c**; complexes of the type $[PtL_2(PR_3)_2]^{2+}$ (L = *N*-methyluracil [8], py [9] or bipy [9]) have been previously reported.

Titration of solutions containing a mixture of **A** and **B** with 0.1 M aqueous NEt_3 to raise the pH to 7 yields **B** exclusively; addition of more NEt_3 leads to decomposition (see below). Species **B** is assigned the binuclear structure **5a** on the basis of its ^{31}P NMR spectrum which shows the characteristic $^1J(PtP)$ and $^3J(PtP)$ coupling (Fig. 1) and the NMR data which are similar to the analogous PMe_3 (**5b**) and PEt_3 (**5c**) complexes (see Table 1). Addition of HPF_6 to **5a** regenerates the dicationic species **3a** (see Scheme 2).

The formation of the third species, **C** from $[PtCl_2\{P(CH_2OH)_3\}_2]$ and Ag^+ is accelerated by the presence of an excess of Ag^+ (see 'Experimental'). Solutions in which **C** is the only phosphorus-containing species had pH of *c.* 1. The ^{31}P and particularly the ^{195}Pt NMR spectrum of **C** strongly supports the presence of a triplatinum species: as illustrated in Fig. 1, the central feature of the ^{31}P NMR spectrum has the 1:8:18:8:1 pattern consistent with the presence of a triplatinum complex (see Table 1 for data) and the observed pattern for the ^{195}Pt resonance is in close agreement with that calculated for a $Pt_3(PR_3)_6$ spin system (see Fig. 2). The $^2J(PtPt)$ for **C** is 869 Hz compared with 120 Hz in the binuclear complex **5a** but no inference can be made from this since $^2J(PtPt)$ are unpredictably sensitive to small structural changes [10]. Addition of HPF_6 to **C** regenerates the aqua species **3a**. We tentatively assign



Scheme 2. Aqueous chemistry with Pt–P(CH$_2$OH)$_3$ systems.

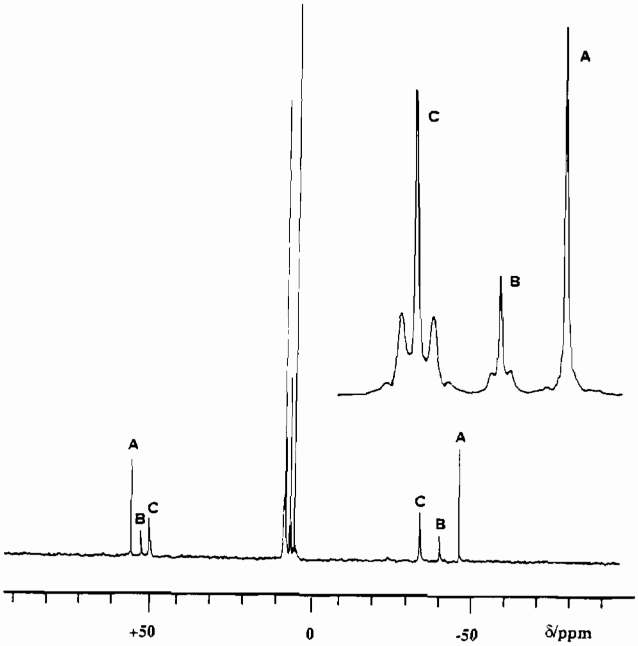


Fig. 1. ^{31}P NMR spectrum (36.2 MHz) of the mixture of mononuclear (**A**), binuclear (**B**) and trinuclear (**C**) species generated by addition of AgNO$_3$ to [PtCl$_2${P(CH$_2$OH)$_2$}] in D$_2$O

TABLE 1. ^{31}P and ^{195}Pt NMR data^a

Complex	δ(P)	^1J(PtP)	^3J(PtP)	δ(Pt)	^2J(PtPt)	Ref
3a	4.6	3647		131		
3b	−25.3	3745		176		3
3c	9.4	3737				
4a	−1.5	3052				
4b	6.9	3208				
4c	8.2	3227				
5a	5.6	3345	13	499	120	
5b	−25.6	3401	10	601	240	3
5c	6.8	3452	12			7
6	8.1	3008	23	646	869	
7	−31.4	3320		414		4

^{a}All spectra measured in D$_2$O at +28 °C. ^{31}P NMR chemical shifts are to high frequency of external 85% H$_3$PO$_4$ and ^{195}Pt shifts are to high frequency of Ξ(Pt) = 21.4 MHz (literature values [3, 4] have been adjusted to this scale).

the structure **6** to **C**, analogous to [Pt$_3$(μ-OH)$_3$(NH$_3$)$_6$]$^{3+}$, one of the proposed metabolites of cisplatin [11]. The mechanism of the formation of **6** and the promoting role of Ag$^+$ remain obscure. Unfortunately repeated attempts to isolate **6** (also **3a** and **5a**) from water have yielded only intractable oils from which pure complexes were not obtained but the ^{31}P NMR spectra of the redissolved oils show that essentially no decomposition of the complexes had occurred.

The aqueous chemistry of the Pt–P(CH$_2$OH)$_3$ and Pt–PMe$_3$ systems can be compared in Schemes 1 and 2. In both systems, the [Pt(OH$_2$)$_2$(PR$_3$)$_2$]$^{2+}$ complexes are formed in high yield in acidic solutions [3] and the water ligands are readily substituted by N-donors [8]. In both systems, addition of alkali gives the binuclear

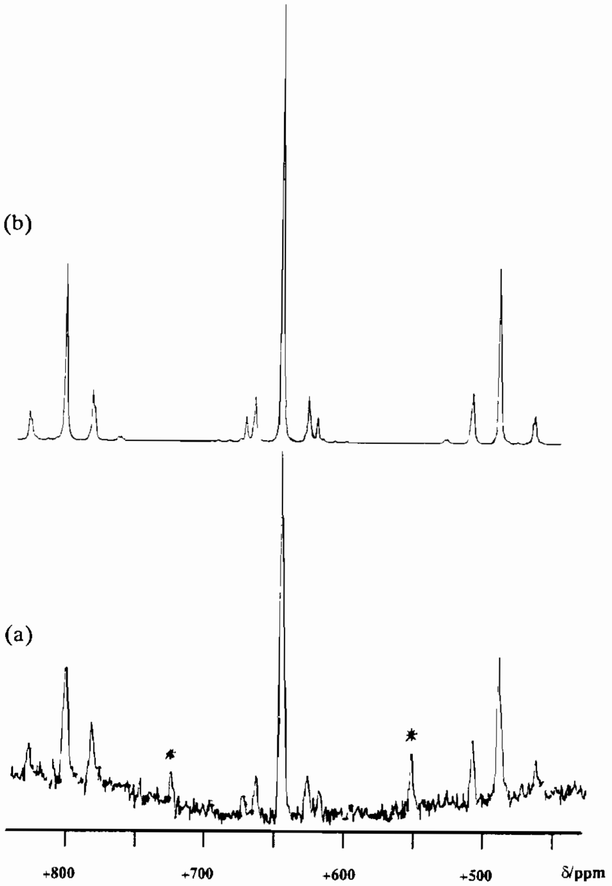


Fig. 2. (a) ^{195}Pt NMR spectrum of **C** in D_2O (peaks marked * are associated with the binuclear complex **B**); (b) spectrum simulated for Pt_3P_6 spin system with $^2J(PtPt) = 869$ Hz, $^1J(PtP) = 3008$ Hz, $^3J(PtP) = 0$ (the true value of 23 Hz obtained from the ^{31}P spectrum was not used because the linewidth of the Pt signals was c. 25 Hz and hence this coupling was lost in the ^{195}Pt spectrum).

species $[Pt_2(\mu\text{-}OH)_2(PR_3)_4]^{2+}$ [3]. At high base concentration, the unusual, terminal hydroxo-platinum complex $[Pt(OH)_2(PMe_3)_2]$ (**7**) is formed [4] but addition of KOH or excess NEt_3 to our $P(CH_2OH)_3$ complexes gave a complex mixture of products possibly because the coordinated hydroxymethylphosphinc is acidic [5] and in the presence of hydroxide, can eliminate formaldehyde in a similar way to hydroxymethylphosphonium salts [12].

A trinuclear complex with $P(CH_2OH)_3$ is formed but the analogous PMe_3 complex has not been observed. Indeed it has been suggested [4] that $[Pt_3(\mu\text{-}OH)_3(PMe_3)_6]^{3+}$ would be a very crowded molecule and thus unlikely to be stable with respect to other species. We have previously shown [5] that hydrogen bonding stabilises complexes of $P(CH_2OH)_3$ and it may be that hydrogen bonding in **6** also explains its stability.

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References

1 (a) H Urata, M Tanaka and T Fuchikami, *Chem Lett.*, (1987) 751; (b) H.C. Apfelbaum, J. Blum and F. Mandelbaum-Shavit, *Inorg. Chim. Acta, 186* (1991) 243.
2 (a) B. Longato, G. Pilloni, G.M. Borona and B. Corain, *J. Chem Soc., Chem Commun*, (1986) 1478; (b) V Scarcia, A. Furlani, B. Longato, B. Corain and G Pilloni, *Inorg Chim. Acta, 153* (1988) 67; (c) B Longato, G Pilloni, G.M Borona and B. Corain, *Inorg Chim Acta, 137* (1987) 75, (d) G. Bandoli, G. Trovó, A. Dolmella and B Longato, *Inorg Chem*, *31* (1992) 45; (e) K S. Wyatt, K N Harrison and C M Jensen, *Inorg Chem*, *31* (1992) 3867.
3 G. Trovó, G. Bandoli, U Casellato, B Corain, M. Nicolini and B. Longato, *Inorg Chem*, *29* (1990) 4616.
4 T.K Miyamoto, Y. Suzuki and H Ichida, *Chem Lett*, (1992) 839.
5 (a) J.W. Ellis, K.N. Harrison, P A T. Hoye, A G Orpen, P G Pringle and M.B. Smith, *Inorg Chem., 31* (1992) 3026; (b) P.A.T. Hoye, P.G Pringle, M.B. Smith and K. Worboys, *J. Chem Soc*, *Dalton Trans.*, (1993) 269.
6 (a) Ferrer Internacional, *Spanish Patent No. ES 548 849* (1986), *Chem. Abstr*, *108* (1988) 197 312, (b) Ferrer Internacional, *Spanish Patent No ES 547 481* (1986) *Chem. Abstr*, *107* (1987) 88 572.
7 G.W. Bushnell, *Can J. Chem*, *56* (1978) 1773
8 G. Trovó and B. Longato, *Inorg Chim Acta, 192* (1992) 13
9 F.R. Hartley, S.G Murray and A Wilkinson, *Inorg Chem*, *28* (1989) 549.
10 R Goodfellow, in J. Mason (ed), *Multinuclear NMR,* Plenum, New York, London, 1987.
11 R. Faggiani, B. Lippert, C J L Lock and B. Rosenberg, *Inorg Chem., 16* (1977) 1192.
12 K A. Petrov and V.A. Parshina, *Russ Chem Rev*, *(Engl Transl), 37* (1968) 532.