Cisplatin as a Synthon. Synthesis and Characterization of Triplatinum Complexes Containing Three *cis*-Pt(amine)$_2$ Units Linked in a Linear Fashion

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The mononuclear platinum complex *cis*-[$PtCl_2(NH_3)_2$] (*cis*-DDP, cisplatin) and related analogues with chelating dicarboxylate ligands such as [$Pt(NH_3)_2$(CBDCA)] (carboplatin, CBDCA = 1,1-cyclobutanedicarboxylate) are well established as anticancer agents.[1,2] Recently dinuclear complexes having the general formula [{$PtCl_m(NH_3)_{3-m}$}$_2$(μ-NH_2–R–NH_2)]$^{2(2-m)+}$ (m = 0–2) and displaying novel antitumor and DNA-binding properties have been described.[3-5] We now report the synthesis and characterization of triplatinum complexes where three *cis*-Pt(amine)$_2$ units are linked together in a linear manner. These complexes represent a unique development in platinum coordination and antitumor chemistry.

Experimental Section

NMR spectra were run on Bruker 250- and 270-MHz spectrometers. Elemental analyses were performed by Robertson Laboratories, Madison, NJ. The blocked diamine $NH_2(CH_2)_4NH$(Boc) was prepared by the literature method.[6]

Complex I, *cis*-[$PtCl_2(H_2N(CH_2)_4NH(Boc))_2$]. To a filtered solution of 0.8579 g of K_2PtCl_4 dissolved in 7 mL of water was slowly added dropwise 0.8371 g of $H_2N(CH_2)_4NH$(Boc) in 5 mL of water. The mixture was stirred for 5 h, during which time a cream-colored solid precipitated. The solid was collected on a sintered-glass funnel, washed with water and acetone, and dried. NMR in DMF: δ(^{195}Pt) –2226 ppm. Anal. Calcd for $C_{16}H_{40}N_4Cl_2O_4Pt$ (I): C, 33.65; H, 6.27; N, 8.72; Cl, 10.83. Found: C, 33.90; H, 6.43; N, 8.80; Cl, 11.23.

Complex II, *cis*-[$PtCl_2(H_2N(CH_2)_4NH_3)_2$]$Cl_2$. A 0.4516-g sample of *cis*-[$PtCl_2(H_2N(CH_2)_4NH(Boc))_2$] was suspended in 10 mL of MeOH with 2 mL water. A 10-mL portion of concentrated HCl was added slowly to the stirred suspension. After some time, the cream-colored solid all dissolved to give a yellow solution. The solution was taken to dryness in a stream of nitrogen, and the resulting yellow solid was washed with acetone and dried in drying pistol over boiling acetone. The complex is quite soluble in water. Anal. Calcd for $C_8H_{26}N_4Cl_4Pt$ (II): C, 18.65; H, 5.09; N, 10.87; Cl, 27.52. Found: C, 18.89; H, 5.40; N, 10.76; Cl, 27.70. NMR in D_2O: δ(^{1}H) 3.04, 2.77, 1.79 ppm; δ(^{195}Pt) –2239 ppm.

Complex IIIa, *cis*-[{*cis*-$PtCl_2(NH_3)$(μ-$H_2N(CH_2)_4NH_2$)}$_2$$PtCl_2$]. A 0.713-g sample of *cis*-[$PtCl_2(H_2N(CH_2)_4NH_3)_2$]$Cl_2$ was dissolved in 3 mL of H_2O, and a solution of 1.5828 g of K[$PtCl_3(NH_3)$] in 12 mL of H_2O was added. A solution of 0.18 g of KOH in 5 mL of H_2O was added dropwise with stirring. A yellow precipitate began to form within 3 min. After 1 h, the solid IIIa was filtered off, washed with water and acetone, and dried. Anal. Calcd for $C_8H_{30}N_6Cl_6Pt_3$ (IIIa): C, 9.53; H, 3.00; N, 8.33; Cl, 21.10. Found: C, 9.34; H, 2.90; N, 8.02; Cl, 20.30.

Complex IIIc, *cis*-[{*cis*-Pt(mal)(NH_3)(μ-$H_2N(CH_2)_4NH_2$)}$_2$Pt(mal)]. The malonate was prepared by the standard method of ref 4 by stirring a suspension of IIIa in H_2O with 3 equiv of silver malonate for 48 h. The AgCl was precipitated off, the solution evaporated to half-volume, and the product precipitated with acetone. The white complex was then recrystallized from H_2O/acetone. Anal. Calcd for $C_{17}H_{36}N_6O_{12}Pt_3\cdot 3H_2O$ (IIIc): C, 17.67; H, 3.66; N, 7.27. Found: C, 17.66; H, 3.72; N, 6.57. MS(FAB)$^+$ parent ion: 1102 (calcd 1102).

Complex IV, *cis*-[$Pt(NH_3)_2(H_2N(CH_2)_4NHBoc)_2$]$Cl_2$. A 0.45-g quantity of *cis*-DDP was suspended in 75 mL of H_2O at 70–80 °C with stirring. To the suspension was added 0.6 g of $H_2N(CH_2)_4NHBoc$ (slight excess of 1:2 stoichiometry) dissolved in 10 mL of H_2O. Stirring was continued for 4 h at 70–80 °C, during which time a colorless solution formed. Upon cooling, the solution was filtered with activated carbon through Celite. The filtrate was evaporated to 2 mL, and 50 mL of acetone was added. After the mixture was cooled at 3 °C overnight, the white product precipitated and was filtered off and washed with acetone. Anal. Calcd for $C_{16}H_{46}N_6Cl_2O_4Pt$(IV): C, 31.95; H, 6.85; N, 12.42; Cl, 10.48. Found: C, 31.75; H, 6.90; N, 12.12; Cl, 10.29. NMR in D_2O: δ(^{1}H) 3.08, 2.72, 1.74, 1.54, 1.43 ppm; δ(^{195}Pt) –2681 ppm.

Complex V, *cis*-[$Pt(NH_3)_2(H_2N(CH_2)_4NH_3)_2$]$Cl_4$. A 0.8-g sample of complex IV was suspended in 10 mL of MeOH and 2 mL of H_2O. Concentrated HCl (10 mL) was added slowly to the stirred suspension. After 2 h, the solution was filtered and the filtrate evaporated to dryness. MeOH (200 mL) was added with stirring for 2 h and the solution filtered. The filtrate was evaporated to 10 mL and, upon cooling, the product precipitated. Anal. Calcd for $C_8H_{32}N_6Cl_4Pt$ (V): C, 17.49; H, 5.96; N, 15.30; Cl, 25.82. Found: C, 17.20; H, 5.96; N, 15.01; Cl, 25.53. NMR in D_2O: δ(^{1}H) 3.02, 2.75, 1.73 ppm; δ(^{195}Pt) –2651 ppm.

Complex VIa, *cis*-[{*cis*-$PtCl_2(NH_3)$(μ-$H_2N(CH_2)_4NH_2$)}$_2$$Pt(NH_3)_2$]-[$PtCl_3(NH_3)$]$_2$. A 0.1-g sample of complex V was dissolved in 2 mL of H_2O, and 0.5 mL of 1 M KOH was added. The solution was added dropwise to a solution of K[$PtCl_3(NH_3)$] (0.15 g) in 5 mL of H_2O with stirring for 2 h. The solution was filtered and 30 mL of MeOH added, precipitating a light yellow product. Anal. Calcd for $C_8H_{42}N_{10}Cl_{10}Pt_5$ (VIa): C, 5.97; H, 2.63; N, 8.71; Cl, 22.04. Found: C, 6.72; H, 2.57; N, 8.71; Cl, 20.89.

Complex VIb, *cis*-[{*cis*-$PtCl_2(NH_3)$(μ-$H_2N(CH_2)_4NH_2$)}$_2$$Pt(NH_3)_2$]-$Cl_2$. A 0.3-g sample of complex VIa was dissolved in 40 mL of H_2O at 40–50 °C, and 0.1 g of [$Pt(NH_3)_4$]Cl_2 in 1 mL of H_2O was added. Cooling the solution to 3 °C overnight gave a golden yellow precipitate [$Pt(NH_3)_4$][$PtCl_3(NH_3)$]$_2$, and the supernatant was decanted and evaporated to half-volume. The supernatant was again decanted from a further precipitate of the tetraamine salt and evaporated to 5 mL. Addition of 20 mL of MeOH and cooling overnight gave a small quantity of product. Anal. Calcd for $C_8H_{36}N_8Cl_6Pt_3$ (VIb): C, 9.22; H, 3.48; N, 10.75; Cl, 20.41. Found: C, 8.99; H, 3.61; N, 10.28; Cl, 20.25.

Discussion

Dinuclear platinum complexes may be divided into two classes—those containing equivalent coordination spheres and those where the coordination units are inequivalent. In the former case, the complexes are prepared by reaction of 2 equiv of a suitable monomeric platinum complex with the bridging diamine:[7,8]

$$2K[PtCl_3(NH_3)] + H_2N\text{–}R\text{–}NH_2 \rightarrow [\{cis\text{-}PtCl_2(NH_3)\}_2(\mu\text{-}H_2N\text{–}R\text{–}NH_2)]$$

or

$$2\ trans\text{-}[PtCl_2(NH_3)_2] + H_2N\text{–}R\text{–}NH_2 \rightarrow [\{trans\text{-}PtCl(NH_3)_2\}_2(\mu\text{-}H_2N\text{–}R\text{–}NH_2)]^{2+}$$

For complexes with inequivalent coordination spheres, a precursor monomer must first be prepared containing a "dangling" H_2N–R–NH_2 group, with one end uncomplexed in the form of either

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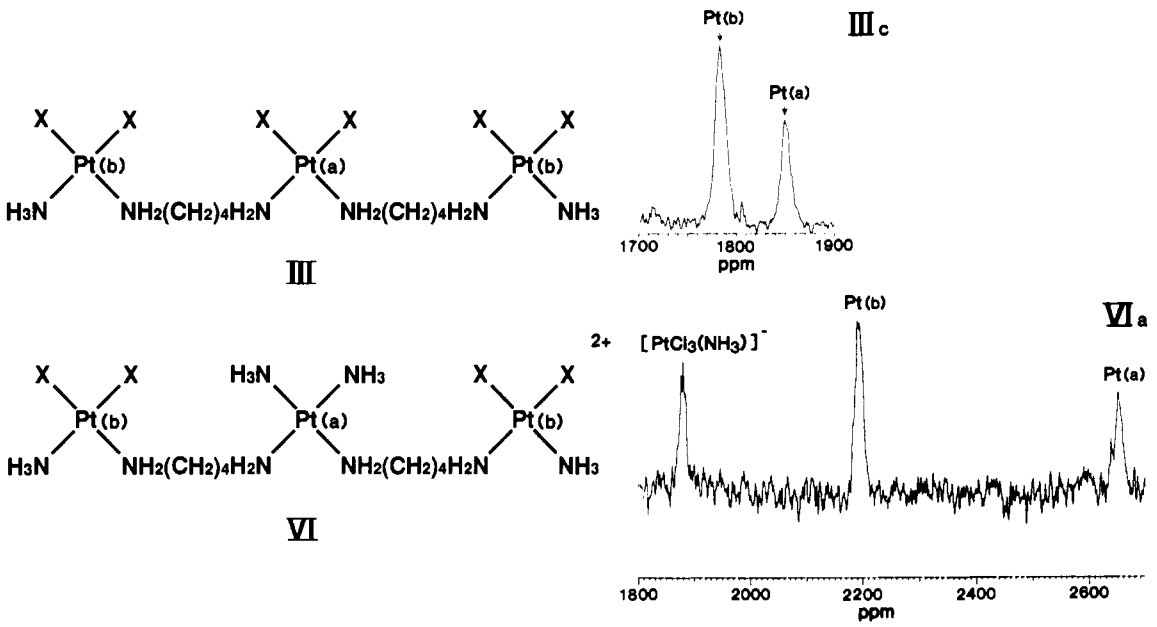


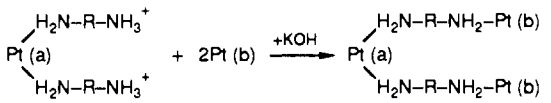
Figure 1. Structures and ^{195}Pt NMR spectra for the triplatinum complexes. Note that the central Pt atom in a triplatinum unit is bound to two alkanediamine (RNH_2) chains and is in an environment slightly different from those of the other two (equivalent) Pt atoms. Substitution of NH_3 by RNH_2 usually results in an upfield shift in the ^{195}Pt NMR spectrum[17]—thus the upfield peaks (Pt(a)) for all complexes are approximately half the intensity of the accompanying peak (Pt(b)). In structure III, X = Cl (IIIa), H_2O (IIIb) and X_2 = malonate (IIIc). The spectrum for the malonate derivative is shown. In structure VI X = Cl and the counteranions are $[PtCl_3(NH_3)]$ (VIa) or Cl(VIb). The ^{195}Pt NMR spectrum of VIa with its $[PtCl_3(NH_3)]$ counteranion is shown. The multiple nature of the ^{195}Pt peak of the $[PtCl_3(NH_3)]$ anion is due to observed ^{14}N–^{195}Pt coupling.[18]

a blocking agent (BOC, *tert*-butoxycarbonyl)[6] or NH_3^+ salt. Subsequent reaction with a suitable target gives the dinuclear species:

$$\text{Pt(a)–H}_2\text{N–R–NH}_3^+ + \text{Pt(b)} \xrightarrow{+KOH} \text{Pt(a)–H}_2\text{N–R–NH}_2\text{–Pt(b)}$$

Specific examples are the complex [{*cis*-$PtCl_2(NH_3)$}-μ-$NH_2(CH_2)_4NH_2$-{*trans*-$PtCl_2(NH_3)$}], containing two coordination spheres differing only in geometry,[4] and the complex [{*cis*-$PtCl_2(NH_3)$}-μ-$NH_2(CH_2)_4NH_2$-{*cis*-$PtCl_2(Me_2SO)$}], containing two inequivalent coordination spheres.[9]

We have now extended this linking concept to prepare triplatinum complexes containing three *cis*-Pt(amine)$_2$ units (Figure 1). The general preparation involves synthesis of a suitable precursor containing two monoprotected diamines (step 1); treatment with acid to give the protonated amine $RNH_3^+Cl^-$, which may then be used as a source for further metalation (step 2); and reaction with 2 equiv of an appropriate target molecule to afford the desired product (step 3):



Step 1. Specifically, reaction of K_2PtCl_4 with 2 equiv of $H_2N(CH_2)_4NH(Boc)$ gives the cisplatin analog:

$$K_2PtCl_4 + 2H_2N(CH_2)_4NH(Boc) \rightarrow \underset{\text{I}}{\textit{cis}\text{-}[PtCl_2(H_2N(CH_2)_4NH(Boc))_2]}$$

Step 2. Treatment of I with acid gives the protonated diamine:

$$\underset{\text{I}}{\textit{cis}\text{-}[PtCl_2(H_2N(CH_2)_4NH(Boc))_2]} \rightarrow \underset{\text{II}}{\textit{cis}\text{-}[PtCl_2(H_2N(CH_2)_4NH_3)_2]Cl_2}$$

Step 3. To prepare a triplatinum complex with three *cis*-Pt(amine)$_2$ units, the target molecule is $K[PtCl_3(NH_3)]$ because substitution occurs cis to the NH_3 ligand:

$$2K[PtCl_3(NH_3)] + \underset{\text{II}}{\textit{cis}\text{-}[PtCl_2(H_2N(CH_2)_4NH_3)_2]Cl_2} \xrightarrow{+KOH} \underset{\text{IIIa}}{\textit{cis}\text{-}[\{\textit{cis}\text{-}PtCl_2(NH_3)(\mu\text{-}H_2N(CH_2)_4NH_2)\}_2PtCl_2]}$$

The product is obtained in high purity and in good yield with no other detectable platinum species as contaminants. Addition of excess $AgNO_3$ to an aqueous suspension of IIIa followed by centrifugation of precipitated AgCl gave a supernatant solution of the hexaaqua species, IIIb. Treatment of IIIa with 3 equiv of Ag_2(malonate) afforded upon workup a white water-soluble solid analyzing for [{Pt(mal)$(NH_3)(\mu$-$H_2N(CH_2)_4NH_2)$}$_2$Pt(mal)] (IIIc). The ^1H and ^{195}Pt NMR spectra (Table I) of all derivatives were entirely consistent with these formulations, and the ^{195}Pt

Table I. NMR Spectroscopic Data for Triplatinum Complexes[a]

complex[b]	$\delta(^1H)$, ppm	$\delta(^{195}Pt)$, ppm[c]
IIIa	2.83, 1.83	−2151, −2209
IIIb		−1651, −1710
IIIc	3.7, 2.6, 1.8[d]	−1785, −1851
VIa	2.8, 1.9, 1.8[e]	−1881, −2193, −2652
VIb	2.8, 1.9, 1.8	

[a] ^1H relative to TMS; ^{195}Pt relative to Na_2PtCl_6 in D_2O. Solvent: DMF for IIIa; D_2O for IIIb, IIIc, VIa, and VIb. [b] See Figure 1 for structures. [c] For complex III the upfield chemical shift in all cases refers to the central Pt of the trimer. For complex VI the chemical shift in the −2600 to −2700 ppm range is typical of a [Pt(amine)$_4$] coordination sphere while the [$PtCl_2$(amine)$_2$] shifts appear as expected at approximately −2200 ppm. For complex VIa the ^{14}N–^{195}Pt coupling observed in the $[PtCl_3(NH_3)]$ anion gives rise to a 1:1:1 triplet as expected. [d] Assignments are 3.7 (malonate $-CH_2$), 2.6 (C1 and C4 $-CH_2NH_2$), and 1.8 ppm (C2 and C3 $-CH_2$) with the expected integration ratios. At the field strength employed, we cannot observed the differences between the two diamine chains. In Me_2SO-d_6, the malonate protons of IIIc appear as two very closely spaced singlets at 3.2 ppm and the amine resonances are observed at 4.3 (NH_3) and 5.1 ($-NH_2$) ppm. [e] The CH_2 protons of the central C2 and C3 carbon atoms give rise to a broad doublet with the maxima at the indicated values.

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chemical shifts confirm the formation of the $[PtCl_2(amine)_2]$ coordination sphere from the $[PtCl_3(NH_3)]^-$ anion.[10,11] The FAB/MS of IIIc gave a parent peak at m/z 1102, consistent with the proposed structure.

The synthetic scheme detailed above is applicable to a wide range of structures, and complexes containing two inequivalent coordination spheres may also be prepared. Reaction of *cis*-$[PtCl_2(NH_3)_2]$ with $H_2N(CH_2)_4NH(Boc)$ affords the tetraamine:

$$cis\text{-}[PtCl_2(NH_3)_2] + 2H_2N(CH_2)_4NH(Boc) \rightarrow cis\text{-}[Pt(NH_3)_2(H_2N(CH_2)_4NHBoc)_2]Cl_2$$
IV

and

$$cis\text{-}[Pt(NH_3)_2(H_2N(CH_2)_4NHBoc)_2]Cl_2 \rightarrow cis\text{-}[Pt(NH_3)_2(H_2N(CH_2)_4NH_3)_2]Cl_4$$
IV V

Reaction of V with $K[PtCl_3(NH_3)]$ gives the cation containing two *cis*-$[PtCl_2(amine)_2]$ groups linked through a $[Pt(amine)_4]$ unit:

$$2K[PtCl_3(NH_3)] + cis\text{-}[Pt(NH_3)_2(H_2N(CH_2)_4NH_3)_2]Cl_4 \rightarrow cis\text{-}[\{cis\text{-}PtCl_2(NH_3)(\mu\text{-}H_2N(CH_2)_4NH_2)\}_2Pt(NH_3)_2]^{2+}$$
V VIa

Interestingly, the complex initially precipitates with the $[PtCl_3(NH_3)]$ counteranion, as evidenced by elemental analysis and a ^{195}Pt NMR peak at −1881 ppm (Table I and Figure 1). Metathesis of VIb may be achieved by treatment of VIa with $[Pt(NH_3)_4]Cl_2$ in H_2O/MeOH, which selectively precipitates the highly insoluble $[Pt(NH_3)_4][PtCl_3(NH_3)]_2$ salt, leaving the triplatinum cation in solution as the chloride salt.

The complexes described here will be expected to have further unusual biological properties in comparison with the monomers and even the dimers. The development of the methodology to obtain in good yield chemically pure linear arrays containing specific Pt–amine units is also of considerable interest from the coordination chemistry point of view, including their use in catalysis, possible electron transfer within the array,[12,13] and their role as Pt(II) precursors for study of the mixed-valence phenomena in both the "platinum blues"[14,15] and simple platinum–amine salts.[16]

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