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Platinum Antitumor Agent Coordination Chemistry. Syntheses of Linked Purines and Their Platinum Complexes. Crystal and Molecular Structures of Bis[μ-1,4-bis(hypoxanthin-9-yl)butane]bis[(diaminoethane)platinum(II)] Tetrakis(hexafluorophosphate) Hydrate

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Platinum coordination complexes involving linked purines are investigated as models for the interaction of platinum antitumor drugs with DNA. The syntheses of several linked purines, 1,3-bis(adenin-9-yl)propane, 1,4-bis(adenin-9-yl)butane, 1,3-bis(hypoxanthin-9-yl)propane, 1,4-bis(hypoxanthin-9-yl)butane, 1,3-bis(adenin-9-yl)-2-propanol, and 1,3-bis(hypoxanthin-9-yl)-2-propanol, are reported. Platinum coordination complexes of some of these ligands, bis[μ-1,4-bis(hypoxanthin-9-yl)butane]bis-[(diaminoethane)platinum(II)] tetrakis(hexafluorophosphate) hydrate, [(1,3-bis(hypoxanthin-9-yl)propane)(diaminoethane)-platinum(II)] chloride trihydrate, [(1,3-bis(hypoxanthin-9-yl)-2-propanol)(diaminoethane)platinum(II)] chloride tetrahydrate, and [μ-1,4-bis(hypoxanthin-9-yl)butane]bis[*cis*-chlorodiammineplatinum(II)] chloride dihydrate, are reported. The X-ray crystal structure of the dimer, bis[μ-1,4-bis(hypoxanthin-9-yl)butane]bis[(diaminoethane)platinum(II)] tetrakis(hexafluorophosphate) hydrate, $C_{32}H_{44}F_{24}N_{20}O_4P_4Pt_2 \cdot H_2O$, is reported. The dimer crystallizes in the triclinic space group $P\bar{1}$, with a = 11.182 (2) Å, b = 13.654 (3) Å, c = 12.376 (2) Å, α = 103.88 (2)°, β = 125.82 (1)°, γ = 97.60 (2)°, V = 1395.4 (5) Å^3, and Z = 2. The data were collected with graphite-monochromatized Mo Kα radiation, and the structure was solved by standard heavy-atom Patterson and Fourier techniques. There were 4841 total observed data and 420 parameters varied to give a final R = 0.0314 and R_w = 0.0375. Each base in the 1,4-bis(hypoxanthin-9-yl)butane ligand is coordinated to a different Pt via N7. Each Pt coordinates to both N's of the diaminoethane ligand. The two units of the dimer are related by an inversion center, but each unit lacks the common $C2$ symmetry often found with bis(purine) complexes. The complex exhibits no intramolecular base–base overlap as evidenced by a very large base–base dihedral angle of 107.6° and a large O6′–C8 interbase distance of 3.25 (1) Å. Also there is no intermolecular base stacking. There is intramolecular hydrogen bonding between one O6 and a H on the diaminoethane ligand with an O–N distance of 2.86 (1) Å and an intermolecular H bond between the other O6 and an adjacent N with an O–N distance of 2.89 (1) Å. The pyrimidine moieties are on opposite sides of the coordination plane in the head-to-tail (htt) arrangement. Thus, this is the first htt cis bis N7-bound 6-oxopurine complex where only one O6 participates in an intramolecular H bond. The displacement of the Pt out of the purine plane is in the "–" direction for both bases, and, again, this is the first example of a "–,–" combination. These results greatly expand the range of conformational features found in models of the Gua–Pt–Gua cross-link. Such a cross-link is suspected to be the lethal DNA lesion caused by cis Pt type antitumor agents.

Introduction

The biological target of Pt antitumor agents appears to be DNA.[1,2] Considerable evidence exists that guanine (Gua) bases are attacked preferentially and that runs of Gua on the same strand are particularly reactive.[3-5] For example, Eastman has shown that when radiolabeled [dichloro(diaminoethane)platinum(II)], $Pt(en)Cl_2$, is added to DNA and the treated DNA is enzymatically digested, the predominant product formed at low Pt/P ratios contains two Gua attached to Pt.[6] Other products are formed at higher Pt/ratios.[6] These contain both Gua and adenine (Ade) bases attached to Pt. Reedijk and co-workers have shown for *cis*-$[Pt(NH_3)_2Cl_2]$ at low ratios that there is a second, less abundant product that contains both Gua and Ade.[7] In both cases the nucleic acid bases are linked by a phosphodiester group.

At this time, there are no crystalline products reported in the literature for which an X-ray structure reveals Pt bound to two bases that are linked together. The paucity of such information arises from the difficulty of obtaining crystalline compounds of nucleotide species. Since dinucleoside monophosphates have not until recently been available in large quantities and since difficulties of crystallization are expected to be even greater than for mononucleotides, the shortage of structural data is readily explained. We and others[8] have circumvented the crystallization problems in the past by substituting an alkyl group for the sugar of a nucleoside. In this paper we report synthetic and crystallographic studies on Pt compounds containing purine bases bonded together by organic groups. Evidence exists that the bases in such molecules stack,[9] and thus these would be good models for dinucleoside monophosphates. We had hoped efforts at crystallization would be more successful. To some extent our predictions were fulfilled, but in fact, the problem of low solubility limited the scope of the investigation. However, some novel compounds were obtained and are reported here. In particular, several new structural features, not previously observed, were found in the X-ray crystal structure of the title complex.

Experimental Section

Materials. Adenine (Sigma), dibromoalkanes (Aldrich) and 1,3-dibromo-2-propanol (Fisher) were used as received. All other materials were of reagent grade and were obtained from standard sources.

Instrumentation. NMR spectra were taken in Me_2SO-d_6 and referenced to Me_4Si, unless otherwise noted. FT ^{13}C NMR spectra (20 MHz) were obtained with a Varian CFT20. ^1H NMR spectra were recorded with a CW instrument at 90 MHz (Varian 390) or with a FT spectrometer at 200 MHz (IBM WP200SY).

Elemental Analysis. All analyses were performed by Atlantic Microlabs, Atlanta, GA.

Preparations of Ligands. 1,3-Bis(adenin-9-yl)propane (Ade-$(CH_2)_3$-Ade). Adenine (10 g, 0.074 mol) was added to a solution of NaOH (5 g/100 mL) in DMF/H_2O (95:5) at 50 °C. After the solid dissolved, 1,3-dibromopropane (7.4 g, 0.037 mol) was added and heating was continued for 4 h. The solution was cooled to room temperature, and the resulting suspension was stirred overnight. The white solid was collected and washed with water, acetone, and then diethyl ether. It was air-dried. The crude material (3.2 g) was recrystallized from 100 mL

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of acetic acid/water (50:50); yield 2.45 g (21%). ^{1}H NMR (90 MHz, ppm): H8 (s), 8.25; H2 (s), 8.20; NH_2 (br), 7.2; NCH_2 (m), 4.2; CH_2 (m); 2.3. ^{13}C NMR (ppm): C2, 152.34; C4, 149.45; C5, 118.64; C6, 155.82; C8, 140.81; NCH_2, 43.10; CH_2, 19.46. The NMR spectrum in TFA (H8, 9.2 ppm; H2, 8.7 ppm; NCH_2, 4.9 ppm; CH_2, 2.8 ppm) agrees with that in the literature.[9]

1,4-Bis(adenin-9-yl)butane (Ade-$(CH_2)_4$-Ade) was prepared as above from 1,4-dibromobutane (7.92 g, 0.037 mol). The crude material (4.5 g) was recrystallized from a minimum of hot DMF; yield 4.02 g (33%). ^{1}H NMR (90 MHz ppm): H8 (s), 8.21; H2 (s), 8.20; NH_2 (br), 7.2 NCH_2 (m), 4.21; $(CH_2)_2$ (m), 1.8. ^{13}C NMR (ppm): C2, 152.31; C4, 149.41; C5, 118.62; C6, 115.80; C8, 140.83; NCH_2, 42.50; $(CH_2)_2$, 26.56. Anal. Calcd for $C_{14}H_{16}N_{10}\cdot{}^1/_2H_2O$: C, 50.45; H, 5.10; N, 42.04. Found: C, 50.42; H, 5.18; N, 41.99.

1,3-Bis(hypoxanthin-9-yl)propane (Hyp-$(CH_2)_3$-Hyp). Ade-$(CH_2)_3$-Ade (1 g) was dissolved in H_2O (10 mL) containing 1 mL of concentrated H_2SO_4. A solution of $NaNO_2$ (4 g in 5 mL of H_2O) was added very slowly to the purine-containing solution. The solution was then heated to 70 °C and stirred for 5 min. After it had cooled to room temperature, the solution was treated with 1 N NH_4OH to pH 8. The yellow precipitate formed was collected, washed with acetone and then diethyl ether, and air-dried. The crude product (0.92 g) was recrystallized from 600 mL of hot water; yield 0.88 g (88%). This compound was previously prepared by Lister,[10,11] but no NMR data were reported. ^{1}H NMR assignments for this compound were made by comparison with the adenine compound.[9] ^{1}H NMR (90 MHz, TFA, ppm): H8 (s), 9.5; H2 (s), 8.6; NCH_2 (m), 4.9; $(CH_2)_2$ (m), 2.9. ^{13}C NMR (DCl (30%)/D_2O (1:1), ppm): C2, 150.32; C4, 148.10; C5, 116.38; C6, 154.77; C8, 140.49; NCH_2, 44.27; CH_2, 29.44; dioxane 67.39. Anal. Calcd for $C_{13}H_{12}N_8O_2\cdot{}^1/_4H_2O$: C, 49.29; H, 3.98; N, 35.37. Found: C, 49.34; H, 4.02; N, 35.39.

1,4-Bis(hypoxanthin-9-yl)butane (Hyp-$(CH_2)_4$-Hyp) was prepared as above. The crude product (0.9 g) was recrystallized from 500 mL of hot water; yield 0.81 g (81%). ^{1}H NMR (90 MHz, TFA, ppm): H8 (s), 9.4; H2 (s), 8.6; NCH_2 (m), 4.7; $(CH_2)_2$ (m), 2.25. ^{13}C NMR (Me_2SO/DCl (30%) (10:1), ppm): C2, 148.22; C4, 146.89; C5, 107.21; C8, 124.84; C6, 152.78; NCH_2, 36.08; $(CH_2)_2$, 25.24. Anal. Calcd for $C_{14}H_{14}N_8O_2\cdot{}^1/_4H_2O$: C, 50.83; H, 4.42; N, 33.87. Found: C, 50.77; H, 4.45; N, 33.82.

1,3-Bis(adenin-9-yl)-2-propanol (Ade-$(CH_2CHOHCH_2)$-Ade). Under N_2, 2.48 g of NaH (60%) was added to 200 mL of dry DMF. To this suspension was added 5 g of 6-acetoamide purine (prepared by the method of Kassel[12]). This suspension was stirred for 1 h. The N_2 was removed and the reaction exposed to the air. To the resulting suspension was added 1,3-dibromo-2-propanol (3.7 g), and the reaction mixture was stirred at room temperature for 3 days. The solvent was then removed by rotoevaporation. The sticky solid was dissolved in 200 mL of an ice water mixture. The solution was stirred, and after several hours, a white precipitate formed. After a total of 6 h of stirring, the white solid was collected and washed with acetone. The crude material was recrystallized first from water and then from acetic acid; yield 1.4 g (27%). ^{1}H NMR (200 MHz, ppm): H8 (s), 8.13; H2 (s), 8.08; NH_2 (br), 7.2; OH (br), 5.6; CH_2CHCH_2 (br), 3.9–4.36. ^{13}C NMR (ppm): C2, 152.28; C4, 149.59; C5, 118.46; C6, 155.85; C8, 141.46; CH_2, 67.17; NCH_2, 46.70. Anal. Calcd for $C_{13}H_{14}N_{10}O\cdot 2H_2O$: C, 43.09; H, 5.01; N, 38.66. Found: C, 43.16; H, 4.59; N, 38.60.

1,3-Bis(hypoxanthin-9-yl)-2-propanol (Hyp-$(CH_2CHOHCH_2)$-Hyp). A solution of 0.6 g of Ade-$(CH_2CHOHCH_2)$-Ade (10 mL of H_2O/1 mL of concentrated H_2SO_4) was heated to 60 °C. A solution of $NaNO_2$ (3 g in 7 mL of H_2O) was added very slowly (~1 h), with stirring. After the addition was complete, the solution was maintained at 60 °C for 1 h and then cooled to room temperature. The pH was adjusted to 5 with 4 M NH_4OH. A yellow precipitate was collected, washed with water, and air-dried. It was recrystallized from a minimum amount of warm DMF; yield 0.32 g (53%). ^{1}H NMR (200 MHz, ppm): H8 (s), 8.04; H2 (s), 8.03; OH (br), 5.7; CH_2CHCH_2 (m), 4.07–4.33. ^{13}C NMR (ppm): C2, 148.48; C4, 145.36; C5, 123.68; C6, 156.57; C8, 140.89; CH, 46.94; NCH_2, 42.56. Anal. Calcd for $C_{13}H_{12}N_8O_3\cdot{}^1/_2H_2O$·DMF: C, 46.85; H, 4.79; N, 30.72. Found: C, 46.81; H, 4.90; N, 30.67.

Preparations of Complexes. Bis[μ-1,4-bis(hypoxantbin-9-yl)butane]-bis[(diaminoethane)platinum(II)] Tetrakis(hexafluorophosphate), [Pt(en)(Hyp-$(CH_2)_4$-Hyp)]$_2(PF_6)_4$. A warm aqueous solution (300 mL, 60 °C) of Hyp-$(CH_2)_4$-Hyp (0.2 g, 6×10^{-4} mol) was added to a warm aqueous solution (100 mL, 60 °C) of Pt(en)Cl_2[13] (0.2 g, 6×10^{-4} mol). The solution was stirred at 60 °C for 48 h, cooled to room temperature, and filtered to remove a small amount of unreacted Pt(en)Cl_2. The solution was reduced in volume to 50 mL by rotoevaporation. A solution of $AgNO_3$ (0.2 g, 10 mL of of H_2O) was added. The resulting suspension was stirred in the dark, with heating (60 °C), for 45 min. After it had cooled to room temperature, the solution was filtered to remove AgCl. The filtrate was added to a NH_4PF_6 solution (0.3 g, 3 mL of H_2O), and the resulting soluton was stirred at 60 °C for 3 h and then allowed to evaporate slowly at room temperature. After 48 h, a white solid was collected; yield 75 mg (14%). The product was washed with acetone and then diethyl ether and air-dried. ^{1}H NMR (200 MHz, D_2O, ppm): H8 (s), 8.31; H2 (s), 8.20; NCH_2 (m), 4.18; en (m), 2.80; $(CH_2)_2$ (m), 1.75. Anal. Calcd for $C_{32}H_{44}F_{24}N_{20}O_4P_4Pt_2\cdot H_2O$: C, 21.83; H, 2.63; N, 15.90. Found: C, 22.11; H, 2.76; N, 15.87. Crystals for X-ray diffraction studies were obtained by slow evaporation to dryness from water.

[(1,3-Bis(hypoxanthin-9-yl)propane)(diaminoethane)platinum(II)] Chloride Trihydrate. A warm aqueous solution (60 mL, 60 °C) of Pt(en)Cl_2 (0.1 g, 3×10^{-4} mol) was added to a warm aqueous suspension (400 mL, 60 °C) of Hyp-$(CH_2)_3$-Hyp (0.096 g, 3×10^{-4} mol). After it was heated (60 °C) for 5 h, the suspension became clear. Heating was continued for 48 h. The solution was reduced in volume to 25 mL by rotoevaporation and then allowed to evaporate at room temperature. After 3 days, 25 mg of a yellow solid was collected and air-dried: yield 12%. ^{1}H NMR (90 MHz, D_2O, ppm): H8 (s), 8.45; H2, 8.25; NCH_2 (m), 4.2; en (m), 2.8; CH_2 (m), 2.2. Anal. Calcd for $C_{15}H_{20}Cl_2N_{10}O_2Pt\cdot 3H_2O$: C, 26.04; H, 3.76; N, 20.26. Found: C, 26.23; H, 3.46; N, 20.05.

[(1,3-Bis(hypoxanthin-9-yl)-2-propanol)(diaminoethane)platinum(II)] Chloride Tetrahydrate. A warm aqueous solution (60 mL, 60 °C) of Pt(en)Cl_2 (0.2 g, 6×10^{-4} mol) was added to a warm aqueous solution (300 mL, 60 °C) of Hyp-$(CH_2CHOHCH_2)$-Hyp (0.2 g, 6×10^{-4} mol). The solution was stirred at 60 °C for 48 h. The volume was reduced to 10 mL by rotoevaporation. The solution was then placed on a Sephadex G-120 column (3-cm, diameter, 25-cm length) and the column eluted with water. After an initial fraction of 30 mL, fractions of 20 mL were collected and allowed to evaporate to dryness. Fractions 2 and 3 yielded 59 mg of the desired compound, which was air-dried; yield 15%. ^{1}H NMR (90 MHz, D_2O, ppm): H8 (s), 8.45; H2 (s), 8.41; NCH_2 (m), 4.3; CH (m), 3.2; en (m), 2.95. Anal. Calcd for $C_{15}H_{22}Cl_2N_{10}O_3Pt\cdot 4.5H_2O$: C, 24.52; H, 3.67; N, 19.07. Found: C, 24.60; H, 3.67; N, 18.97.

[μ-1,4-Bis(hypoxanthin-9-yl)butane]bis[*cis*-chlorodiammineplatinum-(II)] Chloride Dihydrate. A warm aqueous solution (150 mL, 60 °C) of Hyp-$(CH_2)_3$-Hyp (0.096 g, 3×10^{-4} mol) had an initial pH of 6.8. The pH was lowered to 5.2 with 1 N HNO_3. This solution was added to a warm aqueous soluton (80 mL, 60 °C) of *cis*-[Pt$(NH_3)_2Cl_2$] (0.09 g, 3×10^{-4} mol). The solution was allowed to slowly evaporate at 60 °C for 36 h. When the solution was cooled to room temperature, the pH was 3.25. The volume was further reduced to 25 mL under vacuum. The pH was raised to 6.5 with 1 N NaOH. After 24 h, 0.041 g of yellow solid was collected by filtration. The solid was recrystallized from a small amount of hot water; yield 0.038 g (14%). ^{1}H NMR (90 MHz, D_2O, ppm): H8 (s), 8.35; H2 (s), 8.2; NCH_2 (m), 4.3; CH_2 (m), 2.4. Anal. Calcd for $C_{13}H_{28}Cl_4N_{12}Pt_2\cdot 2H_2O$: C, 15.84; H, 3.11; N, 17.13. Found: C, 16.13; H, 3.05; N, 16.80.

X-ray Data Collection. Structure Determination and Refinement. Diffraction data on the crystal of the title compound were collected at 22 °C on an automated Syntex $P2_1$ diffractometer, located at Georgia Institute of Technology, utilizing graphite-monochromatized Mo K$\bar{\alpha}$ radiation (λ = 0.710 69 Å) in the θ–2θ scan mode, with a takeoff angle of 6.75°, 2θ range of 4–50°, variable scan rate of 2.02–23.9°/min, and a scan width of 2°. Stationary background counts were measured at the beginning (bgd1) and at the end (bgd2) of each scan with a total background to scan time ratio, TR, of 1. Intensities were calculated from the total scan count (CT) and background counts by the relationship I = CT–(TR)(bgd1 + bgd2). The intensities were assigned standard deviations according to the formula $\sigma^2(I)$ = [CT + (TR)^2(bgd1 + bgd2)]. Lorentz and polarization corrections were made. There were no significant variations in the three standard reflections (006; 0,10,0; 500) that were repeated every 100 reflections. There were 5084 total data collected in octants $-h$ to $+h$, $-k$ to $+k$, and 0 to $+l$. Computations were performed with the SHELXTL system, version 3, a minicomputer version of the SHELX program system, on a Data General Eclipse S/140 computer located at Emory University. The merging R factor was 0.0394 as in SHELXTL data reduciton. There were 4871 total observed data having $F > 3\sigma_F$. There were 420 parameters varied. Standard scattering factors, F_o, f', and f'', for atoms were used.[14] The structure was solved by standard heavy-atom Patterson and Fourier techniques and refined

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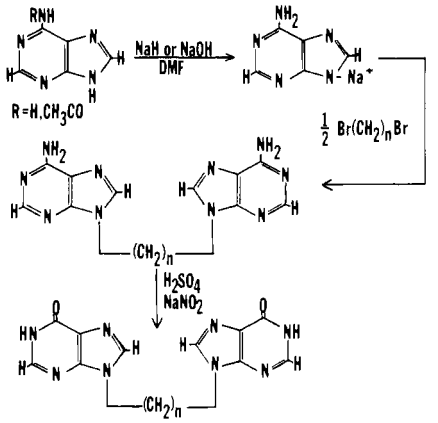
Table I. Experimental Data for the X-ray Diffraction Study of $C_{32}H_{44}F_{24}N_{20}O_4P_4Pt_2 \cdot H_2O$

a, Å	11.182 (2)	d(calcd)	2.12
b, Å	13.654 (3)	space gp	$P\bar{1}$ [a]
c, Å	12.376 (2)	cryst size, mm³	0.52 × 0.22 × 0.15
α, deg	103.88 (2)	μ, cm^{-1}	53.32
β, deg	125.82 (1)	color, habit	colorless, irregular polyhedron
γ, deg	97.60 (2)		
V, Å³	1395.4 (5)	F(000)	1014
Z	1	wt scheme [b]	$1/(\sigma^2(F) + 0.1240F^2)$
mol wt	1760.74	R [c]	0.0314
		R_w [d]	0.0375

[a] The structure refined successfully as $P\bar{1}$. [b] $\sigma(F) = \sigma(I)/(2F)$. [c] $R = \Sigma(|F_o - F_c|)/\Sigma(F_o)$. [d] $R_w = \Sigma[(|F_o - F_c|)w^{1/2}]/\Sigma[(F_o)w^{1/2}]$.

Scheme I



by full-matrix least-squares analysis. The quantity minimized in the least-squares minimization was $\sum(|F_o| - |F_c|)^2$. An overall scale factor was varied and the x, y, z coordinates of all non-hydrogen atoms were refined. The Pt, P, and O atoms were refined anisotropically, and the remaining atoms were refined isotropically. Some of the hydrogens were located by difference Fourier, and some were placed at calculated points. An absorption correction was applied with the program XEMP, a semi-empirical absorption correction program included in SHELXTL, and no corrections for extinction were made. The maximum and minimum transmission coefficients were 0.960 and 0.745, respectively. Crystal data and other experimental parameters are given in Table I.

Results

Preparation of Ligands. The closest models for an intrastrand cross-link would involve bis(purines) of the type Gua–$(CH_2)_n$–Gua. However, Gua derivatives are usually insoluble, and it is well documented that 9-alkylated hypoxanthine (Hyp) derivatives have very similar coordination chemistry to 9-alkylated Gua derivatives.[8] Hyp differs from Gua by lacking a C2 NH_2 group.

We prepared Hyp–$(CH_2)_n$–Hyp derivatives by combining several different reaction schemes that have been reported to yield bis(purine) compounds (Scheme I).

This scheme has advantages over previously published methods since NaOH is satisfactory rather than NaH and no ring closures are involved. Several other related compounds were made by this route and are described elsewhere.[15] Although the compounds were formed readily and in good yield, they were usually poorly soluble. Introduction of an OH group in the bridge via alkylation with $BrCH_2CH(OH)CH_2Br$ improved solubility only marginally.

We assigned alkylation at N9 by the following criteria: First, some of the adenine compounds were prepared previously[9-12] by a more circuitous route but one that leaves little doubt as to the structure. Our compounds can be compared to these by melting point and by ^1H NMR. The Ade–$(CH_2)_3$–Ade compound was prepared and compared to the previously reported literature value.[9] In addition, the ^{13}C NMR data values of various related compounds were compared.[9]

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Table II. Non-Hydrogen Atom Coordinates (×10⁴) for $[Pt(en)(Hyp\text{-}(CH_2)_4\text{-}Hyp)]_2(PF_6)_4$

atom	x/a	y/b	z/c
Pt	2100 (1)	2047 (1)	2393 (1)
N(a)	1757 (4)	1187 (4)	3371 (4)
N(b)	3937 (5)	1518 (3)	3024 (4)
N1	−742 (6)	3378 (4)	4133 (5)
N3	−2669 (5)	3326 (4)	1809 (5)
N7	209 (4)	2501 (3)	1756 (4)
N9	−2031 (4)	2749 (3)	260 (4)
N1′	884 (5)	1930 (3)	−2287 (4)
N3′	3024 (4)	3543 (3)	−914 (4)
N7′	2715 (4)	2924 (3)	1565 (4)
N9′	4212 (4)	4199 (3)	1620 (4)
C2	−2103 (7)	3482 (5)	3118 (7)
C4	−1732 (6)	2993 (4)	1548 (5)
C5	−356 (5)	2842 (3)	2479 (5)
C6	266 (5)	3032 (4)	3925 (5)
C8	−838 (5)	2469 (4)	446 (5)
C2′	1865 (6)	2738 (4)	−2142 (5)
C4′	3128 (5)	3474 (3)	214 (5)
C5′	2188 (5)	2695 (4)	173 (5)
C6′	949 (6)	1811 (4)	−1163 (5)
C8′	3922 (5)	3847 (3)	2384 (4)
C(a)	3214 (7)	982 (5)	4358 (6)
C(b)	3831 (7)	675 (5)	3586 (7)
C(c)	−3441 (5)	2759 (4)	−1098 (5)
C(d)	3523 (5)	6123 (4)	904 (5)
C(e)	4992 (5)	6175 (3)	2319 (5)
C(f)	5451 (5)	5189 (4)	2176 (5)
O6	1416 (4)	2908 (3)	4900 (3)
O6′	−21 (5)	1050 (3)	−1399 (4)
P1	7409 (2)	157 (1)	3039 (2)
P2	1894 (2)	5991 (1)	3393 (2)
F1	6047 (6)	−0 (5)	3111 (6)
F2	7912 (7)	−695 (4)	3725 (6)
F3	8785 (5)	275 (4)	2949 (6)
F4	6882 (6)	997 (4)	2331 (6)
F5	6307 (7)	−770 (4)	1508 (5)
F6	8527 (6)	1072 (4)	4585 (4)
F7	2136 (9)	5278 (5)	4317 (7)
F8	1448 (8)	5020 (4)	2155 (5)
F9	2496 (10)	6973 (4)	4772 (8)
F10	268 (7)	5745 (7)	2962 (8)
F11	3640 (7)	6225 (9)	4030 (8)
F12	1713 (17)	6675 (7)	2570 (12)
O1	3039 (9)	10 (5)	365 (7)

Finally, we have completed the X-ray structure of one compound coordinated to Pt and show the alkylation site to be N9. Efforts to investigate extensively the metal complex chemistry of these compounds in solution and to explore fully the preparative chemistry of the compounds were greatly hampered by the low solubility of the bis(purine) compounds. In view of the rapid advances in oligonucleotide synthesis, this research effort was terminated. However, we were successful in crystallizing one complex that exhibits unusual structural features. We describe this compound in the Discussion.

Discussion

Coordination Environment. The complex, $[Pt(en)(Hyp\text{-}(CH_2)_4\text{-}Hyp)]_2(PF_6)_4$, crystallizes in the triclinic system, $P\bar{1}$ space group. The complex is a dimer. Each Pt atom is coordinated to two nonlinked Hyp bases via N7 and to both N's of an en ligand. The four N's form a distorted planar arrangement (Figure 1). Two Hyp bases are linked through N9 by a tetramethylene chain, forming a Hyp–$(CH_2)_4$–Hyp ligand. Each Hyp in this ligand coordinates via N7 to a different Pt. Each unit of the dimer is related by an inversion center. Atomic coordinates are given in Table II. All bond lengths and internal bond angles (Table III) for the bases are close to those found for uncoordinated inosine.[16] The average Pt–N7 bond distance for this complex at 2.032 (7) Å is typical for Pt bound to N7 of hypoxanthine moieties and can

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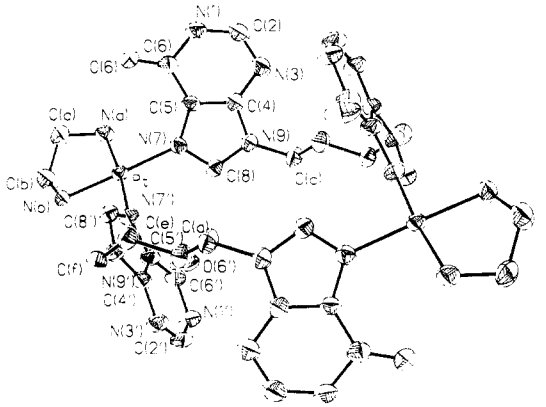


Figure 1. Stereochemistry and atomic numbering for $[Pt(en)(Hyp-(CH_2)_4-Hyp)]_2^{4+}$.

Table III. Selected Bond Lengths and Angles

A. Selected Bond Lengths (Å)

Pt-N(a)	2.024 (7)	Pt-N(b)	2.033 (7)
Pt-N7	2.027 (6)	Pt-N7′	2.037 (7)
N7-C5	1.398 (9)	N7′-C5′	1.385 (8)
N7-C8	1.316 (7)	N7′-C8′	1.332 (6)
C8-N9	1.341 (9)	C8′-N9′	1.328 (9)
C5-C4	1.364 (7)	C5′-C4′	1.362 (9)
C5-C6	1.423 (9)	C5′-C6′	1.424 (6)
C6-O6	1.215 (6)	C6′-O6′	1.236 (8)
C6-N1	1.408 (11)	C6′-N1′	1.400 (10)
N1-C2	1.349 (9)	N1′-C2′	1.344 (9)
C2-N3	1.292 (10)	C2′-N3′	1.309 (5)
N3-C4	1.364 (11)	N3′-C4′	1.359 (9)
C4-N9	1.362 (9)	C4′-N9′	1.366 (6)
N9-C(c)	1.491 (7)	C(c)-C(d)	1.511 (8)

B. Selected Bond Angles (deg)

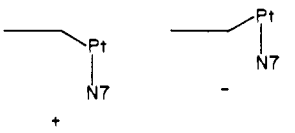
N(a)-Pt-N(b)	83.9 (3)	N9-C(c)-C(d)	111.5 (3)
N7-Pt-N7′	92.8 (2)	C(c)-C(d)-C(e)	108.7 (3)
Pt-N7-C5	131.3 (3)	Pt-N7′-C5′	131.4 (3)
Pt-N7-C8	124.1 (5)	Pt-N7′-C8′	123.3 (4)
N7-C5-C4	108.7 (5)	N7′-C5′-C4′	108.8 (4)
C5-C4-N9	107.3 (6)	C5′-C4′-N9′	107.0 (6)
C4-N9-C8	106.5 (4)	C4′-N9′-C8′	107.1 (4)
C4-N9-C(c)	126.4 (6)	C4′-N9′-C(f′)	126.3 (6)
C8-N9-C(c)	127.1 (6)	C8′-N9′-C(f′)	126.6 (4)
N9-C8-N7	113.1 (6)	N9′-C8′-N7′	112.2 (4)

be compared to 2.036 (8) Å for *cis*-$[Pt(NH_3)_2(5'\text{-IMP})_2]^{2-}$[17] and 2.029 (9) Å for $[Pt(dien)(Ino)]^{2+}$[18] (see Table IV for abbreviations).

Relative Orientation of the Hyp Bases. The C6–O6 groups of the two purine bases bound to each Pt atom are on opposite sides of the coordination plane in the so-called head-to-tail (htt) geometry. This is the common orientation of the bis complexes of Pt-containing nucleobases[19,20] and also the orientation typically found for other metal species.[21,22] There is only one report of a head-to-head (hth) compound, namely several salts of the *cis*-$[Pt(NH_3)_2(9\text{-EtGua})_2]^{2+}$ cation.[23]

The base–base dihedral angle (B/B) is a useful parameter for comparing structural features of purine complexes. B/B is the angle formed by the intersection of the planes that pass through two bases in a cis arrangement. The angle is calculated according to the method outlined by Kistenmacher et al.[19,20] by placing one base in plane so that the N→Pt vector is leftward and the second base is outward to determine whether the angle is greater than or less than 90°. The B/B angle for the title complex is quite large at 107.6° in comparison to other Pt complexes with coordinated purines (Table IV). The nucleotide complexes have the smallest angles in the 40–50° range, and the nucleoside complexes have angles in an intermediate range 70–74°. The unusually large B/B angle found here is probably due to conformational restrictions resulting from the tetramethylene bridge.

Scheme II



In several Pt complexes, *cis*-$[Pt(NH_3)_2(5'\text{-IMP})_2]^{2-}$,[17] *cis*-$[Pt(tn)(5'\text{-IMP})_2]^{2-}$,[24] and $[Pt(tn)(Me\text{-}5'\text{-GMP})_2]$,[25] there is a relatively short intramolecular O6–C8′ distance (av = 3.00 (2) Å) with overlap of the 6-membered pyrimidine rings. The complex described here has a longer average O6′–C8 distance of 3.25 (1) Å due to the large base–base dihedral angle.

Relative Orientation of the Base and Metal Coordination Planes: Intramolecular H Bonding. A common feature of 6-oxopurine complexes is the H-bonding interaction of the O6 with another ligand in the coordination sphere (interligand H bonding).[26] For a series of Cu(II)–theophyllinato Schiff base complexes O6 interacts with the Cu(II), H bonds to another ligand,[28,29] or shows neither interaction.[30] The dihedral angle between the base plane and the metal coordination plane (B/M, see ref 31) is small (~40–60°) when H bonding is found and larger (>62°) when it is absent. In the present structure the base indicated without primes has a small dihedral angle, 45.7°, and a significant H-bonding interaction (O6–N(a) = 2.86 (1) Å). The primed base shows no intramolecular H-bonding interaction and has a large B/M dihedral angle of 78.9°. O6′ does participate in an intermolecular H-bonding interaction with a H on N(a) of an adjacent complex (O6′–N(a) ~2.89 (1) Å).

Relative Values of the M–N7–C5 and M–N7–C8 Angles. The extensive studies on Cu–theophyllinato Schiff base complexes have also revealed a relationship between the M–N7–C5 and M–N7–C8 angles and the involvement of O6 in H bonding and M bonding.[27-30] In particular, for intramolecular interligand H bonding the Cu–N7–C5 angle is appreciably greater (by >15°) than Cu–N7–C8.[28,29] The reverse relationship holds when O6 interacts with the Cu.[27] These angles are nearly equal when there is no evident Cu or H-bonding interaction.[30]

With this relationship in mind, we reviewed the literature on Pt–6-oxopurine complexes.[17,18,23-25,32-37] First, as is now widely

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Table IV. Selected Structural Parameters for Pt Complexes with Two Purines in Cis Positions[a]

complex	Pt-N7	B/B	B/M[b]	Pt-N···O6	ref
$[Pt(en)(Hyp)-(CH_2)_4-Hyp)]_2(PF_6)_4$	2.027 (6)	107.6	45.7	2.86	this work
	2.032 (7)		78.9		
cis-$[Pt(NH_3)_2(9\text{-EtGua})_2]Cl_2$	2.03 (1)	68	75.4		23
	2.03 (1)		49.2	2.92 (1)	
cis-$[Pt(NH_3)_2(9\text{-EtGua})_2]Cl_{1.5}(HCO_3)_{0.5}$	2.02 (1)	70	74.4		23
	2.03 (1)		50.6	2.96 (1)	
$[Pt(en)(1,3,9\text{-TMX})_2](NO_3)_2$	2.010 (3)	87.3	63.2	3.13 (1)	32
	2.021 (4)		60.5	3.04 (1)	
$[Pt(en)(1,3,9\text{-TMX})_2](PF_6)_2$	2.018 (4)	70.6	58.6	2.99 (1)	32
$[Pt(en)(Guo)_2]Cl_{1.5}I_{0.5}$	1.967[c,d]	71	*d*	*d*	34
cis-$[Pt(NH_3)_2(Guo)_2]Cl_{1.5}(ClO_4)_{0.5}$	1.99 (1)	74	74	4.51 (2)	35
	2.02 (1)		70	4.44 (2)	
Na_2-*cis*-$[Pt(en)(5'\text{-GMP})_2]$	1.97[c,d]	54	*d*	*d*	36
Na_2-*cis*-$[Pt(NH_3)_2(5'\text{-IMP})_2]$	2.036 (8)	40.7	61.8	4.61 (2)	17
$Na_2[Pt(tn)(5'\text{-IMP})_2]$	2.08 (1)	38.2	63.9	4.60[c]	24
$[Pt(tn)(Me\text{-}5'\text{-GMP})_2]$	2.02 (1)	39.6	127	4.90 (2)	25

[a] Abbreviations: 9-EtGua = 9-ethylguanine; 1,3,9-TMX = 1,3,9-trimethylxanthine; tn = trimethylenediamine; 5'-IMP = inosine 5'-monophosphate; 5'-GMP = guanosine 5'-monophosphate; Me-5'-GMP = methyl guanosine 5'-monophosphate phosphodiester; Ino = inosine; Guo = guanosine; dien = diethylenetriamine. [b] See ref 31. [c] Information on standard deviations was not available. [d] Information on coordinates was not available.

established, there is no evidence for a Pt–O6 interaction since the Pt–N7–C5 angle is never found to be appreciably smaller than the Pt–N7–C8 angle, except on deprotonation of N1 (see below). In most cases, Pt–N7–C5 angles are ca. 4–10° greater than the corresponding Pt–N7–C8 angle in the same base, regardless of whether or not O6 participates in intramolecular H-bonding interactions. There are, however, some cases where the angles are nearly equal, and in these cases there is no intramolecular interaction. First, this situation is found in the related complexes $[Pt(dien)(Guo)]^{2+}$ [18] and $[Pt(dien)(Ino)]^{2+}$ [18] and in [*cis*-chlorodiammine(N^2,N^2-dimethyl-9-methylguanine)platinum(II)](1+).[33] For these three compounds, only one 6-oxopurine is found in the coordination environment. Second, near equality of these angles is found in *cis*-$[Pt(NH_3)_2(9\text{-EtGua})_2]^{2+}$ cations for the one base that is not intramolecularly H bonded.[23] This cation has the rare hth configuration whereas all other Pt structures with two N7-coordinated 6-oxopurines have the htt configuration. Except for the present structure, all of these htt compounds have both ligands participating or both not participating in intramolecular H-bonding interactions. The present compound is unique for a htt compound since only one base participates in an intramolecular H bond.

In the two independent forms of the cation, *cis*-$[Pt(NH_3)_2(9\text{-EtGua})(1\text{-MeCyt})]^{2+}$(where 1-MeCyt = 1-methycytosine), where O6 does not participate in an intramolecular H bond, Pt–N7–C5 is slightly but not significantly greater than Pt–N7–C8.[37] For some derivatives deprotonated at N1 the Pt–N7–C8 is actually larger than Pt–N7–C5 and this effect was attributed to internal H bonding. The structures of these latter derivatives are complex, and the reader is referred to the original paper.[37]

Perpendicular Displacement of the Pt from the Base Plane. An analysis of the displacement of the Pt from the base plane of Pt complexes has appeared.[20] Illustrated in Scheme II is the sign convention. (The data in supplementary table Table S1 use the usual convention, however.) For a + sign, the Pt and the N7 of the other base are on the same side of the base plane whereas they are on opposite sides for a − sign. Three situations are possible when considering two bases attached to Pt: +,+; +,−; −,−. From an analysis of complexes with Pt bound to pyrimidines,[20] the transition across this series corresponded both to increasing B/B dihedral angle and to increased steric crowding (substituents on the pyrimidine ring). The present structure supports the relationship that large dihedral angles correspond to a −,− displacement of Pt with respect to the base planes with displacement from the nonprimed base plane of Pt and N7′ at −0.1043 and +1.3735 Å, respectively, and displacement from the primed base plane of Pt and N7 at −0.2429 and +1.7163 Å, respectively. However, the steric bulk of the ring substituents is not important. Thus, it is clear that the −,− situation can be produced by steric restrictions elsewhere in the complex. Thus, at this time and on the basis of structural results on models, a −,− type of complex can not be excluded in $Pt(Gua)_2$ adducts in DNA.

Stacking Interactions. The molecules pack such that there is a 3.0-Å intermolecular base stacking distance but with no overlap or close approach of the bases. Guanosine,[16] inosine,[16] and guanine[38] all crystallize such that the bases stack with a 3.3-Å separation. Both $[Pt(en)(Guo)_2]^{2+}$ [34] and $[Pt(tn)(Me\text{-}5'\text{-GMP})_2]$[25] show intermolecular stacking such that each base stacks with a base in the adjacent molecule forming a spiral arrangement.[8] *cis*-$[Pt(NH_3)_2(9\text{-EtGua})_2]^{2+}$ [23] also exhibits intermolecular base stacking, whereas *cis*-$[Pt(NH_3)_2(1,3,9\text{-TMX})_2]^{2+}$ [32] does not. Two 5'-IMP complexes, *cis*-$[Pt(NH_3)_2(5'\text{-IMP})_2]^{2-}$ [17] and *cis*[$Zn(H_2O)_4(Me\text{-}5'\text{-IMP})_2$][21] have IMP bases that are parallel but are not in close enough proximity for intermolecular interactions. The large base–base dihedral angle of the structure presented here positions the bases such that any sort of intermolecular or intramolecular base interaction is sterically impossible. However, we have noted previously that intermolecular stacking is often found in N7-bound 2-amino-6-oxopurine complexes but not in complexes of 6-oxopurines lacking a 2-amino group.[21] Therefore, the absence of intermolecular stacking interactions is not surprising.

Summary. As we had hoped, the attachment of the Hyp base to another Hyp base via a $-(CH_2)_n-$ chain did lead to some unique structural features, although the desired monomeric complex was not synthesized. The differences between the present structure and previous relevant Pt complexes are instructive and suggest that Pt can accommodate a wide range of 6-oxopurine orientations ranging in B/B dihedral angles from 38 to 107°. In addition, the relative displacement of the Pt can be −,−, and the B/M dihedral angles can be quite different, with only one base participating in interligand H bonding. Such diversity may well be important in the functioning of Pt complexes as antitumor agents since evidence continues to mount that the DNA conformation in nucleosomes[39] and in solution[39,40] is distorted by antitumor Pt binding. The extent of the distortion is uncertain and H-bonding interactions may be maintained. However, several different intermediate conformations are likely to arise as the Pt–DNA interaction proceeds from the double helix to the final distorted conformation. When the nature of the conformation in Pt–dinucleotide or Pt–oligonucleotide

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complexes is more carefully defined, it will be interesting to compare with results with those found for model compounds such as those discussed here.

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Supplementary Material Available: Tables of least-squares planes and deviations of individual atoms from these planes, atom coordinates, bond lengths, bond angles, anisotropic temperature factors, hydrogen coordinates and temperature factors, and observed and calculated structure factors (36 pages). Ordering information is given on any current masthead page.

Contribution from the Department of Chemistry, University of Queensland, Brisbane, Australia 4067

Platinum Complexes with Iminodiacetate and (Methylimino)diacetate, Including Genuine Meridional Complexes

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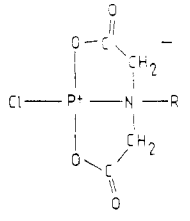
Reactions of $PtCl_4^{2-}$ with LH_2 (iminodiacetic acid, $idaH_2$, or (methylimino)diacetic acid, $midaH_2$) have been reported in the literature to yield platinum(II) complexes with the ligand meridional, K[Pt(ida)Cl]·2HCl and H[Pt(mida)Cl]·2HCl. These compounds are platinum(IV) complexes, $Pt(L)Cl_3^-$, with the ligand facial, which may be prepared directly from K_2PtCl_6 and LH_2. Reaction of K_2PtCl_4 with LH_2 at ambient temperature gives $K[Pt(LH)Cl_2]$, in which the ligand is bidentate, coordinating through the N atom and one O atom. Genuine *mer*-$Pt(L)Cl^-$ may be obtained (more readily for L = mida) by careful addition of alkali to a solution of $Pt(LH)Cl_2^-$. Heating a solution of K_2PtCl_4 with excess LH_2 gives sparingly soluble $Pt(LH)_2$ (previously reported for L = ida), which, with alkali, gives soluble $Pt(L)_2^{2-}$. These compounds contain bidentate ligand. For $Pt(ida)_2^{2-}$, slow cis-trans isomerization occurs in solution. At high pH, inversion about coordinated nitrogen becomes rapid. In alkaline D_2O solutions, the methylene group of the coordinated arm is specifically deuterated. The compound described in the literature as $H_{2n}[Pt(mida)_2]_n$ is the platinum(IV) compound $Pt(mida)_2$. This complex, and $Pt(ida)_2$, may be prepared by reaction of the corresponding platinum(II) complex, $Pt(LH)_2$, with hydrogen peroxide.

Introduction

Iminodiacetic acid, $HN(CH_2CO_2H)_2$ ($idaH_2$), and its *N*-methyl analogue, $CH_3N(CH_2CO_2H)_2$ ($midaH_2$), coordinate to most metal ions. In the vast majority of these complexes, the ligand coordinates facially through the N atom and two deprotonated carboxylate groups (e.g., *trans*-$Ni(ida)_2^{2-}$,[1] *cis*- and *trans*-$M(ida)_2^-$ (M = Co, Rh)[2,3]). This preference for facial coordination is thought to be due to significant angle strain at nitrogen in the alternative meridional configuration.[2] *mer* coordination has been claimed, however, for two types of complexes: (i) octahedral complexes where this configuration has been forced by the disposition of the other ligands (e.g., *trans-mer*-$Co(dien)(ida)^+$,[4] dien = $NH_2CH_2CH_2NHCH_2CH_2NH_2$); (ii) complexes with metal ions with a strong preference for square-planar coordination, for which *fac* coordination is not possible (e.g., $Pd(L)(H_2O)$[5] and $Pt(L)Cl^-$ (I)[6] (LH_2 = $idaH_2$ or $midaH_2$)).



I

Close reading of the report by Smith and Sawyer on the platinum compounds[6] indicated that a reexamination of this system was warranted. The proposed *mer* compounds were isolated only with "hydrochloric acid of crystallization", as K[Pt(ida)Cl]·2HCl and H[Pt(mida)Cl]·2HCl, with no report of acid-free material. Also, bis(ligand) complexes were reported—$Pt(idaH)_2$, with the ligand bidentate (through N and one O atom), soluble, as expected, in dilute alkali, and "$H_{2n}[Pt(mida)_2]_n$", quite insoluble in water or alkali. It was difficult to see why two ligands, so similar, would behave so differently.

When we commenced this work, the only platinum(IV) compounds known involving these ligands were *fac*-$Na[Pt(CH_3)_3(L)]$, where facial coordination of the tridentate ligand is forced by the *fac* disposition of the three methyl groups.[7]

We describe here the preparation of platinum(IV) complexes with these ligands, the results of our attempts to reproduce the preparations reported by Smith and Swayer,[6] and the characterization by NMR of the platinum(II) complexes that are actually formed in reactions between K_2PtCl_4 and these ligands.

Results

^1H NMR data are given in Table I and ^{13}C data in Table II . Satisfactory analytical data were obtained for all compounds isolated (Table III).

Platinum(IV) Complexes, K[Pt(L)Cl$_3$]. Heating K_2PtCl_6 with K(midaH) in aqueous solution at pH 5-6 gave a yellow microcrystalline solid that was analyzed as $K[Pt(mida)Cl_3]$. Its IR spectrum shows $\nu_{C=O}$ at 1660 cm^{-1}. Since uncoordinated -COOH groups usually absorb above 1700 cm^{-1},[8] both ligand carboxyl groups are coordinated. A band assignable to ν_{Pt-Cl} occurs at 334 cm^{-1}. Molar conductance of a 10^{-3} M aqueous soluton was 136 Ω^{-1} cm^2 mol^{-1} (cf. 147 Ω^{-1} cm^2 mol^{-1} for 10^{-3} M $[N(CH_3)_4]Cl$).

The ^1H NMR spectrum in D_2O (Table I) shows a singlet for the *N*-methyl group, with "satellites" from coupling to ^{195}Pt (I = $^1/_2$, 34% abundance). The methylene protons give an AB pattern, superimposed on an ABX pattern (half the total intensity of the AB pattern, X = ^{195}Pt).

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