Outer-Sphere Macrochelation in [Pd(en)(5′-GMP-*N7*)$_2$]·9H$_2$O and [Pt(en)(5′-GMP-*N7*)$_2$]·9H$_2$O: X-ray Crystallography and NMR Spectroscopy in Solution

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X-ray crystallography shows that [Pd(en)(5′-GMP-*N7*)$_2$]·9H$_2$O and [Pt(en)(5′-GMP-*N7*)$_2$]·9H$_2$O are isostructural square-planar complexes with the bases coordinated head-to-tail in the Δ configuration. The sugar conformations are C3′-*endo* (N-type), *anti* ($\chi = -155.6$ and $-155.5°$, Pd and Pt), *gauche*$^+$. Macrochelate rings are formed via intramolecular H-bonding between the monoanionic 5′-phosphate groups and coordinated ethylenediamine NH (N···OP 2.92 Å). Electrostatically-bonded axial water molecules (Pd−O = 3.365 Å, Pt−O = 3.493 Å) play key roles in a network of H-bonding involving the phosphate oxygens, ethylenediamine NH, and C6O. ^{1}H{^{15}N} NMR shifts together with ^{31}P{^{1}H} NOE's show that macrochelation involving NH···5′-phosphate H-bonding is present in solution both at pH 7 where the coordinated nucleotide is dianionic and also at low pH (2−3) where it is monoanionic (as in the crystal). The Pt complex is relatively nontoxic to cells in culture (IC_{50} > 0.5 mM for H9 and C8166 cells), and the Pd complex, which dissociates in solution to give 5′-GMP and an *N1,N7*-bridged oligomer as a minor product below pH 6 but as the major product at pH > 7.6, exhibits marginal anti-HIV activity.

Introduction

Adducts of platinum ammine and amine anticancer drugs with guanine derivatives have been widely studied because this base is a major DNA target site for Pt.[4,5] There is also much interest in Pd(II) analogues because they are usually isostructural with those of Pt(II) but equilibria are reached more quickly (ca. $10^4\times$ faster kinetics). The high affinity for N7 of G can be attributed to its high basicity, being more basic than adenine by ΔpK_a ca. 2.3.[6,7] The factors which stabilize nucleotide adducts of Pt(II) ammines and amines have received much attention, particularly the possible roles of C6O and 5′-phosphate in H-bonding interactions with PtNH groups. Reactions of *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ with guanosine 5′-monophosphate (5′-GMP)[8] and 5′-dGMP are considerably faster than those with 3′-GMP or guanosine,[9,10] and this has led to the proposal that Pt−NH···5′-phosphate H-bonding is involved in stabilizing intermediates.[11] There do not appear to be any reports of Pt−NH···5′-phosphate H-bonding in crystalline Pt(II) complexes of mononucleotides. Such H-bonding has been reported for *cis*-[Pt(NH$_3$)$_2${d(pGpG)-*N7*(1),*N7*(2)}]$^{2+}$, crystallized at pH 3.8 with a monoanionic 5′-phosphate,[12] although it is absent in *cis*-[Pt(NH$_3$)$_2${d(CpGpG)-*N7(2),N7(3)*}]$^{2+}$.[13] H-bonds involving PtNH and both C6O and 5′-phosphate are present in [Pt(dien){d(ApGpA)-*N7*(2)}]$^{2+}$.[14] Very few X-ray structures of Pt(II) ammine/amine bis(mononucleotide) complexes have been reported. That of [Pt(en)(5′-GMP)$_2$]·3H$_2$O contains only intermolecular H-bonding between C6O and PtenNH$_2$ of a neighboring molecule,[15] and no such intramolecular interactions appear to be present in either *cis*-[Pt(NH$_3$)$_2$(5′-IMP)]$^{2-}$ or [Pt(tn)(Me-5′-GMP)$_2$]·11H$_2$O.[16,17]

The lowering of the 5′-phosphate pK_a provides evidence for intramolecular Pt−NH···5′-phosphate H-bonding in [Pt(en)(5′-AMP)$_2$] and [Pt(en)(5′-GMP)$_2$],[18,19] and the pH dependence of the PtNH ^{1}H NMR chemical shift confirms this interaction. However, at low pH where the 5′-phosphate is monoanionic, the NH shifts are similar to those of the guanosine analogue and so do not provide evidence for such an interaction.[19]

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We report here evidence for Pt−NH···5′-phosphate H-bonding in the isostructural complexes [Pd(en)(5′-GMP-*N7*)$_2$]·9H$_2$O and [Pt(en)(5′-GMP-*N7*)$_2$]·9H$_2$O both in the solid state and in solution, suggesting that outer-sphere macrochelation makes a substantial contribution to their stabilities, as has been suggested from potentiometric studies of the stabilities of nucleotide complexes of alkaline earth and first transition series divalent metal ions.[6] Intriguingly electrostatically-bonded axial water molecules also play a role in the H-bonding network.

Experimental Section

Materials. K_2PdCl_4, K_2PtCl_4, and $AgNO_3$ were purchased from Johnson Matthey plc, and Na_2-5′-GMP was purchased from Sigma. Isotopically-enriched [Pd(15*N*-en)Cl$_2$] and [Pt(15*N*-en)Cl$_2$] were prepared by standard methods.[20]

Preparation of Complexes. [Pd(en)(5′-GMP-*N7*)$_2$]·9H$_2$O (1). A suspension of [Pd(en)Cl$_2$] (134.3 mg; 0.566 mmol) and 5′-GMPNa$_2$·3H$_2$O (522.2 mg; 1.13 mmol) in H$_2$O (25 mL) was heated at ca. 60 °C until it became a clear solution, and 1 M HNO$_3$ (1.13 mL) was added giving a pH of 2.60. After a further 30 min the volume was reduced to 15 mL and the solution was filtered. Yellow crystals were obtained from the filtrate at 5 °C. Yield: 501.7 mg; 0.47 mmol (83%).

Anal. Calcd for $C_{22}H_{52}N_{12}O_{25}P_2Pd$: C, 25.09; H, 4.98; N, 15.96; P, 5.88. Found: C, 24 .79; H, 4.85; N, 15.50; P, 6.47.

[Pt(en)(5′-GMP-*N7*)$_2$]·9H$_2$O (2) was prepared by reacting [Pt(en)-Cl$_2$] (166.1 mg; 0.51 mmol) with 5′-GMPNa$_2$·3H$_2$O (469.9 mg; 1.02 mmol) in H$_2$O (20 mL) at 60 °C. When the solution became colorless, 1 M HNO$_3$ was added (1 mL) to lower the pH from 6.64 to 2.21, and heating was continued for a further 5 h. On cooling of the solution at 5 °C, white crystals were obtained (357.2 mg; 0.31 mmol; yield 62%).

Anal. Calcd for $C_{22}H_{52}N_{12}O_{25}P_2Pt$: C, 23.14; H, 4.95; N, 14.72. Found: C, 23.43; H, 4.48; N, 14.81.

Solution-State NMR Spectroscopy. Single pulse 270 MHz ^{1}H and 67.9 MHz ^{13}C{^{1}H} NMR spectra were recorded on a JEOL GSX270 spectrometer at 293 K with TSP as internal reference. ^{15}N-edited ^{1}H and [^{1}H,^{15}N] NMR spectra were recorded on a Bruker AM500 spectrometer, as previously described,[19] or on a Varian VXR500 instrument.

The 162 MHz ^{31}P{^{1}H} NOE measurements were made on a Bruker AM400 spectrometer at 298 K using 10 mM solutions of complex **2** in 10% D$_2$O/90% H$_2$O pH* 3.87 and pH* 7.2. About 64 000 transients were collected using 4.2 μs (90°) pulses, 32 K computer points, acquisition time of 0.82 s, and relaxation delay (decoupler gated off) of 0.1 s. Blocks of transients were acquired with the ^{1}H decoupler (power ca. 15 Hz) alternately on resonance and off resonance by ±10 000 Hz and were subtracted to give NOE difference spectra.

Solid-State NMR Spectroscopy. The 75.45 MHz CP-MAS ^{13}C NMR spectra were obtained on a Bruker MSL spectrometer by the University of London Intercollegiate Research Service (University College). Cross polarization times of ca. 1.5 ms and magic angle spinning speeds of ca. 4.5 kHz were used. The chemical shift reference was adamantane (external, 38.56 ppm relative to TSP).

X-ray Crystallography. The same procedure was used for both complexes. The values for the Pd complex **1** are given together with those for the Pt complex **2** in brackets. For Pd, yellow rectangular crystals were obtained from a solution at pH 2.6, and for Pt white crystals were obtained at pH 2.2.

Crystal Data: $C_{22}H_{46}N_{12}O_{22}P_2Pd$ [$C_{22}H_{46}N_{12}O_{22}P_2Pt$], M = 999.05 [1087.74], trigonal, $a = b$ = 12.218(3) [12.212(2)] Å, c = 28.499(2) [28.604(2)] Å, $\alpha = \beta = \gamma$ = 90°, space group $P4_322$, Z = 4, U = 4254(2) [4266(2)] Å^3, D_c = 1.560 [1.694] Mg m^{-3}, F(000) = 2056 [2184], μ(Mo Kα) = 20.285 cm^{-1}.

Data Collection. Unit cell dimensions and intensity data were obtained at 293 K using an Enraf-Nonius diffractometer and area detector with graphite monochromated Mo Kα radiation (λ = 0.710 69 Å), following previously described procedures[21] (D = 60 mm for **1** and 50 mm for **2**, 2ϑ = 20°). A total of 13 161 [18 806] reflections were measured, of which 2637 [3527] were unique.

Solution of the Structure. The heavy atom method[22] was used and refined by full matrix least squares methods (SHELX-93).[23] Absorption corrections were applied at the isotropic refinement stage using the DIFABS procedure adapted for FAST geometry. H atoms were allowed to ride on their parent carbon atoms in their calculated positions (C−H = 0.96 Å): H atoms of water molecules which were located in the difference map were refined with the O(W)−H distance constrained to 1 Å and the H−O(W)−H angle to 108°. The final $R1$ and w$R2$ values for Pd and [Pt] complexes are 0.0338 [0.0289] and 0.0806 [0.0667], respectively. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, Cambridge, U.K.

pH Measurements. Values of pH were measured on a Corning 145 pH meter using an Aldrich microcombination electrode calibrated with Aldrich buffer solutions at pH 4.00 and pH 7.00. Readings of the pH meter for D$_2$O solutions were recorded directly in NMR tubes without being corrected for deuterium isotope effects and are designated as pH* values.

Anti-HIV Tests. These were carried out by Dr. Naheed Mahmood at the MRC Collaborative Centre, Mill Hill, London, U.K., using chronically-infected H9 cells and C8166 cells infected with HIV-I 111B, in RPMI-1640 medium supplemented with 10% fetal calf serum. Antigen (p24 and gp120 proteins) assays were carried out after 5 days' cell growth.

Table 1. Solid-State ^{13}C NMR Shifts (δ) for Complexes **1** and **2**

	C(2)	C(4)	C(5)	C(6)	C(8)	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	C(en)
1	155.6	148.5	115.1	154.4[a]	141.8	89.8	76.1	66.7	83.1	63.3	49.3
2	156.0	148.7	115.5	154.0[a]	140.7	89.9	76.1	66.8	82.9	63.4	48.9

[a] Shoulder.

Results

Our preparative procedure gave high yields of stable, well-defined yellow crystals of the Pd(II) complex **1** and white crystals of the Pt(II) complex **2** at pH 2−3. At this pH the complexes are neutral and contain monoprotonated GMP 5′-phosphate.[24] No sodium was detected in the crystals by ICP−AES (data not shown).

Solid-State Studies. NMR and IR. The CP-MAS-TOSS ^{13}C{^{1}H} spectra of complexes **1** and **2** are very similar. The peaks were assigned on the basis of solution data[25] and solid-state data for Pd(II) nucleoside complexes,[26] Table 1. Only the C8 resonance has a shift different by more than 0.4 ppm in the two complexes.

X-ray Crystallography. Crystals of complexes **1** and **2** are isomorphous, and a crystallographic 2-fold axis passes through the metal and the midpoint of the en C−C bond. The molecular structure is shown in Figure 1, and the positional parameters are listed in Table 2. Thus the two coordinated GMP ligands have the same bond lengths and angles. Also all the bond lengths and angles are very similar for both **1** and **2**, as expected from the similar radii of Pd(II) and Pt(II), 64 and 60 pm, respectively.[27] The unit cell is chiral about the c axis, with the molecules forming a left-handed helix. The stacking of molecules in the unit cell is shown in Figure 2.

The complexes are closely square-planar, Figure 1, and selected bond lengths and angles are listed in Table 3. The two guanine bases are in the head-to-tail configuration (H8's

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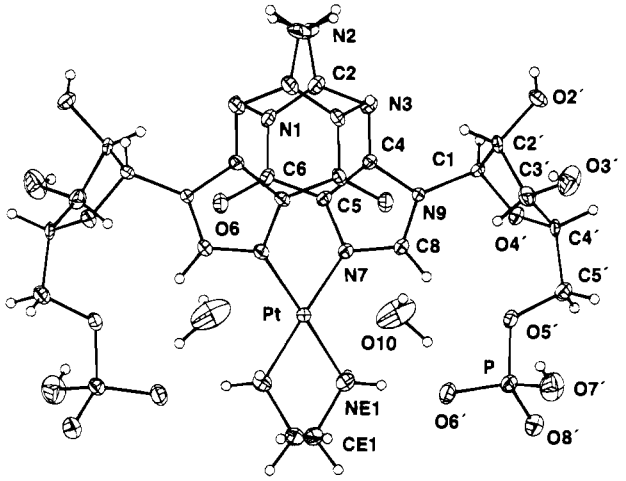

Figure 1. Molecular structure of complex **2** and atom-numbering scheme. Complex **1** is isostructural. Only the axial water molecules (OW10; 100% occupancy) are shown.

of the two nucleotides on opposite sides of the coordination plane) in the Δ configuration.[28] The base−base dihedral angle (B/B′)[29] of 36° is small, and the interbase O6···C8 distances of 2.934 Å (2.895 Å) are indicative of intramolecular base stacking. The nucleobase−MN_4 angle is 48° for **1** and **2**. The ribose rings are in the *anti* configuration with respect to the guanine bases, with glycosidic torsion angles of $\chi = -155.6°$ for **1** and −155.5° for **2**. The values of the phase angles, *P*, for pseudorotation between the five torsion angles $\nu_0-\nu_4$ as defined by Altona and Sundaralingam,[30] are 5.9° for **1** and 4.6° for **2**, and there is a maximum pucker τ_m of 36.3° for **1** and 35.2° for **2**. These values are consistent with a type N ($P = 0 \pm 90°$) or 3′-endo sugar conformation (C3′ above the plane described by C1′, C2′, C4′, and O4′ and on the same side as O5′).

The positions of seven water molecules were located in each of the two structures with the following percentage occupancies: OW9, 100; OW10, 100; OW11, 50; OW12, 76.5; OW13, 33.3; OW14, 56.7; OW15, 32.4. The water molecules corresponding to OW10 are notable because they are pseudo-axial ligands to the metal, Figure 1, with metal−O(W)10 distances of 3.365 Å for Pd and 3.493 Å for Pt (OW10−Pd[Pt]−OW10 = 179.6° [179.0°]). These water molecules are in close contact with both the guanine base and phosphate group: O(W)-10···O6′P = 2.926 Å [2.966 Å], Figure 3. This phosphate O atom has the shortest P−O distance of 1.484 Å [1.490 Å] and is H-bonded to one NH proton of en with an PO6′···NE1 distance of 2.925 Å [2.922 Å] and O6′−H1EB distance of 2.062 Å [2.060 Å]. The corresponding angle PO6′−HE1B−NE1 is 160.3° for **1** [160.1 Å for **2**]. Only one of the two NH_2 protons of en is involved in H-bonding in the crystal. However, the position adopted by the phosphate groups in the crystal is probably influenced also by a strong intermolecular H-bond to the hydroxyl group on the sugar ring of a molecule in an adjacent unit cell with a PO6′−O2′ distance of 2.716 [2.711] Å (PO6′···H-O2′ = 170°).

As well as the axial water OW10, a second water molecule OW9 also has 100% occupancy. This is involved in H-bonding to the phosphate oxygen O8 (PO8′···O9 = 2.779 Å [2.800 Å]), to another water molecule OW13 (OW9···OW13 = 2.723 Å [2.681 Å]), and to the C3′OH of an adjacent molecule

Table 2. Positional Parameters and *U*(eq) Values

atom	*x*	*y*	*z*	*U*(eq)
		(A) Complex **1**		
Pd	2009(1)	2009(1)	1250	22(1)
P	204(1)	5648(1)	980(1)	36(1)
O6	1813(3)	−777(3)	870(1)	37(1)
O2′	−3825(3)	2138(4)	591(1)	45(1)
O3′	−3393(4)	3877(3)	1191(1)	64(1)
O4′	−1791(3)	3215(2)	182(1)	28(1)
O5′	−596(3)	4732(3)	784(1)	38(1)
O6′	1058(3)	5026(3)	1237(1)	46(1)
O7′	−477(4)	6378(4)	1305(1)	66(1)
O8′	582(4)	6378(3)	590(1)	49(1)
NE1	2477(4)	3315(4)	856(1)	33(1)
N1	136(4)	−1351(4)	625(2)	39(1)
N2	−1444(5)	−2081(4)	334(2)	78(2)
N3	−1344(4)	−205(4)	390(2)	34(1)
N7	786(3)	1576(3)	802(1)	24(1)
N9	−888(3)	1693(3)	499(1)	22(1)
CE1	3584(5)	3649(5)	994(2)	49(2)
C2	−894(5)	−1177(5)	454(2)	44(2)
C4	−664(4)	600(4)	524(1)	23(1)
C5	383(4)	525(4)	708(2)	23(1)
C6	871(4)	−536(4)	748(2)	29(1)
C8	3(4)	2236(4)	673(1)	26(1)
C1′	−1956(4)	2142(4)	360(2)	24(1)
C2′	−2742(4)	2238(4)	771(2)	32(1)
C3′	−2510(4)	3401(4)	944(2)	33(1)
C4′	−2292(4)	4024(4)	491(2)	27(1)
C5′	−1560(5)	4993(4)	527(2)	36(1)
O9	2844(5)	3689(7)	4509(2)	114(2)
O10	3520(5)	512(5)	500(2)	92(2)
O11	5000	3477(7)	0	107(3)
O12	4201(10)	689(8)	5300(3)	153(4)
O13	4544(11)	4370(13)	5054(6)	85(5)
O14	3864(9)	2968(12)	5316(4)	130(4)
O15	−3954(7)	6046(7)	1250	129(6)
		(B) Complex **2**		
Pt	2005(1)	2005(1)	1250	22(1)
P	213(1)	5656(1)	971(1)	35(1)
O6	1805(3)	−783(3)	877(2)	36(1)
O2′	−3826(3)	2125(4)	595(2)	44(1)
O3′	−3404(4)	3888(4)	1191(2)	62(1)
O4′	−1802(3)	3216(3)	183(1)	30(1)
O5′	−593(3)	4738(3)	780(2)	39(1)
O6′	1073(3)	5034(3)	1227(2)	46(1)
O7′	−460(4)	6414(4)	1289(2)	63(1)
O8′	584(4)	6387(4)	578(2)	48(1)
NE1	2479(4)	3308(4)	854(2)	32(1)
N1	126(4)	−1347(4)	615(2)	36(1)
N2	−1448(5)	−2088(4)	325(3)	75(2)
N3	−1333(4)	−210(4)	381(2)	35(1)
N7	753(4)	1568(4)	813(2)	26(1)
N9	−887(3)	1703(3)	500(2)	25(1)
CE1	3589(6)	3644(6)	993(2)	55(2)
C2	−899(5)	−1184(5)	451(2)	40(2)
C4	−653(5)	599(4)	526(2)	24(1)
C5	383(5)	524(4)	710(2)	26(1)
C6	873(5)	−537(4)	748(2)	28(1)
C8	−20(4)	2234(4)	683(2)	26(1)
C1′	−1962(4)	2144(4)	361(2)	25(1)
C2′	−2740(4)	2242(4)	771(2)	28(1)
C3′	−2522(5)	3407(5)	942(2)	33(1)
C4′	−2294(4)	4031(4)	492(2)	23(1)
C5′	−1571(5)	5000(5)	521(2)	35(2)
O9	2865(5)	3686(7)	4511(2)	107(3)
O10	3577(5)	399(7)	495(3)	109(3)
O11	5000	3451(7)	0	100(3)
O12	4262(11)	695(10)	5334(4)	154(5)
O13	4536(12)	4360(13)	5047(7)	82(6)
O14	3884(11)	2951(13)	5305(5)	132(5)
O15	−3949(7)	6051(7)	1250	117(6)

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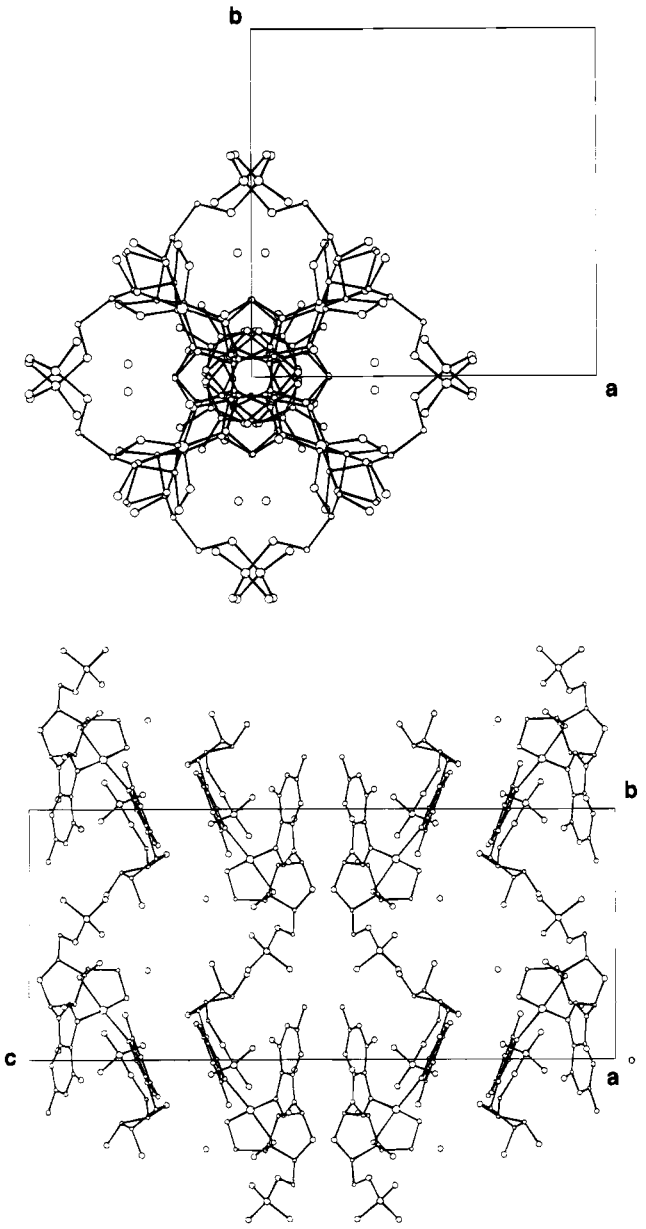

Figure 2. Projections of the X-ray structure of complex **2** including water molecules O9 and O10. (A) Top: Projection down the *c* axis. For clarity the stacking of 8 molecules at one corner of the unit cell is shown. The stacking at the other corners is similar. (B) Bottom: Projection down the *a* axis.

Table 3. Selected Bond Lengths (Å) and Angles (deg) for **1** and **2**

	1	**2**
	Bond Lengths	
M−NE1	2.032(4)	2.036(5)
M−N7	2.036(4)	2.045(4)
P−O5′	1.587(4)	1.588(4)
P−O6′	1.484(4)	1.490(4)
P−O7′	1.532(4)	1.536(5)
P−O8′	1.500(4)	1.505(5)
	Bond Angles	
NE1−M−NE1*	82.1(2)	82.2(3)
NE1−M−N7*	174.7(2)	176.1(2)
NE1−M−N7	93.7(2)	94.4(2)
N7−M−N7*	90.6(2)	89.0(3)
C8−N7−M	123.6(3)	123.7(4)
C5−N7−M	128.0(3)	127.9(4)

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Table 4. Sugar Phosphate Backbone Torsion and Endocyclic Sugar Torsion Angles (deg) for Complexes **1** and **2**

angle	atoms defining angle	**1** (Pd)	**2** (Pt)
α_1	O6′−P−O5′−C5′	177.7	177.9
α_2	O7′−P−O5′−C5′	58.5	57.7
α_3	O8′−P−O5′−C5′	−55.9	−55.3
β	P−O5′−C5′−C4′	−165.5	−165.8
γ	O5′−C5′−C4′−C3′	47.9	48.3
δ	C5′−C4′−C3′−O3′	85.9	85.0
χ	O4′−C1′−N9−C4	−155.6	−155.5
χ'	C8−N9−C1′−O4′	32.2	34.4
ν_0	C4′−O4′−C1′−C2′	8.2	8.6
ν_1	O4′−C1′−C2′−C3′	−27.7	−27.4
ν_2	C1′−C2′−C3′−C4′	36.1	35.1
ν_3	C2′−C3′−C4′−O4′	−32.0	−30.6
ν_4	C3′−C4′−O4′−C1′	15.2	14.1

Table 5. Intra- and Intermolecular Hydrogen Bonding and Close Contacts to H_2O Molecules for **1** (Pd) and **2** (Pt, in Parentheses)

acceptor atom (A)	hydrogen (H)	donor atom (D)	distance (D···A)/Å
(C)O6	H10A	OW10	2.819 (2.822)
(P)O6′	HE1B	NE1	2.925 (2.922)
(P)O6′	H10B	OW10	2.926 (2.966)
(P)O8′	H9A	OW9	2.779 (2.800)
OW13	H9B	OW9	2.723 (2.681)
OW14	H9B	OW9	2.760 (2.741)
PO6′	H2″	O2′	2.716 (2.711)
OW9	H3″	O3′	2.676 (2.679)

(C3′O···OW9 = 2.676 Å [2.679 Å]), with which it is not base-stacked. The latter H-bond may play a role in determining the sugar ring pucker in the crystal.

Both coordinated bases take part in planar intermolecular stacking with bases of a complex in an adjacent unit cell with an interplanar separation of 3.3 Å. The same stacking has been reported for $[Pt(tn)(Me\text{-}5'\text{-}GMP)_2]\cdot 11H_2O$.[17]

NMR Spectroscopy in Solution. Complexes **1** and **2** have similar ^1H NMR shifts over a wide range of pH* values. However, whereas aqueous solutions of the Pt complex **2** gave rise to only one set of peaks, those of **1** gave two other sets of resonances assignable to unbound GMP and to N1/N7-bound GMP peaks. The latter are characterized[31,32] by larger downfield shifts of H8 and H1′ peaks (8.54 and 6.56 ppm) and the smaller value of ^3J(H1′−H2′) (ca. < 1 Hz) (Table 3). These additional peaks were minor at pH* <6, but predominated by pH* 7.6.

The conformations of the ribose rings were deduced from the ^3J coupling constants (Table 6) using the formula[33]

$$\%\ \text{S (C2′-endo)} = {}^3J(\text{H1′−H2′})/\{{}^3J(\text{H1′−H2′}) + {}^3J(\text{H3′−H4′})\}$$

where ^3J(H1′−H2′) values are reported[34] to be 0.5 and 8 Hz for N and S conformations, respectively. For both **1** and **2**, the proportions of type S (C2′-endo) and type N (C3′-endo) ribose conformations were calculated to be about equal.

The half-life for NH−ND exchange in ammine and amine complexes is usually only a few minutes at 293 K,[35] but it was found that for complex **1** NH_2 resonances were observable for >72 h when the complex was dissolved in 99.9% D_2O at pH* <6, with one peak at pH* 5.25 and two NH peaks at pH* 5.58 (5.28 and 5.38 ppm). Complex **2** appeared to behave similarly, but no attempt was made to study H−D exchange kinetics. The NH resonances were further investigated with the aid of ^{15}N-enriched complexes and [^1H,^{15}N] HMQC NMR spectroscopy in 90% H_2O/10% D_2O.

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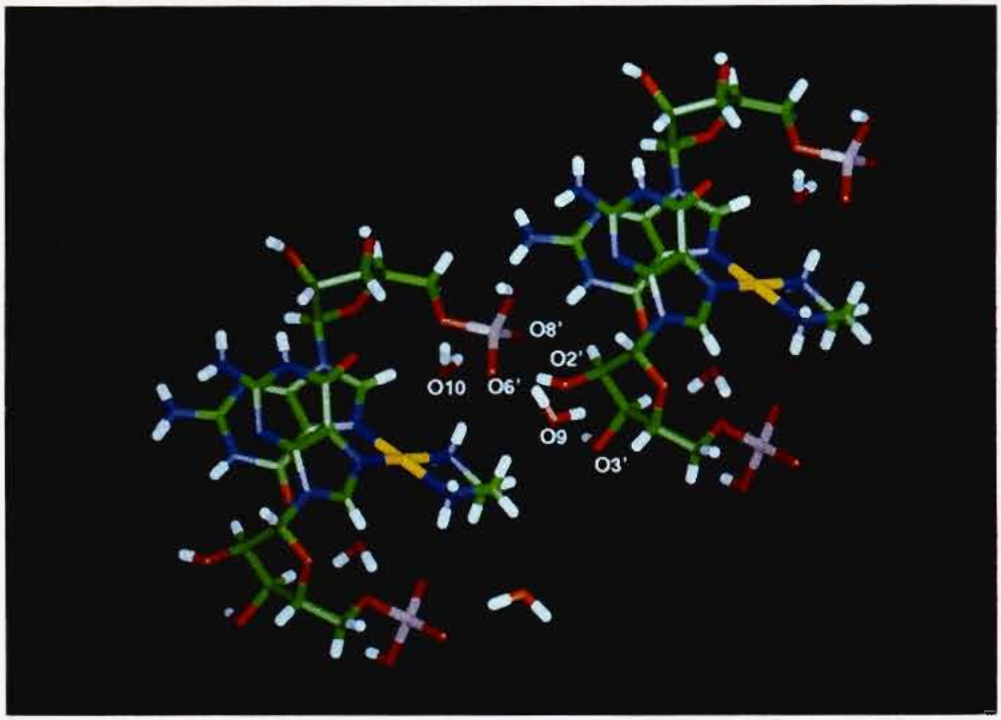

Figure 3. Intra- and intermolecular H-bonding interactions involving the water molecules O(W)9 and O(W)10, phosphate PO6', and sugar hydroxyl groups. The two molecules shown are related by translation along the *b* axis. Color code: Pt, yellow; C, green; N, blue; O, red; P, purple; H, white.

Table 6. ^{1}H and ^{15}N NMR Shifts (δ) and Coupling Constants (Hz) for Complexes Detected in Solutions of [Pd(^{15}*N*-en)(H_2O)$_2$]$^{2+}$ and 5'-GMP (10 mM:20 mM Ratio in 90% H_2O/10% D_2O)

		5'-GMP		en NH_2	
Complex	pH	δ(H8)	δ(H1')(*J*)[a]	δ(^{1}H)	δ(^{15}N)
[Pd(en)(5'-GMP-*N7*)$_2$]	3.40	8.44	5.91 (4.7)	5.27	−16.3
	6.64	8.59	5.92 (4.1)	5.55, 5.32	−16.2
[Pd(en)(5'-GMP-*N1,N7*)]$_n$	3.40	8.54	6.56 (2.2)	4.45, 4.43	−20.4
				4.96, 4.94	−14.4
	6.64	8.73	6.53 (<1)	4.42, 4.40	−20.4
				4.70, 4.67	−13.7
	9.03	8.80	6.53 (2.1)	4.40, 4.37	−20.3
				4.58, 4.55	−13.6
[Pd(en)(5'-GMP-*N1*)$_2$][b]	3.40	*b*	*b*	5.74	−14.4
	6.64	*b*	*b*	6.47	−13.7
	9.03	*b*	*b*	6.72	−13.6

[a] Coupling constant for ribose protons ^3J(H1'−H2'). [b] Possible structure, ^{1}H NMR peaks not assigned.

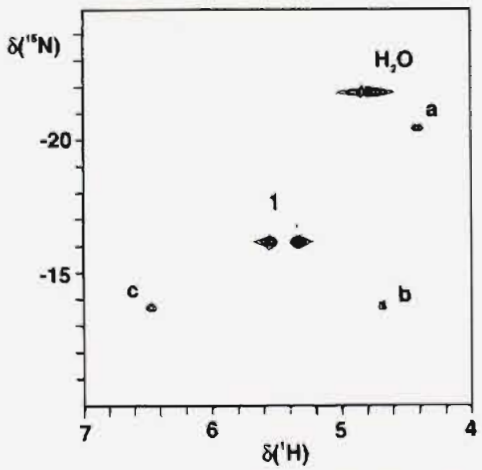

Figure 4. 500 MHz [^{1}H,^{15}N] (50.67 MHz ^{15}N) NMR spectra of [Pd(^{15}*N*-en)(H_2O)$_2$]$^{2+}$ and 5'-GMP (1:2 mol ratio) at 298 K and pH 6.64. The two sets of NH peaks for **1** coalesce at low pH (4). The minor peaks a and b are assigned to [Pd(en)(5'-GMP-*N1, N7*)]$_n^{n-}$, and peak c is tentatively assigned to [Pd(en)(5'-GMP-*N1*)$_2$]$^{4-}$.

A solution of [Pd(^{15}*N*-en)(H_2O)$_2$]$^{2+}$ (10 mM) and 5'-GMP (20 mM) gave one major [^{1}H,^{15}N] peak at −16.3/5.27 ppm at pH 3.40 indicating that all the NH protons of complex **1** are equivalent (supplementary Figure D1). A minor pair of doublets at −20.4/4.44, 4.43 and −14.3/4.96, 4.94 are assigned to the N1/N7-bridged complex [Pd(en)(5'-GMP-*N1,N7*)]$_n$, and a further minor peak is found at at −14.4/5.74 ppm which may be [Pd(en)(5'-GMP-*N1*)$_2$].[36] At higher pH, the behavior of the NH_2 resonances for **1** was similar to that observed previously for **2**,[19] shifting downfield and resolving into two distinct sets of peaks, Figure 4. A detailed study of the pH dependence was hampered by the disproportionation of **1** into the N1,N7-bridged species and 5'-GMP, such that by pH 9 no peaks for **1** were detectable. There was no evidence for formation of the bis adduct [Pd(en)$_2$]$^{2+}$ in any of the spectra.

^{31}P{^{1}H} NOEs. Relatively weak heteronuclear NOEs of 0.5 and 0.3% were observed for the ^{31}P 5'-phosphate NMR peak of the Pt complex **2** at pH* 7.2 on irradiating the low-field and high-field NH ^{1}H NMR resonances, respectively. At pH* 3.87 a much stronger NOE of 5.6% was observed on irradiating the single NH peak for **2** at this pH*.

Anti-HIV Activity. Complexes **1** and **2** and the ligand 5'-GMP were tested in HIV-1 111B infected C8166 cells and also in chronically-infected H9 cells for inhibition of virus production. Both the Pd(II) complex **1** and 5'-GMP itself showed a small degree of inhibition of infection, but it is difficult to differentiate this from cytotoxicity, Table 7. All three compounds are relatively nontoxic, especially the Pt(II) complex **2**.

(36) For both Pt and Pd(II) the ^{15}N chemical shift is diagnostic of the *trans* ligand with approximate ranges (ppm) as follows:

	trans ligand		
	O	N, Cl	S
Pd	−35 to −25	−25 to −15	−5 to +5
Pt	−50 to −40	−35 to −25	−15 to −5

Table 7. Anti-HIV Tests on Complexes **1** and **2** and 5′-GMP

Chronically-infected H9 cells

compnd	conc (μM)	virus yield (%)	p24[a] (%)	cell growth (%)	EC_{50}[b] (μM)	IC_{50}[c] (μM)
1	200	12.5	40	41	100	200
	40	100	80	95		
	8	100	93	100		
2	500	100	100	100	>500	>500
$Na_2$5′-GMP	200	12.5	25	20	100	100
	40	100	62	100		
	8		100			

HIV-1 111B Infected C8166 Cells

compnd	conc (μM)	gp120[a] %	cell growth		EC_{50}[b] (μM)	IC_{50}[c] (μM)
			infected	uninfected		
1	1000		30	31	200	400
	200	53	37	63		
	40	100	24	96		
2	1000	58	27	58	>1000	1000
	200	96	23	88		
	40		21	99		
$Na_2$5′-GMP	400	52	33	47	400	400
	80	104	21	87		
	16		23	100		

[a] Production of viral proteins measured by antibody tests. [b] EC_{50} is the concentration which reduces production of gp 24 or gp120 by 50%. [c] IC_{50} is the concentration which reduces cell growth by 50%.

Discussion

Macrochelation appears to play an important role in the selective recognition of metal ions by nucleic acid derivatives, as discussed recently by Sigel et al.[6] In the case of 5′-GMP complexes of general formula [M(5′-GMP)$(H_2O)_5$], where M is Mn(II), Fe(II), Co(II), Ni(II), or Cd(II), the octahedral metal ion is coordinated to N7 of 5′-GMP and the 5′-phosphate is H-bonded to a coordinated water in a second-sphere interaction giving a 13-membered macrochelate ring.[37] Usually a further H-bond between coordinated water and CO6 of the purine base is present in the structure. Chelation by N7/O6 of guanine derivatives is not normally observed.[38]

Both 5′-phosphate ^{31}P and amine NH $^{1}H/^{15}N$ NMR shifts of 5′-GMP and 5′-AMP complexes of $[Pt(en)]^{2+}$ strongly suggest the presence of strong PtNH•••dianionic 5′-phosphate H-bonding, which accounts for a lowering of the 5′-phosphate pK_a by 0.5−1 units. This is also the case for the dinucleotide complex [Pt(en){d(pGpG)-*N7(1),N7(2)*}]$^-$, but NH shifts do not provide evidence for such H-bonding in the latter complex at low pH (monoanionic phosphate) or in phosphate esters such as [Pt(en){d(TpGpG)-*N7(2),N7(3)*}]$^-$.[39] Also such H-bonding appears to be very weak in crystals of *cis*-[$Pt(NH_3)_2${d(CpGpG)-*N7(2),N7(3)*}] (PO•••NH_3 = 3.31 Å).[13] On the other hand, other workers have correlated the ^{31}P NMR shifts in related polynucleotide complexes of Pt(II) amines with possible Pt-NH•••monoanionic 5′-phosphate ester H-bonding,[40,41] and such H-bonding occurs in at least three of the four molecules in the asymmetric unit of crystalline of *cis*-[$Pt(NH_3)_2${d(pGpG)}].[12] This complex was crystallized at pH 3.8 and has a monoanionic terminal 5′-phosphate. PtNH•••5′-phosphate H-bonding (direct and through an intervening water molecule) has also been observed by molecular mechanics calculations.[42,43]

The present results clearly demonstrate that outer-sphere macrochelate ring formation involving PtNH•••5′-phosphate H-bonding in bis(mononucleotide) Pd(II) and Pt(II) ethylenediamine complexes can occur in the solid state with monoanionic 5′-phosphates and in solution with both mono- and dianionic phosphates and appear to provide the first examples of such intramolecular H-bonding in crystalline Pt(II) or Pd(II) amine adducts of mononucleotides.

There appear to be no previous reports of the X-ray structures of Pd(II) bis(mononucleotide) complexes, although N7 coordination has been confirmed in complexes such as [Pd(diethylenetriamine)(guanosine)]$(ClO_4)_2$[44] and *trans*-[Pd(inosine)$_2Br_2$].[26] X-ray crystal structures of complexes **1** and **2** are closely related to that of [Pt(tn)(Me-5′-GMP)$_2$]•11H_2O reported by Marzilli et al.[17] All three complexes crystallize in the same space group with very similar unit cell dimensions, and the orientations of the bases with respect to each other and to neighboring molecules are almost the same. However there are subtle differences between the structures. In [Pt(tn)(Me-5′-GMP)$_2$]•11H_2O the Pt*N*H..O*P* contact distance (3.44 Å) is ca. 0.52 Å longer than for **1** and **2** and outside the commonly-accepted maximum donor•••acceptor distance for H-bonding (3.3 Å). The intramolecularly H-bonded axial water molecules (W3) are slightly further away from Pt (3.513 Å) but have H-bonding distances similar to those of CO6 (2.89 Å) and PO6′ (2.85 Å).

Another related structure is that of *cis*-[$Zn(H_2O)_4$(Me-5′-GMP)$_2$]•6H_2O in which ammines are replaced by aqua ligands and the axial Zn−O bond lengths are normal for octahedral Zn(II) (2.083 Å).[45] There is H-bonding between equatorial water and a 5′-phosphate oxygen (P•••OW = 2.86 Å) and between an axial water and CO6 (CO6•••OW = 2.73 Å). This complex has similar orientations of the bases and similar sugar conformations as complexes **1**, **2**, and [Pt(tn)(Me-5′-GMP)$_2$]•11H_2O.

The molecular mechanics calculations of Krauss et al.[46] have shown that favorable phosphate−amine interactions can occur through axial water ligands in the system [Pt-$(NH_3)_4]^{2+}$•••H_2O•••$H_2PO_4^-$. They have pointed out that strictly axial water molecules are not bound at 2 Å because of the antibonding character of the bond formed. At larger distances the overlap of ligand orbitals and the Pt d_{z^2} orbital becomes small, and there can be substantial bonding of electrostatic origin. Axial interactions of lone pairs of electrons on exocyclic oxygens of N3-bound thymine or uracil in adducts with Pt(II)

(37) E.g.: (a) [Mn(5′-GMP)$(H_2O)5]$•3H_2O: de Meester, P.; Goodgame, D. M. L.; Jones, T. J.; Skapski, A. C. *Biochem. J.* **1974**, *139*, 791−792. 5′-GMP was formulated as a dianion in this complex although a monoanion would be expected since it was reported to have been crystallized at pH 4.19, which is presumably well below the second pK_a value. (b) [Ni(5′-GMP)$(H_2O)_5$]•3H_2O: de Meester, P.; Goodgame, D. M. L.; Skapski, A. C.; Smith, B. T. *Biochim. Biophys. Acta* **1974**, *340*, 113−115.

(38) N7, O6 chelation has been reported for bis(η^5-cyclopentadienyl)-(theophyllinato)titanium(III): Cozak, D.; Mardhy, M. J.; Beauchamp, A. L. *J. Am. Chem. Soc.* **1986**, *25*, 2600−2606. N7, O6 bridging for [$Rh_2(O_2CCH_3)_2$(9-EtG)$_2$(MeOH)$_2$] and [$Rh_2(O_2CCF_3)_2$(9-EtGH)$_2]^{2+}$ (where 9-EtGH is 9-ethylguanine) has been reported: Dunbar, K. R.; Matonic, J. H.; Saharan, V. P.; Crawford, C. A.; Christou, G. *J. Am. Chem. Soc.* **1994**, *116*, 2201−2201.

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(42) Kozelka, J.; Chottard, J.-C. *Biophys. Chem.* **1990**, *35*, 165−178.

(43) E.g.: (a) Kozelka, J.; Petsko, G. A.; Lippard, S. J.; Quigley, G. J. *J. Am. Chem. Soc.* **1985**, *107*, 4079−4081 (b) Hambley, T. W. *Inorg. Chem.* **1991**, *30*, 937−942.

(44) Rochon, F. D.; Kong, P. C.; Coulombe, B.; Melanson, R. *Can. J. Chem.* **1980**, *58*, 381−386.

(45) Miller, S. K.; VanDerveer, D. G.; Marzilli, L. G. *J. Am. Chem. Soc.* **1985**, *107*, 1048−1055.

(46) Krauss, M.; Basch, H.; Miller, K. J. *J. Am. Chem. Soc.* **1988**, *110*, 4517−4521.

diammines have been postulated to play a role in the reduced reactivity of these complexes toward cyanide.[47]

The existence of $^{31}P\{^1H\}$ NOEs of 0.3−5% between the 5′-phosphate P and NH protons confirms that these atoms are on average less than 4 Å apart in complex **2**, both at low pH where the phosphate is monoanionic and at high pH where it is dianionic. This strongly suggests the presence of PtNH···5′-phosphate H-bonding in solution as is observed in the solid state where the (N)H···P distance is ca. 3.1 Å. Since $\gamma^1H/\gamma^{31}P$ is >2.38, NOE's are expected to be positive irrespective of the correlation time.[48] It is possible that the stronger NOE at low pH is related to a closer approach than at high pH or to a more favorable position of the equilibrium between macrochelate ring-opened and ring-closed forms than at high pH. However, a more detailed interpretation of these NOE data is unwarranted since it was not possible to analyze the relaxation processes or make kinetic NOE measurements on account of the weakness of the effects and long spectral accumulation times required to give reasonable signal-to-noise ratios at millimolar concentrations of the complex.

The N-type sugar ring pucker has been observed on the 5′-G of all characterized single- and double-stranded GpG-platinated oligonucleotides in solution and in crystals.[42] In model calculations, repuckering from S to N alleviates the repulsive contact between the C2′ methylene of the preceding 5′-nucleotide and NH protons and optimizes NH···phosphate H-bonding.[49]

The ability of Pd(II) to enhance N1 deprotonation by up to 2 log units on binding to N7 of purines is well-known,[50] and the increasing tendency of complex **1** to disproportionate into N1,N7-bridged species and unbound 5′-GMP as the pH is raised above 3 is a behavior commonly observed with Pd(II) complexes of guanine derivatives.[51] Uchida et al.[52] have proposed that the Pd(en) complex of 5′-GMP is a tetrameric 4/4 cyclic adduct with N7−Pd-deprotonated N1 linkages between adjacent guanine rings, stabilized (as deduced from Raman band shifts) by 5′-phosphate···NH_2 H-bonding. At the pH which they used in their investigations (7.5) the N1,N7-bridged species would have been the predominant species, with very little of complex **1** being present.

There has been previous interest in the antiviral activity of both modified nucleobases and of Pt and Pd amine complexes,[53] and therefore it was considered worthwhile to investigate the activity of complexes **1** and **2**. Although the Pd(II) complex **1** exhibits apparent anti-HIV activity, it is difficult to distinguish this from cytotoxicity, and perhaps the more notable finding is the relatively low cytotoxicity of both **1** and Pt(II) complex **2**, as has been reported previously[54] for $[Pt(NH_3)_2(guanosine)_2]Cl_2$. With four strongly-bound N ligands, complexes **1** and **2** are very stable, although the Pd(II) complex would be expected to be more kinetically labile than the Pt(II) complex and this may account for its higher activity. The complexes might be taken up by cells more effectively and be more active if they were neutral at physiological pH rather than negatively-charged.

Conclusions

High yields of good quality crystals of the neutral complexes $[Pd(en)(5'\text{-GMP-}N7)_2]\cdot 9H_2O$ and $[Pt(en)(5'\text{-GMP-}N7)_2]\cdot 9H_2O$ can readily be obtained at pH 2−3 from reactions of 5′-GMP with the en dichloro complexes. They are isostructural square-planar complexes with the bases coordinated head-to-tail in the Δ configuration and C3′-*endo* (N-type), *anti*, *gauche*$^+$ sugar conformations. Other notable features of the X-ray structures are the 13-membered macrochelate rings involving intramolecular H-bonding between the monoanionic 5′-phosphate groups and coordinated ethylenediamine NH and the electrostatically-bonded axial water molecules (Pd−O = 3.365 Å, Pt−O = 3.493 Å) which play key roles in a network of H-bonding involving the phosphate oxygens, ethylenediamine NH, and C6O. $^1H\{^{15}N\}$ NMR shifts together with $^{31}P\{^1H\}$ NOE's show that macrochelation involving NH···5′-phosphate H-bonding is present in solution both at pH 7 where the coordinated nucleotide is dianionic and also at low pH (2−3) where it is monoanionic (as in the crystal). Intramolecular (and weaker intermolecular) base-stacking is also observed in crystals of these complexes, and the delicate balance which appears to exist between H-bonding interactions involving CO6 and phosphate groups and base-stacking has also been noted in the recent studies by Kiser et al.[55] of bis-GMP−Pt(II) complexes containing chiral diamine ligands. The Pd complex dissociates in solution to give 5′-GMP and an *N1,N7*-bridged oligomer as a major product at pH >7.6 and exhibits marginal anti-HIV activity. The Pt complex is relatively nontoxic to cells in culture (IC_{50} > 0.5 mM for H9 and C8166 cells). This work provides the first X-ray structure of a Pd(II) nucleotide complex and the first well-defined example of intramolecular NH···5′-phosphate H-bonding in a crystalline Pt(II) mononucleotide complex.

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Supplementary Material Available: 500 MHz $[^1H, ^{15}N]$ (50.67 MHz ^{15}N) NMR spectra of $[Pd(^{15}N\text{-en})(H_2O)_2]^{2+}$ and 5′-GMP (1:2 mol ratio), at 298 K and at pH 4 (Figure D1), and tables of crystal data, bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates and thermal parameters (15 pages). Ordering information is given on any current masthead page.

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