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Synthesis and structural characterization of platinum(II)-acyclovir complexes

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The hybrid drug $[Pt(en)(acv)_2]^{2+}$ (en = 1,2-diaminoethane) has been prepared by direct reaction between acyclovir [9-(2-hydroxyethoxymethyl)guanine (acv), a nucleoside analog with potent antiviral activity] and the platinum complex [PtCl(dmso)(en)]Cl (dmso = dimethyl sulfoxide). Multinuclear NMR spectroscopy data indicated a bifunctional complex with two acv molecules N(7)-co-ordinated to the platinum atom and involved in fast conformational equilibrium with no preferred conformational state along the N(7)–Pt or N(9)–CH_2 bonds. Comparison between the crystal structure of $[Pt(en)(acv)_2]^{2+}$ and the closely related *cis*-$[Pt(NH_3)_2(acv)_2]^{2+}$ indicates that the guanine planes can assume very different orientations with respect to the co-ordination plane; slant by *ca.* 50° in the former case, nearly perpendicular in the latter case. A O(6) · · · H–N–Pt hydrogen bond interaction is responsible for deviation from the upright position in the compound. On the basis of the observed correlation between strength of the hydrogen bond and deviation from orthogonality, the bond must be considered rather weak. Such a hydrogen bond was not formed in the closely related $[Pt(NH_3)_2(acv)_2]^{2+}$ complex having the nucleobases nearly perpendicular to the co-ordination plane. However in the latter case the observed trends in Pt–N(7)–C(5) and Pt–N(7)–C(8) angles are in accord with an attractive interaction between the O(6) and platinum atoms. Therefore the arrangements of the nucleobases in $[Pt(en)(acv)_2]^{2+}$ and $[Pt(NH_3)_2(acv)_2]^{2+}$ represent two conformational energy minima with involvement of O(6) in either hydrogen bonding (former case) or a platinum attractive interaction (latter case).

Acyclovir [9-(2-hydroxyethoxymethyl)guanine, acv] is a nucleoside analog with potent antiviral activity. Acyclovirtriphosphate is preferentially formed in infected cells and selectively inhibits viral DNA polymerases as compared to cellular polymerases.[1] The metal-co-ordinating properties of acyclovir are also of current interest,[2–5] in view of the fact that some DNA polymerases contain (Zn^{2+}) and/or are activated by metal ions (Mg^{2+}, Mn^{2+} or Co^{2+}).

On the other hand *cis*-diamminedichloroplatinum(II) (*cis*-DDP) is one of the most successful antitumour drugs developed in recent years and many studies of the molecular mechanism of antitumour effect of platinum drugs have revealed that the antitumour activity stems from the interaction of these compounds with intracellular DNA.[6] The complex *cis*-DDP and related platinum(II) analogs cross-link adjacent purine bases (two guanines or one adenine and one guanine) of a DNA strand that are capable of inhibiting replication and transcription.[7] Thus complexes of platinum with acyclovir could represent hybrid drugs and exhibit antiviral or anticancer activity different from those of the constituents.[8] Investigation of the platinum co-ordination properties of acyclovir led to the isolation of several compounds[9] one of which, namely *cis*-$[PtCl(NH_3)_2(acv)]NO_3$, revealed interesting antitumour and antiviral activities.[10] We also isolated a bis(acyclovir) derivative, $[Pt(en)(acv)_2]^{2+}$ (en = 1,2-diaminoethane), a compound resembling the major adduct of *cis*-$[PtCl_2(NH_3)_2]$ with DNA. Moreover preliminary crystal structure parameters were different from those for the analogous complex $[Pt(NH_3)_2(acv)_2]^{2+}$,[11] which prompted us to carry out a X-ray investigation. As suspected, despite the close similarity between the bidentate en and two *cis* NH_3 ligands, the two complexes have different conformations. The determinants for these different conformations will be discussed.

Experimental

Starting materials

1,2-Diaminoethane, K_2PtCl_4, and KPF_6 were from Fluka, and acyclovir (acv) was a gift from KRKA, Pharmaceutical Works, Slovenia. The complex [PtCl(dmso)(en)]Cl was prepared following the method by Romeo *et al.*[12]

Preparation

The complex $[Pt(en)(acv)_2][PF_6]_{1.5}Cl_{0.5}\cdot 3H_2O$ was synthesized by mixing acv (1.0 mmol) and [PtCl(dmso)(en)]Cl (0.50 mmol) in water (10 cm^3) keeping the solution under stirring for 48 h at 60 °C. After addition of KPF_6 the solution was evaporated in open air. Colorless crystals suitable for X-ray analysis were obtained in a few days. (Found: C, 22.3; H, 3.5; N, 17.9, Pt, 20.8. Calc. for $C_{18}H_{32}Cl_{0.5}F_9N_{12}O_7P_{1.5}Pt$: C, 22.5; H, 3.4; N, 17.5, Pt, 20.4%).

Physical measurements

Infrared spectra in the range 4000–370 cm^{-1} were recorded as Nujol mulls on a Perkin-Elmer System 2000 FT spectrophotometer, NMR spectra on Varian Unity Inova 600 (^1H at 600.139 MHz, ^{15}N at 60.815 MHz) or Unity plus 300 (^1H at 299.982 MHz, ^{13}C at 75.439 MHz, ^{195}Pt at 64.299 MHz) spectrometers. The sample concentration was 18 mg in 0.6 cm^3 of D_2O (99.9% deuterium). Acetonitrile was used as internal reference [$\delta(^1H)$ 2.00, $\delta(^{13}C)$ 1.3, $\delta(^{15}N)$ 135.8 relative to nitromethane]. Platinum-195 shifts are referenced to H_2PtCl_6 which was recorded separately. The sample temperature was set at 298 K and controlled to approximately ±0.5 K.

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One-dimensional spectra. ^1H: 10 ppm sweep width, 32K time domain, zero filling to 64K, and slight apodization to give resolution enhancement. For ^{13}C: 15 kHz sweep width, 16K time domain, line broadening of 1 Hz before Fourier transformation, decoupling using the WALTZ-16 sequence, and 20 000 transients collected. For ^{195}Pt: 64.4 kHz sweep width, 16K time domain, 1000 scans, line broadening of 50 Hz prior to Fourier transformation, left shift of 4 to remove baseline roll.

Two-dimensional spectra. Heteronuclear single quantum coherence (HSQC): [^1H–^{13}C] with gradients for coherence selection, 4096 (ω_2) 256 (ω_1) data points, four scans per free induction decay (FID), 16 dummy scans, phase-sensitive (States–Haberkorn method), globally optimized alternating-phase rectangular pulses (GARP) ^{13}C decoupling during t_2, 4.4 kHz (ω_2) × 25 kHz (ω_1) spectral width transformed after multiplication with a sine-square filter shifted by $\pi/2$ in both ω_2 and ω_1 to give 4K × 1K matrix. Heteronuclear multiple bond correlation (HMBC): [^1H–^{13}C] with gradients for coherence selection, 4096 (ω_2) × 256 (ω_1) data points, 16 scans per FID, 16 dummy scans, approximate delays calculated from $^1J_{CH} = 140$ and $^nJ_{CH} = 8$ Hz, 4.4 kHz (ω_2) × 25 kHz (ω_1) spectral width transformed after multiplication with a sine-square filter in both ω_2 and ω_1 to give 4K × 1K matrix; [^1H–^{15}N] with gradients for coherence selection, 2048 (ω_2) × 256 (ω_1) data points, 53 scans per FID, 16 dummy scans, appropriate delays calculated according to $^1J_{NH} = 90$ and $^nJ_{NH} = 8$ Hz, 4.4 kHz (ω_2) × 25 kHz (ω_1) spectral width transformed after multiplication with a sine-square filter in both ω_2 and ω_1 to give 4K × 1K matrix.

X-Ray crystallography

A well formed colorless parallelepiped (0.1 × 0.1 × 0.4 mm) was selected and mounted on a glass fiber. Preliminary X-ray diffraction experiments were performed *via* the oscillation and Weissenberg techniques, which showed the pattern attributable to the monoclinic system and the systematic absences of the $P2_1/c$ (no. 14) space group. The crystal was then analyzed on a Siemens P4 automatic four-circle diffractometer. Accurate cell constants were obtained from the refinement of the values of 29 carefully centred randomly selected reflections ($10 < 2\theta < 40°$). Crystallographic data are reported in Table 1. The data, collected at 298 K, by using Mo-Kα graphite-monochromatized radiation (λ 0.710 73 Å), were corrected for Lorentz-polarization and absorption effects (ψ-scan technique based on the reflections 0 0 −4, 0 0 4, 3 −7 3). The structure solution and refinement [(based on F^2, mean $|E^2 - 1|$ 0.904; 0.968 for centrosymmetric and 0.736 for non-centrosymmetric space group)] were performed through Patterson, Fourier and full-matrix least-squares methods. All the non-hydrogen atoms of the complex molecule were easily located from the Fourier-difference map and refined anisotropically. The H atoms were set at calculated positions *via* the AFIX option of SHELXL 93[13] and their thermal parameters refined isotropically. The structure is affected by a high disorder which involves the two crystallographically independent PF_6^- anions. The Fourier-difference analysis showed twelve peaks around one peak assigned as phosphorus (occupancy factor 1.0). They were assigned the scattering factor of fluorine. The two sets, of six atoms each, were refined isotropically and the occupancy factors converged to 0.55(3) and 0.45(3), respectively. The Fourier-difference analysis showed also a group of peaks of small height and located near an inversion center. This electron density was interpreted as due to the presence of a second PF_6^- anion (occupancy factor 0.5). It must be affected by a statistical disorder. All the atoms of this anion were refined isotropically. The charge balance of the crystal is assured by the presence of a Cl^- anion located in general position in the proximity of the HN(1) moiety of a guanine system. Its occupancy factor was fixed at 0.5 and the thermal parameter refined isotropically. Finally, two more peaks in general positions were assigned as oxygen atoms of two water molecules; their occupancy factor was assigned the value of 0.5 and they were refined isotropically. The hydrogen atoms of the two crystallographically independent water molecules were not located. The scattering factors were those of SHELXS 86[14] and SHELXL 93.[13] All the calculations were carried out on PC-Pentium Olidata machines using SHELXS and PARST 95.[15] Molecular graphics were made through the ZORTEP package.[16]

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Results and Discussion

Comparison of the FTIR spectra of the complex and of free acv indicates that the binding of Pt^{II} to N(7) shifts bathochromically the carbonyl frequency, ν[C(6)=O], which occurs at 1717 cm^{-1} for uncomplexed acv and at 1686 cm^{-1} for the complexed species. Platinum complexation shifts also the vibration at 1483 to 1503 cm^{-1} as observed in related cases.[17] Stretching (ν_3) and bending (ν_4) frequencies of PF_6^- are identified as very strong bands at 845 and 559 cm^{-1}, respectively.[18]

A detailed NMR characterization in aqueous solution has been performed in order to determine the structure and conformational features. Only one set of guanine H(8) (δ 8.18) and other proton resonances ($\delta_{N(9)C(1')H_2}$ 5.43, $\delta_{OCH_2CH_2}$ 3.55 and 3.49, δ_{NCH_2} 2.77) was observed suggesting free rotation of the two guanine bases around the N(7)–Pt bonds as proposed earlier for similar bifunctional platinum complexes.[19] One set of resonances has also been found for the ^{13}C NMR spectrum ($\delta_{C(6)}$ 157.39, $\delta_{C(2)}$ 155.16, $\delta_{C(4)}$ 151.45, $\delta_{C(8)}$ 142.13, $\delta_{C(5)}$ 114.49, δ_{NCH_2O} 74.03, δ_{OCH_2C} 70.97, δ_{CH_2OH} 60.50, δ_{CH_2N} 48.16). The magnitude of $^3J_{C(4)\text{-}H(1')}$ of 3.4 Hz and of $^3J_{C(8)-H(1')}$ of 4.4 Hz offers no clear indication on the preferred orientation among the three staggered rotamers along the N(9)–C(1′) bond {χ[C(4)–N(9)–C(1′)–O] = 60, 180 or 300°}, Fig. 1.

Three cross-peaks are observed in the [^1H–^{15}N] HMBC spectrum: δ 8.18/−197.0 [H(8)/N(9)], 8.18/−226.1 [H(8)/N(7)], and 2.77/−380.3 (CH_2/N of 1,2-diaminoethane), Fig. 2. The signal for N(7) has therefore moved upfield considerably (by *ca.* 94 ppm) upon binding to Pt relative to the N(7) in uncomplexed guanine residues (δ −132.2 for guanosine in dmso).[20,21]

The ^{195}Pt spectrum showed a signal at δ −2664 which is in the expected chemical shift range for bifunctional *cis*-DDP complexes.

In conclusion, the multinuclear NMR spectroscopy data indicated a bifunctional complex with two acv molecules N(7)-co-ordinated to the platinum atom. The molecule is involved in fast conformational equilibrium in solution and there is no preferred conformational state along the N(7)–Pt or N(9)–CH_2 bond.

Crystallographic studies

The complex molecule is shown in Fig. 3, selected geometrical parameters in Table 2. The platinum(II) has the usual square-planar geometry, the donors being the two nitrogen atoms from 1,2-diaminoethane and the N(7) atoms from two acyclovir ligands. Most of the atoms of the complex molecule, especially those closer to the co-ordination sphere, are related by an approximate non-crystallographic C_2 symmetry axis which can be drawn through the metal center and the middle point of the CH_2–CH_2 bond of en. However, the atoms of the aliphatic chain of acv and those of the counter ions and the water molecules are far from this pseudo-C_2 symmetry. The presence of disordered hexafluorophosphate anions and water molecules together with the poor quality of the crystal are responsible for the relatively high estimated standard deviations of the positions for some of the atoms in the present structure.

The metal center deviates 0.0142(7) Å from the least-squares plane of the donors. The N–Pt–N angle of the five-membered chelate ring is 82.2(6)° in agreement with the corresponding

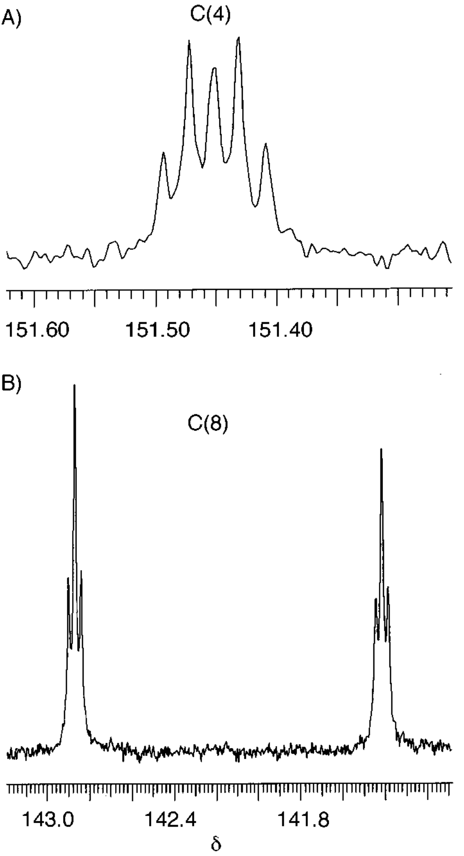

Fig. 1 Two regions of the gated ^{1}H-coupled ^{13}C NMR spectrum showing the C(4) resonance in (A) and C(8) resonance in (B)

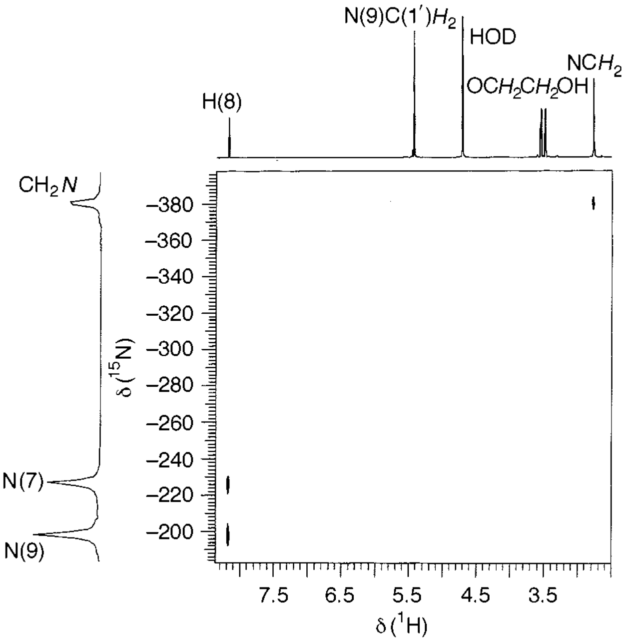

Fig. 2 The [^{15}N–^{1}H] HMBC spectrum of [Pt(en)(acv)$_2$][PF$_6$]$_{1.5}$-Cl$_{0.5}$·H$_2$O in D$_2$O showing long-range correlations of H(8) with N(7) and N(9) and of the protons with the nitrogen atoms of the 1,2-diaminoethane ligand

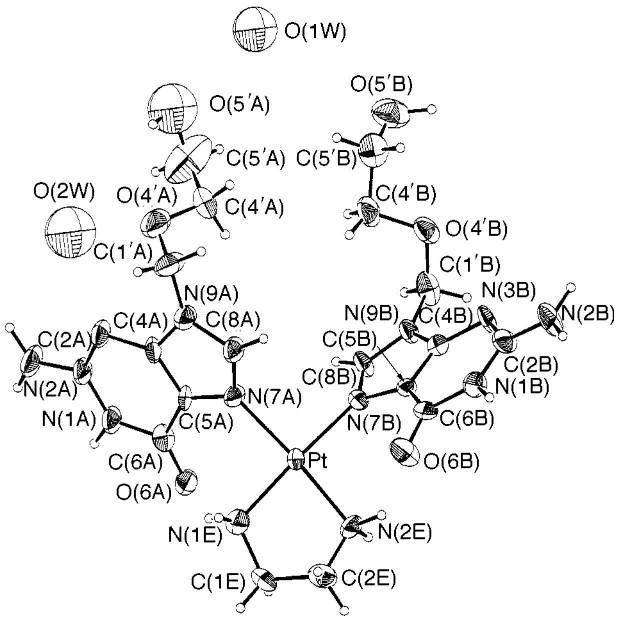

Fig. 3 The complex molecule [Pt(en)(acv)$_2$][PF$_6$]$_{1.5}$Cl$_{0.5}$·H$_2$O and the two water molecules linked *via* hydrogen bonds

Table 1 Selected crystallographic data for [Pt(en)(acv)$_2$][PF$_6$]$_{1.5}$Cl$_{0.5}$·H$_2$O

Formula	$C_{18}H_{32}Cl_{0.5}F_9N_{12}O_7P_{1.5}Pt$
M	958.85
Crystal system	Monoclinic
Space group	*P*2$_1$/*c* (no. 14)
a/Å	10.568(1)
b/Å	23.714(2)
c/Å	14.759(3)
β/°	96.74(1)
U/Å^3	3673.2(8)
Z	4
D_c/Mg m^{-3}	1.734
μ/mm^{-1}	4.080
Crystal dimensions/mm	0.1 × 0.1 × 0.4
2θ Range/°	5–47
Reflections collected	5932
Independent reflections (R_{int})	5434 (0.0404)
Data, restraints, parameters	2894, 6, 429
R_1, wR_2 ($I > 2.5\sigma_I$)	0.0565, 0.1378
(all data)	0.1278, 0.2040

values previously found for some related complexes such as [PtCl(en)(mim)]$^{3+}$ (1 mim = 1-methylimidazole) [83.4(4)°][22] and [Pt(en)(Guo)$_2$]$^{2+}$ (Guo = guanosine) [83.9(9)°].[23] The N(7A)–Pt–N(7B) bond angle is very close to 90° [90.7(6)°] whereas the N–Pt–N bond angles involving acv and en [average 93.6(6)°] are a little larger than the idealized value for the square-planar geometry. The Pt–N(7) bond distances [average 2.03(1) Å] are in good agreement with the values previously reported for [Pt(NH$_3$)$_2$(acv)$_2$]$^{2+}$ [2.02(1) Å],[11] [Pt(en)-(tmx)$_2$]$^{2+}$ (tmx = 1,3,9-trimethylxanthine) [average 2.016(4) Å],[24] [Pt(tmen)L$_2$]$^{2+}$ {tmen = *N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminoethane; L = 9-methylguanine [average 2.017(5) Å], 9-ethylguanine [2.010(8) Å] or 1,3-dimethylxanthine [2.01(1) and 2.03(3) Å]}.[25]

Acyclovir ligand. Bond distances and angles involving the purine system are in good agreement with those listed for a number of nucleosides and nucleotides,[26] for free acyclovir,[27] and for the complexes *trans*-[PtCl$_2$(η^2-C$_2$H$_4$)(acacv)] [acacv = 9-(2-acetoxyethoxymethyl)guanine][9] and [Cu(acv)(H$_2$O)$_3$]$^{2+}$,[28] and *cis*-[Pt(NH$_3$)$_2$(acv)$_2$]$^{2+}$.[11]

The purine systems are nearly planar, the largest deviations from the least-squares planes defined by the endocyclic atoms being those of N(9A) [0.038(16) Å] and H(2B1) [0.138(17) Å]. The NH$_2$ group has the sp^2 character usually found for the guanine system. The C(6)–O(6) bond is close to a double bond as shown by its length of 1.24(2) Å. The two guanine moieties are oriented in a head-to-tail fashion and both are involved in intramolecular hydrogen bonds which involve the O(6) and the NH$_2$ groups of en: O(6A)···N(1E) 2.92(2) Å; O(6A)···H(1EB)–N(1E) 147(2)°; O(6B)···N(2E) 2.99(2) Å; O(6A)···

Table 2 Selected bond lengths (Å) and angles (°) for $[Pt(en)(acv)_2][PF_6]_{1.5}Cl_{0.5}\cdot H_2O$

Pt–N(7A)	2.061(14)	Pt–N(7B)	2.013(14)	C(5A)–N(7A)	1.38(2)	C(5B)–N(7B)	1.40(2)
Pt–N(1E)	1.998(16)	Pt–N(2E)	2.046(14)	C(6A)–O(6A)	1.23(2)	C(6B)–O(6B)	1.26(3)
N(1E)–C(1E)	1.47(2)	N(2E)–C(2E)	1.42(3)	C(6A)–N(1A)	1.37(2)	C(6B)–N(1B)	1.38(2)
C(1E)–C(2E)	1.53(3)			N(7A)–C(8A)	1.27(2)	N(7B)–C(8B)	1.29(2)
N(1A)–C(2A)	1.37(3)	N(1B)–C(2B)	1.39(3)	C(8A)–N(9A)	1.38(2)	C(8B)–N(9B)	1.29(2)
C(2A)–N(2A)	1.36(2)	C(2B)–N(2B)	1.33(2)	N(9A)–C(1′A)	1.45(3)	N(9B)–C(1′B)	1.48(3)
C(2A)–N(3A)	1.34(2)	C(2B)–N(3B)	1.31(2)	C(1′A)–O(4′A)	1.33(3)	C(1′B)–O(4′B)	1.41(3)
N(3A)–C(4A)	1.36(2)	N(3B)–C(4B)	1.38(2)	O(4′A)–C(4′A)	1.39(3)	O(4′B)–C(4′B)	1.43(3)
C(4A)–C(5A)	137.(2)	C(4B)–C(5B)	1.35(2)	C(4′A)–C(5′A)	1.50(5)	C(4′B)–C(5′B)	1.48(4)
C(4A)–N(9A)	1.40(2)	C(4B)–N(9B)	1.36(2)	C(5′A)–O(5′A)	1.56(6)	C(5′B)–O(5′B)	1.41(3)
C(5A)–C(6A)	1.43(2)	C(5B)–C(6B)	1.38(3)				
N(7A)–Pt–N(7B)	90.7(6)			C(4A)–C(5A)–C(6A)	118(2)	C(4B)–C(5B)–C(6B)	119(2)
N(1E)–Pt–N(2E)	82.2(6)			C(4A)–C(5A)–N(7A)	108(1)	C(4B)–C(5B)–N(7B)	109(1)
N(7A)–Pt–N(1E)	92.7(6)	N(7B)–Pt–N(2E)	94.5(6)	C(6A)–C(5A)–N(7A)	134(1)	C(6B)–C(5B)–N(7B)	132(2)
N(7A)–Pt–N(2E)	174.0(6)	N(7B)–Pt–N(1E)	176.3(6)	C(5A)–C(6A)–N(1A)	111(1)	C(5B)–C(6B)–N(1B)	114(2)
Pt–N(1E)–C(1E)	111(1)	Pt–N(2E)–C(2E)	111(1)	C(5A)–C(6A)–O(6A)	128(2)	C(5B)–C(6B)–O(6B)	128(2)
N(1E)–C(1E)–C(2E)	108(2)	N(2E)–C(2E)–C(1E)	107(2)	O(6A)–C(6A)–N(1A)	121(2)	O(6B)–C(6B)–N(1B)	118(2)
Pt–N(7A)–C(5A)	127(1)	Pt–N(7B)–C(5B)	130(1)	C(5A)–N(7A)–C(8A)	109(1)	C(5B)–N(7B)–C(8B)	102(1)
Pt–N(7A)–C(8A)	124(1)	Pt–N(7B)–C(8B)	127(1)	N(7A)–C(8A)–N(9A)	111(2)	N(7B)–C(8B)–N(9B)	111(2)
C(2A)–N(1A)–C(6A)	126(2)	C(2B)–N(1B)–C(6B)	123(2)	C(8A)–N(9A)–C(4A)	105(1)	C(8B)–N(9B)–C(4B)	106(1)
N(1A)–C(2A)–N(2A)	117(2)	N(1B)–C(2B)–N(2B)	116(2)	C(8A)–N(9A)–C(1′A)	125(2)	C(8B)–N(9B)–C(1′B)	128(1)
N(1A)–C(2A)–N(3A)	125(2)	N(1B)–C(2B)–N(3B)	123(2)	C(4A)–N(9A)–C(1′A)	129(2)	C(4B)–N(9B)–C(1′B)	125(1)
N(2A)–C(2A)–N(3A)	119(2)	N(2B)–C(2B)–N(3B)	120(2)	N(9A)–C(1′A)–O(4′A)	111(2)	N(9B)–C(1′B)–O(4′B)	115(2)
C(2A)–N(3A)–C(4A)	110(1)	C(2B)–N(3B)–C(4B)	112(2)	C(1′A)–O(4′A)–C(4′A)	109(2)	C(1′B)–O(4′B)–C(4′B)	111(2)
N(3A)–C(4A)–C(5A)	130(2)	N(3B)–C(4B)–C(5B)	128(2)	O(4′A)–C(4′A)–C(5′A)	108(3)	O(4′B)–C(4′B)–C(5′B)	105(2)
N(3A)–C(4A)–N(9A)	123(1)	N(3B)–C(4B)–N(9B)	126(2)	C(4′A)–C(5′A)–O(5′A)	97(3)	C(4′B)–C(5′B)–O(5′B)	111(2)
C(5A)–C(4A)–N(9A)	106(1)	C(5B)–C(4B)–N(9B)	106(1)				

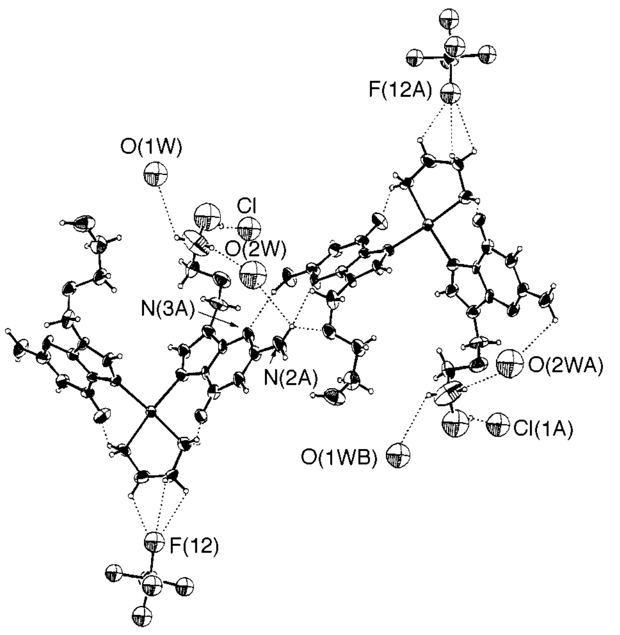

Fig. 4 Base-pairing scheme for $[Pt(en)(acv)_2][PF_6]_{1.5}Cl_{0.5}\cdot H_2O$

H(2ED)–N(1E) 143(2)°. This type of hydrogen bond has previously been found in platinum(II) complexes: $[Pt(NH_3)_2(9\text{-etg})_2]^{2+}$ (9-etg = 9-ethylguanine),[29] $[Pt_2(en)_2\{R_2(CH_2)_4\}_2]^{4+}$ (R = hypoxanthin-9-yl),[30] and $[Pt(NPr^nH_2)_2(9\text{-etg})_2]^{2+}$.[31]

The existence of a hydrogen bond in the present structure is confirmed by the values of the dihedral angle between the purine (B) and the co-ordination (M) planes [B/M, 50.5(3) and 54.3(3)°]. It has previously been noted that in the presence of a O(6) · · · H–N(Pt) interaction the B/M dihedral angle falls in the range 40–60°, whereas in the absence of such an interaction B/M >65°.[30] The presence of such a hydrogen bond, however, is not accompanied by a narrowing of Pt–N(7)–C(5) with respect to the Pt–N(7)–C(8) angle, but instead exactly the opposite trend is observed [Pt–N(7)–C(5) average 128.5(10); and Pt–N(7)–C(8), average 125.5(10)°].

The aliphatic chain bound to N(9) points away from the co-ordination sphere and does not interact intramolecularly with N–H functions of either guanine or en. The values of the glycosidic torsion angles C(4)–N(9)–C(1′)–O(4′) (χ) [−56(2) and −70(2)°] are smaller than those found for free acv [74.4(5)–90.5(6)°][27] and for *trans*-$[PtCl_2(\eta^2\text{-}C_2H_4)(acacv)]$ [χ 74.2(6)°][9] and *cis*-$[Pt(NH_3)_2(acv)_2]^{2+}$ [−60(1) and −61(1)°].[11] The N(9)–C(1′)–O(4′)–C(4′) torsion angle (φ) is −71(2)° (average), whereas the values found for free acv are −76.9, −66.3 and −173.3° and for *trans*-$[PtCl_2(\eta^2\text{-}C_2H_4)(acacv)]$ it is 77.0(5)°. The conformation for the present structure is therefore *gauche* and is consistent with the N(9)–C(1′) bond length of 1.47(3) Å. The C(1′)–O(4′)–C(4′)–C(5′) torsion angle is 178(2)° (average) and corresponds to a *trans* conformation as found for the molecule of free acv and for *trans*-$[PtCl_2(\eta^2\text{-}C_2H_4)(acacv)]$. For *cis*-$[Pt(NH_3)_2(acv)_2]^{2+}$ the conformations around the O(4′)–C(4′) bonds are different [131(2) and −174(2)°].[11] Finally the O(4′)–C(4′)–C(5′)–O(5′) torsion angle of 73(2)° (average) is also consistent with a *gauche* conformation as found for free acv, for *trans*-$[PtCl_2(\eta^2\text{-}C_2H_4)(acacv)]$ and for *cis*-$[Pt(NH_3)_2(acv)_2]^{2+}$ [−74(2) and −71(2)°].[11]

1,2-Diaminoethane ligand. The Pt–N [average 2.025(11) Å], N–C [average 1.45(3) Å], and C(1)–C(2) [1.53(3) Å] bond distances as well as the angles at N and C atoms are in agreement with values reported previously.[22,24] The ring is puckered as shown by the deviations of C(1E) [−0.32(2) Å] and C(2E) atoms [0.40(2) Å] from the least-squares plane of the donors. The conformation of the Pt(en) chelate ring is λ for 50% of the molecules and δ for the other 50%, owing to the presence of a crystallographic inversion center; the λ conformer is shown in Fig. 3.

Crystal packing. Fig 4 shows the relationship between some of the molecules in the crystal. The presence of an unusual base-pairing scheme is evident which involves N(3) and N(2) atoms of the purine system: N(3A) · · · N(2B) (1 + *x*, 0.5 − *y*, 0.5 + *z*) 3.09(2); N(2A) · · · N(3B) (1 + *x*, 0.5 − *y*, 0.5 + *z*) 3.14(2) Å. Hydrogen-bonding interactions involve PF_6^- anions and en groups, Cl^- anion and H–N(1) group, water molecules and the terminal OH function of acv, Table 3.

Conclusion

The comparison between the closely related *cis*-$[Pt(NH_3)_2$-

Table 3 Probable hydrogen bonds which involve the two crystallographically independent water molecules and the Cl^- anions in the structure of $[Pt(en)(acv)_2][PF_6]_{1.5}Cl_{0.5}\cdot H_2O$

O(1W) ··· O(5′A)	$-x, 1-y, 1-z$	2.98(7)
O(1W) ··· O(5′A)	x, y, z	3.03(6)
O(1W) ··· O(6B)	$-x, 0.5+y, 0.5-z$	3.12(6)
O(1W) ··· O(6B)	$x, 0.5-y, 0.5+z$	3.03(6)
O(2W) ··· F(32A)	$-x, -y, 1-z$	2.83(8)
O(2W) ··· N(3B)	$1+x, 0.5-y, 0.5+z$	2.87(7)
O(2W) ··· N(2A)	x, y, z	3.24(7)
O(2W) ··· F(32)	$-x, -y, 1-z$	3.26(7)
Cl ··· H–N(1)	$x, 0.5-y, z-0.5$	2.92(4)

$(acv)_2]^{2+}$ and $[Pt(en)(acv)_2]^{2+}$ molecules indicates that the guanine planes can assume very different orientations with respect to the co-ordination plane: nearly perpendicular in the former case, slant by *ca.* 50° in the latter case. It is reasonable to assume that a weak O(6) ··· H–N–Pt hydrogen bond interaction is responsible for deviation from the upright position in the compound presently investigated. It also appears that there is a direct correlation between the strength of the hydrogen bond and the deviation from orthogonality. For instance in a series of $L_3Pt[N(H)\overset{\cdot\cdot}{-}C(R)\overset{\cdot\cdot}{-}O]$ platinum–amidato complexes the following pairs of values have been found for the distance between the amidato oxygen atom and the donor atom of the *cis* ligand (either N or O) and the dihedral angle between the amidato and the platinum co-ordination planes: 2.94(2) and 40.8(7),[32] 2.79(1) and 19.7(3)[33] and 2.484(6) Å and 7.7(2)°.[34] On this basis the hydrogen bond observed in the present case is considered rather weak and in full accord with the fast conformational equilibrium observed in solution.

The reason why such a hydrogen bond is not formed in the closely related $[Pt(NH_3)_2(acv)_2]^{2+}$ complex deserves further comment. Examination of the crystal packing indicates extensive stacking interactions between acv molecules [distance between N(3A) atoms of two acv molecules in x, y, z and $-x, -x+y, -z+\frac{1}{3}$ as short as 3.29 Å] which could be responsible for the orthogonal orientation of the guanine planes. However it is also evident that such an orientation of the nucleobase brings the O(6) atom close to platinum from an axial position and an interaction with the empty p_z orbital of the metal atom cannot be excluded. Although the Pt ··· O distances are rather long [3.32(1) and 3.41(1) Å] they are shorter than those observed in $[Pt(en)(acv)_2]^{2+}$ [3.48(1) Å] and are in the range of the sum of the van der Waals radii (3.2–3.3 Å).[35] It was shown in a different study that a Pt ··· O distance of 3.229(5) Å was sufficient to ensure a net electron charge donation from an apical amide oxygen onto the platinum.[36] Support for the existence of a weak Pt ··· O(6) interaction in $[Pt(NH_3)_2(acv)_2]^{2+}$ comes also from the observation that the Pt–N(7)–C(5) angle is slightly smaller than Pt–N(7)–C(8) (average values 125.0 and 127.6°, respectively). In most cases, Pt–N(7)–C(5) angles are *ca.* 4–10° greater than the corresponding Pt–N(7)–C(8) angles in the same base,[30] regardless of whether or not O(6) participates in intramolecular hydrogen bonding interaction {for instance the average values for $[Pt(en)(acv)_2]^{2+}$ are 128.5 and 125.5° for Pt–N(7)–C(5) and Pt–N(7)–C(8), respectively}. Therefore an attractive interaction cannot be excluded between O(6) and the platinum atom in $[Pt(NH_3)_2(acv)_2]^{2+}$. If so the two arrangements of the nucleobases observed in $[Pt(NH_3)_2(acv)_2]^{2+}$ and $[Pt(en)(acv)_2]^{2+}$ represent two conformational energy minima with involvement of O(6) in metal and hydrogen bonding, respectively.

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