Synthesis and Structural Characterisation of a New Form of Bis(acyclovir)(ethylenediamine)platinum(II) − Correlation between the Puckering of the Carrier Ligand and the Canting of the Nucleobases

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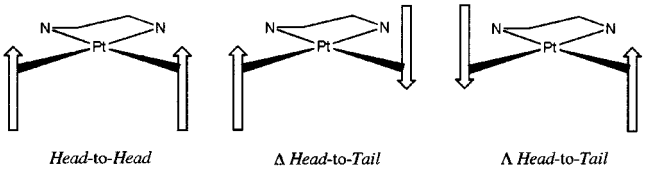
A new conformer of the $[Pt(en)(acv)_2]^{2+}$ cation (en = ethylenediamine; acv = acyclovir = 9-[(2-hydroxyethoxy)methyl]guanine) has been prepared by slow crystallisation of the $[Pt(en)(acv)_2]SO_4 \cdot 2.5H_2O$ salt. X-ray diffraction studies have shown that the guanine moieties have a *Head-to-Head* conformation (*HH*) with the two C(8)-H vectors pointing towards the same side with respect to the platinum coordination plane; the dihedral angles formed by the purine planes and the coordination plane are 58.3(2)° and 41.5(2)°, respectively. There is a correlation between the canting of the purine bases (right or left handed) and the puckering of the ethylenediamine chelate ring (δ or λ). Right-handed canting is associated with λ puckering of the chelate ring and left-handed canting with δ puckering of the chelate ring, so that in both cases one of the two purines forms an O(6)···H–N hydrogen bond with a "quasi equatorial" NH of the ethylenediamine. The "quasi equatorial" character of the NH appears to be a common feature for intramolecular H-bonds between guanine bases and *cis*-amines. The purine not involved in the H-bond has the six-membered ring portion leaning towards the *cis* purine rather than towards the *cis* amine and may give rise to a weak O(6)···Pt attractive interaction. Such an interaction is supported by density functional (DFT) molecular orbital calculations carried out on the model systems $[Pt(NH_3)_4(CH_2O)]^{2+}$ and *Head-to-Tail* *cis*-$[Pt(NH_3)_2\{N(=CH_2)–C(=CH_2)–C(=O)–NH_2\}_2]^{2+}$. The exocyclic chains linked to N(9) each have two different orientations, and all four are stretched away from the metal centre as well as from the purine N(1)H and N(2)H_2 protons. The acv and the en NH protons are instead involved in H-bonds with the sulfate anion.

Introduction

Combination drug chemotherapy has enjoyed much success in the treatment of cancer. This is attributed to the fact that development of resistant cell lines is delayed or prevented and that synergistic interactions between chemotherapeutic agents with different mechanisms of interactions can occur.[1] Observations of this kind have spawned the idea of binding two different cytotoxic moieties within the same molecule, i.e. the creation of multifunctional drugs,[2] and this has become a leading strategy in current studies.

The report that cisplatin was found to be an effective topical treatment in mice[3] prompted some investigators to explore the possibility that platinum(II) or palladium(II) complexes containing antiviral nucleosides might act in a synergistic fashion.[4−6] The prototype complex $[Pt(NH_3)_2(acv)_2](NO_3)_2$ appeared to be equally inhibitory as compared to acv when both were assayed against HSV-1 (KOS). Moreover the complex was not cytotoxic to normal cells at the highest concentration tested (400 mg/cm^3). The reason for such a dramatic decrease in toxicity of $[Pt(NH_3)_2(acv)_2](NO_3)_2$, when compared with the precursor $[Pt(NH_3)_2Cl_2]$, is not fully understood.

In a previous paper we reported the X-ray crystal structure of this multifunctional complex in which the two ammines had been replaced by a chelating ethylenediamine.[7] The two guanine bases adopted the usual *Head-to-Tail* conformation (*HT*) with the two purines tilted over the coordination plane and forming O(6)···H−N H-bonds with the *cis* amine groups. We have now succeeded in crystallising a second conformer of the same complex in which the two guanines are arranged in the very rare *Head-to-Head* (*HH*) conformation (see Scheme 1). To the best of our knowledge this is the only metal *cis*-bis(nucleobase) complex containing identical ligands that has been crystallised in its two possible rotamers to date.



Scheme 1. Representations of the *Head-to-Tail* and *Head-to-Head* orientations of the two guanines with respect to the Pt/N_4 coordination plane

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The results of this investigation are reported here. The discussion will concentrate on the structural motifs induced by platinum coordination and their relevance to the primary lesion responsible for the cytotoxicity of platinum drugs to tumour cells, which involves the cross-linking of two adjacent guanine bases on one strand of the DNA double helix.[8−11]

Results

The preparation of the complex cation was given in the previous paper concerning a *Head-to-Tail* conformer.[7] Comparison of the FTIR spectra of the complex and of free acv indicates that 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 1685 cm^{-1} for the complexed species. Platinum complexation also shifts the frequencies of ν[C(8)−N(7)] and δ[C(8)−H] from 1483 to 1498 cm^{-1}, respectively, as observed in related cases.[12] The typical absorptions for a free SO_4^{2-} ion are identified at 1071 and 630 cm^{-1}.[13]

Only one set of proton resonances [C(8)H: δ = 8.18; N(9)CH_2: δ = 5.43; OCH_2CH_2: δ = 3.55 and 3.49; N(*E*)CH_2: δ = 2.77] was observed suggesting free rotation of the two guanine bases around the Pt−N(7) bonds as proposed earlier for similar bifunctional platinum complexes.[14] The ^{195}Pt spectrum showed a signal at δ = −2664 which is in the expected chemical shift range for bifunctional *cis*-DDP complexes.

The complex cation and the proximal sulfate anion for the [Pt(en)(acv)$_2$]SO_4·2.5H_2O salt (**1**) are depicted in Figure 1, selected geometrical parameters are listed in Table 1 and Table 2.

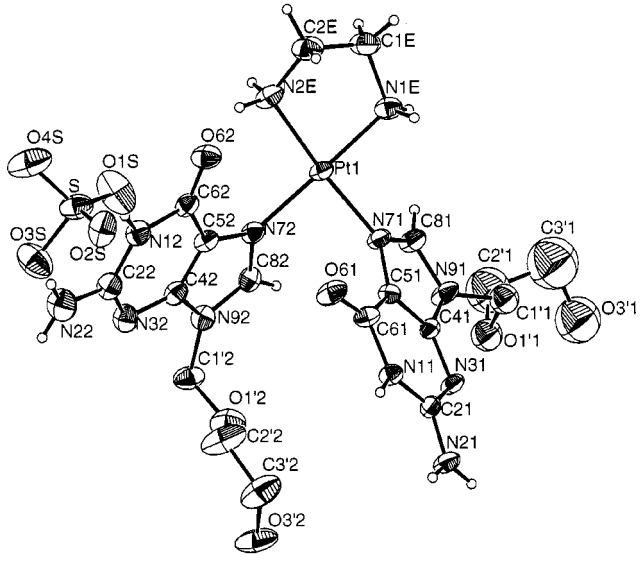

Figure 1. Drawing of the complex molecule and of the sulfate anion from the original set of coordinates; the ellipsoids represent 30% probability

Table 1. Selected bond lengths [Å] for [Pt(en)(acv)$_2$]SO_4·2.5H_2O (**1**)

Vector	Length	Vector	Length
Pt(1)−N(1*E*)	2.021(8)	Pt(1)−N(2*E*)	2.030(7)
Pt(1)−N(71)	2.024(7)	Pt(1)−N(72)	2.037(7)
N(1*E*)−C(1*E*)	1.506(12)	N(2*E*)−C(2*E*)	1.484(13)
C(1*E*)−C(2*E*)	1.485(15)		
O(61)−C(61)	1.213(10)	O(62)−C(62)	1.224(11)
N(11)−C(21)	1.383(11)	N(12)−C(22)	1.375(13)
N(11)−C(61)	1.399(10)	N(12)−C(62)	1.400(11)
N(21)−C(21)	1.335(11)	N(22)−C(22)	1.341(12)
N(31)−C(21)	1.316(11)	N(32)−C(22)	1.322(13)
N(31)−C(41)	1.341(10)	N(32)−C(42)	1.369(12)
N(71)−C(81)	1.288(11)	N(72)−C(82)	1.299(11)
N(71)−C(51)	1.393(11)	N(72)−C(52)	1.397(11)
N(91)−C(81)	1.356(11)	N(92)−C(82)	1.360(12)
N(91)−C(41)	1.386(11)	N(92)−C(42)	1.375(11)
N(91)−C(1′1)	1.491(16)	N(92)−C(1′2)	1.483(12)

Table 2. Selected bond angles [deg] for [Pt(en)(acv)$_2$]SO_4·2.5H_2O **(1)**

Vectors	Angles	Vectors	Angles
N(1*E*)−Pt(1)−N(2*E*)	83.4(3)		
N(1*E*)−Pt(1)−N(71)	91.8(3)	N(2*E*)−Pt(1)−N(72)	95.4(3)
N(1*E*)−Pt(1)−N(72)	177.6(3)	N(2*E*)−Pt(1)−N(71)	174.8(3)
N(71)−Pt(1)−N(72)	89.5(3)		
C(1*E*)−N(1*E*)−Pt(1)	111.8(6)	C(2*E*)−N(2*E*)−Pt(1)	108.2(6)
C(51)−N(71)−Pt(1)	128.5(6)	C(52)−N(72)−Pt(1)	130.5(6)
C(81)−N(71)−Pt(1)	125.7(6)	C(82)−N(72)−Pt(1)	123.3(6)
N(1*E*)−C(1*E*)−C(2*E*)	108.1(8)	N(2*E*)−C(2*E*)−C(1*E*)	109.8(9)
C(21)−N(11)−C(61)	125.9(7)	C(22)−N(12)−C(62)	125.1(8)
C(21)−N(31)−C(41)	112.3(7)	C(22)−N(32)−C(42)	110.9(9)
C(51)−N(71)−C(81)	105.8(7)	C(52)−N(72)−C(82)	105.7(7)
C(41)−N(91)−C(81)	106.4(7)	C(42)−N(92)−C(82)	106.1(8)
C(41)−N(91)−C(1′1)	122.7(10)	C(42)−N(92)−C(1′2)	126.4(8)
C(81)−N(91)−C(1′1)	124.4(10)	C(82)−N(92)−C(1′2)	127.0(8)
N(21)−C(21)−N(11)	117.2(8)	N(22)−C(22)−N(12)	116.6(9)
N(31)−C(21)−N(11)	123.1(8)	N(32)−C(22)−N(12)	124.2(9)
N(31)−C(21)−N(21)	119.7(8)	N(32)−C(22)−N(22)	119.2(10)
N(31)−C(41)−C(51)	129.3(8)	N(32)−C(42)−C(52)	129.2(9)
N(31)−C(41)−N(91)	125.1(7)	N(32)−C(42)−N(92)	123.7(9)
C(51)−C(41)−N(91)	105.6(7)	C(52)−C(42)−N(92)	107.0(8)
C(41)−C(51)−N(71)	109.3(7)	C(42)−C(52)−N(72)	108.9(7)
C(41)−C(51)−C(61)	119.2(8)	C(42)−C(52)−C(62)	119.3(8)
N(71)−C(51)−C(61)	131.4(8)	N(72)−C(52)−C(62)	131.8(9)
O(61)−C(61)−N(11)	120.7(8)	O(62)−C(62)−N(12)	118.3(8)
O(61)−C(61)−C(51)	129.2(8)	O(62)−C(62)−C(52)	130.7(9)
N(11)−C(61)−C(51)	110.1(7)	N(12)−C(62)−C(52)	111.0(9)
N(71)−C(81)−N(91)	112.8(8)	N(72)−C(82)−N(92)	112.4(8)

Platinum Coordination Sphere

The platinum(II) centre has the usual square-planar geometry, the donors being the two nitrogen atoms from ethylenediamine and the N(7) atoms from the two guanine moieties, as recently found for a different salt of the same cation, [Pt(en)(acv)$_2$][PF_6]$_{1.5}$$Cl_{0.5}$·$H_2O$ (**2**),[7] in which, however, the two purine bases have the usual *HT* conformation. The metal centre does not show any appreciable deviation from the plane defined by the donors. The N(1*E*)−Pt−N(2*E*) bond angle is 83.4(3)° in perfect agreement with the values previously reported for the Pt(en) group present in other complexes (ref.[7] and references therein). A strict similarity between the present structure and that of **2** also exists for the N(7)−Pt−N(7) bond angle between the two acv ligands: 89.5(3)° and 90.7(6)° for **1** and **2**, respectively. However, it must be noted that the N(*E*)−Pt−N(7) angles be-

tween *cis* donors are significantly different in the present structure [91.8(3)° and 95.4(3)°, respectively] while they are equal in complex **2** with an *HT* conformation of the acv ligands. The bond lengths for Pt−N(*E*) [2.025(7) Å (average)] and for Pt−N(7) [2.030(7) Å (average)] are in good agreement with previous values for other platinum(II) complexes (ref.[7] and references therein).

The orientation of the two acv ligands with respect to the coordination plane is *HH*, with the C(8)−H vectors pointing towards the same side of the plane. The dihedral angles formed by the two purine systems with the coordination plane are significantly different: 58.3(2)° and 41.5(2)° for acv(1) and acv(2), respectively. It should be noted that the O(6) atom of acv(2) forms a strong intramolecular hydrogen bond with the *cis* amine [N(2*E*)···O(62) = 2.83(2) Å; N−H···O = 153(1)°]. In contrast, the O(61) atom from purine(1) is not involved in any intramolecular hydrogen bond. The different intramolecular contacts found for the two purine systems are reflected by the difference between the Pt−N(7)−C(5) and Pt−N(7)−C(8) bond angles, which is 7.2(6)° for acv(2) and 2.8(6)° for acv(1). Therefore, probably for geometrical reasons, the pseudo macrocycle formed by the O(62)···H−N(2*E*) H-bond linking acv(2) and N(2*E*) requires an opening rather than a narrowing of the Pt−N(7)−C(5) angle. There is also the possibility that the acv(1) ligand, not involved in an H-bond with the *cis*-amine, can feel a Pt···O(61) attractive interaction. This possibility is supported by DFT molecular orbital calculations (see following section) even though the Pt···O(61) contact distance of 3.474(6) Å is rather large [greater than the sum of the Van der Waals radii for Pt (1.8 Å) and O (1.5 Å)][15] and the values of the Pt−N(7)−C(5) and Pt−N(7)−C(8) angles [128.5(6)° and 125.7(6)°, respectively] are equal within two times the estimated standard deviations [it should be recalled, however, that in general the Pt−N(7)−C(5) angle is 4−10° greater than Pt−N(7)−C(8)].[7]

Acyclovir Ligand

The bond lengths and angles relevant to the two guanine systems are in good agreement with those previously reported for other acyclovir complexes (ref.[5,7] and references therein, and ref.[16]). The purine systems are planar, the largest deviations from the least-squares plane defined by the endocyclic atoms being that of N(32) [0.029(8) Å]. The linkages with exocyclic atoms, C(2)−N(2) and C(6)−O(6), have considerable double bond character as can be seen from the bond lengths of 1.338(11) and 1.218(10) Å (averages), respectively.

The aliphatic chains linked to N(9) are stretched away from the coordination sphere, as found for the *HT* conformer **2**. They do not interact intramolecularly with the N−H of the guanine and ethylenediamine systems. Both chains are affected by an extensive statistical disorder (see Experimental Section) which was refined to an acceptable degree of accuracy to permit a reliable analysis of the respective conformations.

The values of the glycosidic torsion angles C(4)−N(9)−C(1′)−O(1′) (χ) are 102(1)° and −101(2)° for acv(1), and −96(1)° and −56(2)° for acv(2). Therefore, all the orientations around N(9)−C(1′) can be described as *gauche*. Interestingly, the values for acv(1) are significantly different from those found for the free ligand [74.4(5)−90.5(6)°][17] and for all Pt−acv complexes so far reported [ref.[16] and references therein]. The N(9)−C(1′)−O(1′)−C(2′) torsion angles (φ) are 107(2)° and −82(3)° for acv(1), and 66(2)° and −64(3)° for acv(2); this *gauche* conformation was also found in the *HT* conformer **2**.[7] The C(1′)−O(1′)−C(2′)−C(3′) torsion angles (γ) are 68(3)° and −94(3)° for acv(1) and 174(1)° and −163(2)° for acv(2), therefore the conformations are *gauche* and *trans*, respectively. The conformations previously reported for this torsion angle were mostly *trans*. Finally, the O(1′)−C(2′)−C(3′)−O(3′) (ω) angles are 73(3)° and −43(4)° for acv(1) and −48(3)° and 69(3)° for acv(2), in agreement with the *gauche* conformation also found for free acv and the previously reported Pt−acv complexes.[5,7]

Ethylenediamine Ligand

The C−N [1.495(12) Å, average] and C−C [1.485(15)] bond lengths and the bond angles around the N and C atoms are in agreement with the typical sp^3 hybridisation of these atoms and with the values reported previously.[7] The five-membered chelate ring is puckered as shown by the deviations of C(1*E*) [−0.06(1) Å] and C(2*E*) [0.51(1) Å] from the least-squares plane of the donors. Both the λ and δ conformations for the Pt(en) chelate ring are present because of the inversion symmetry operation of the *C*2/*c* space group.

Crystal Packing

The sulfate anion has hydrogen bonds with the N(1) and N(2) atoms of acv(2) [N(12)···O(1*S*) = 2.84(3) Å, N−H···O = 161(1)°; N(12)···O(8*S*) = 2.67(2) Å, N−H···O = 165(1)°; N(22)···O(3*S*) = 2.98(2) Å, N−H···O = 160(1)°]. The sulfate anion at (x + 0.5, y + 0.5, z) interacts with the C(8)−H and the N(1*E*)−H groups [C(8)···O(2*S*) = 3.14(2) Å, C−H···O = 134(1)°; N(1*E*)···O(2*S*) = 2.96(2) Å, N−H···O = 170(1)°]. The water molecule O(1 W) (−x, y, −z + 0.5) interacts with N(11) [N···O = 2.85(1) Å, N−H···O = 174(1)°] whereas O(2 W) (−x + 0.5, y − 0.5, −z + 0.5) interacts with N(2*E*) [N···O = 3.03(1) Å, N−H···O = 143(1)°]. Other hydrogen bonds involve the exocyclic chain of the acv moieties and the water molecules, i.e. O(3′1) and O(2 W) (−x + 0.5, y + 0.5, −z + 0.5), O(3′2) and O(3 W) (−x − 0.5, −y + 0.5, −z + 1), and O(3′C) and O(8*S*) (x, y + 1, z) for which the O···O distances are 2.70(2), 2.77(2), and 2.67(1) Å, respectively.

Short contact distances are found between O(3′2), O(3′C) (−x, −y + 1, −z + 1) and C(82) [3.13(2) Å], between O(1′B) (x, y − 1, z) and C(2*E*) [3.39(2) Å], and between O(1′) and O(1′2) (−x, −y + 1, −z + 1) [3.13(1) Å], suggesting a significant repulsive interaction between these

atoms. The attractive and repulsive contacts, which involve several atoms of the exocyclic chains, explain the disorder of the chains themselves and justify the model refined in this work (see Experimental Section).

Finally, an important role for the crystal packing of the present structure is played by the stacking interactions between the purine systems (Figure 2). The shortest interatomic distance is between C(52) and N(32) ($-x$, $-y$, $-z$ + 1) [3.46(1) Å].

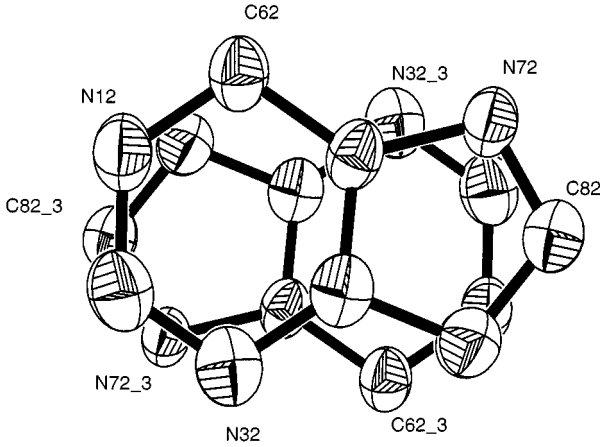

Figure 2. View of the two purine systems from acyclovir(2) which are involved in the strongest stacking interaction; the view is perpendicular to the planes

Molecular Orbital Analysis

The geometry optimized structure for $[Pt(NH_3)_4(CH_2O)]^{2+}$ is reported in Figure 3.

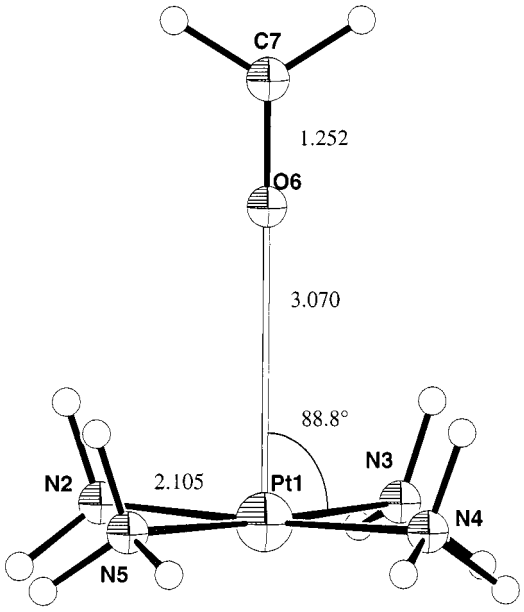

Figure 3. Geometry-optimized structure for $[Pt(NH_3)_4(CH_2O)]^{2+}$

The Pt···O equilibrium distance is 3.070 Å, significantly smaller than the sum of the Van der Waals radii of the two atoms (3.20−3.30 Å).[15] This suggests that an overall attractive interaction between $Pt(NH_3)_4{}^{2+}$ and the CH_2O molecule is operative. The analysis of the MO′s shows that the HOMO for $[Pt(NH_3)_4(CH_2O)]^{2+}$ is composed mostly of *z*-type atomic orbitals from Pt, O and C atoms [Pt: $5d_z^2$ (0.814), $6p_z$ (0.115), and $6d_z^2$ (0.199); O: $2p_z$ (−0.157) and 3s (0.190); C: $2p_z$ (0.120)]. Therefore a covalent interaction exists between the Pt atom and the carbonyl moiety which is assisted by electrostatic and/or hydrogen bonding contributions. In this system, the initial $[Pt(NH_3)_4]^{2+}$ species has an overall positive charge of 2; moreover the O−Pt−N and Pt−N−H (*syn* to O) bond angles (88.8° and 108.4°, respectively) are indicative of weak intramolecular N−H···O hydrogen bonds (N···O = 3.68 Å, N−H···O = 112.3°).

The computed C−O bond length is 1.241 Å in the free molecule and 1.252 Å in the complex molecule. This small lengthening effect might be related to the back donation from the filled Pt $5d_z^2$ orbital to the empty O 3s orbital. The energy of the complex formation for the formal reaction between $[Pt(NH_3)_4]^{2+}$ and CH_2O to form $[Pt(NH_3)_4(CH_2O)]^{2+}$ is −33.942 kcal·mol^{-1}.

The system $[PtCl_4]^{2-}$ and CH_2O was also analyzed. Starting from an initial interatomic Pt···O distance of 2.0 Å the geometry optimization leads to dissociation of the two components. Therefore the electrostatic repulsive interaction between $[PtCl_4]^{2-}$ and the electron rich O atom prevails on the covalent Pt−O linkage. For this latter system, the lack of hydrogen bond interactions is also in favour of dissociation.

The single point calculation on the *HT* isomer of *cis*-$[Pt(NH_3)_2\{N(=CH_2)-C(=CH_2)-C(=O)-NH_2\}_2]^{2+}$ (see Experimental Section) showed that one of the filled frontier orbital consists mostly of Pt $5d_z^2$ (ca. 0.130) and O $2p_z$ (ca. 0.160). The Pt−O distances {from X-ray diffraction on the *HT* *cis*-$[Pt(NH_3)_2(acv)_2]^{2+}$} are 3.320 and 3.409 Å.[18a] Therefore, a covalent interaction between the Pt centre and the O=C function might exist in both the *HT* isomer of *cis*-$[Pt(NH_3)_2(acv)_2]^{2+}$ (compound **3**, ref.[18a]) and *HH* $[Pt(en)(acv)_2]^{2+}$ (present work), although in the latter case the dihedral angle between the acyclovir and platinum-coordination planes is significantly smaller than 90°, and O(6) comes less close to the *z* axis. Intermolecular interactions and/or interligand interactions, related to the canting of the two nucleobases, may be responsible for the deviation of acv1 from orthogonality

Discussion

Nucleobase rotation has been intensively studied for purine complexes of general formula *cis*-$A_2Pt(II)$ (with A_2 = two monodentate or a bidentate amine).[11] The results obtained from these studies are meaningful with regard to the formation and stability of the bifunctional adduct formed in the reaction of the antitumor drug *cis*-$[PtCl_2(NH_3)_2]$ with DNA. Favourable or unfavourable interactions between nucleobases and between these and the carrier ligand are crucial as far as the formation and stability of a given bifunctional adduct are concerned.

In general, for nonbulky carrier ligands (these comprise all primary amines and most of the secondary amines), the rate of rotation of the guanine bases is fast on the NMR

time scale and therefore a single set of signals, which is the average of several possible conformers, is observed. This applies not only to the case of two untethered nucleotides, but also to guanines linked by a phosphodiester chain.[19] Under these circumstances a valuable help in the understanding of factors determining the stability of a given conformation can come from the structural characterisation of various conformers isolated in the solid state. Usually, however, only one of the stable conformers is obtained.

The use of acyclovir as a platinum-coordinating guanine base has been particularly fortunate since it has allowed the crystallisation of three different conformers of the *cis*-$[PtA_2(acv)_2]^{2+}$ species [$A_2 = (NH_3)_2$ or en], all of them possible models of the cisplatin−DNA bifunctional adducts. Two conformers have already been reported,[7,18a] both of which have the guanine base in the most common *HT* arrangement. Such an orientation of the two guanines is favoured by the electrostatic interaction between the two base dipoles. In one case (compound **3**)[18a] the two bases are nearly perpendicular to the coordination plane [dihedral angles of 81.0(4)° and 76.8(4)°]. This positioning of the bases optimises the dipole−dipole interaction but excludes the possibility of H-bond formation between the O(6) of the purine and the *cis* amine group. Interestingly, there was an indication of a possible attractive interaction between the O(6) atoms of the two guanines and the platinum centre. This possibility has been confirmed by the theoretical investigation reported in the present paper.

In the second *HT* conformer (compound **2**)[7] the two purines are tilted over the coordination plane [angles between the purine and the coordination plane of 50.5(3)° and 54.3(3)°]. The tilting of the bases decreases the stabilisation due to the interaction between the base dipoles but allows the formation of H-bonds between the O(6) of the purines and the *cis* amine groups. Interestingly, the two *HT* conformers characterised in the solid state correspond to the two energy minima deduced both from experimental results[20] and theoretical investigations for this type of adduct.[21]

By crystallisation of the same cation under slightly different experimental conditions a new conformer has been obtained (compound **1**). It has the two purines arranged in the rare *HH* conformation; a detailed description of the structure has been given in the previous section. While in the *HT* conformers the two nucleobases within each conformer had comparable inclinations with respect to the coordination plane (difference between dihedral angles $\leq 4°$), in the case of the *HH* conformer the inclination is very different for the two purines (difference between dihedral angles of 17°). The purine with the smaller dihedral angle has the O(6) forming an H-bond with the *cis* amine; such an H-bond is precluded for the second purine which, however, could have O(6) interacting with the platinum centre.

A DFT molecular-orbital analysis carried out on the model system $[Pt(NH_3)_4(CH_2O)]^{2+}$ (C_{2v} symmetry), gave indications of a covalent bonding interaction between the Pt and O atoms. The atomic orbitals mostly involved in this interaction are Pt $5d_z^2$ and $6d_z^2$, and O $2p_z$. The optimized geometry for the $[Pt(NH_3)_4(CH_2O)]^{2+}$ molecule converges to a Pt−O distance of 3.070 Å, a value much shorter than the sum of the Van der Waals radii. The bond formation energy for the formal reaction between $[Pt(NH_3)_4]^{2+}$ and CH_2O is −33.942 kcal·mol^{-1}. A similar DFT molecular-orbital analysis carried out on the *HT cis*-$[Pt(NH_3)_2\{N(=CH_2)-C(=CH_2)-C(=O)-NH_2\}_2]^{2+}$ also gave indications of a covalent bonding interaction between the Pt and O atoms, even though the Pt−O distances were set at 3.320 and 3.409 Å (geometrical parameters of compound **3**). Therefore, it can be concluded that even at long Pt−O distances such as those found in *HT* $[Pt(NH_3)_2(acv)_2]^{2+}$ [18a] and for one acyclovir in *HH* $[Pt(en)(acv)_2]^{2+}$ (present work) an attractive Pt−O interaction may also exist. Such an attractive interaction appears to be weaker in the latter case, where not only is acv1 far from being orthogonal to the coordination plane and the Pt···O distance is longer but also the Pt−N7−C5 angle has failed to become smaller than the Pt−N7−C8 angle (this was the case for the former complex). Moreover, it has to be noted that, for previously reported platinum complexes of guanine derivatives, Pt···O contact distances as short as 3.526(7) Å[18b] and 3.39(1) Å[18c] were found.

There is a correlation between the canting of the purine bases (right or left handed) and the puckering of the ethylenediamine chelate ring (δ or λ). Right-handed canting is associated with λ puckering of the chelate ring and left-handed canting with δ puckering of the chelate ring, so that in both cases one purine forms an H-bond with a "quasi equatorial" NH. Therefore, the H-bond between O(6) of the guanine and the NH of the *cis* carrier ligand appears to be preferentially formed with NH protons having a "quasi equatorial" character than with protons of the "quasi axial" type. This is true for both the *HH* conformation (only one guanine forming the H-bond, present work) and the *HT* conformation (both guanines forming H-bonds, ref.[7]).

It is also likely that in the case of chiral carrier ligands such as 1,2-diaminocyclohexane (DAC) and 2,3-diaminobutane (DAB) the effect of chirality is transmitted from the carrier ligands to the coordinated nucleobases via the stereochemistry of the hydrogen atoms on the coordinated amino nitrogens. Recent results on modifications of natural DNA and synthetic oligodeoxyribonucleotide duplexes by *cis*-$[PtCl_2(DAB)]$ complexes were consistent with the distortion induced in the platinated DNA being determined by hydrogen-bond formation between the carbonyl oxygen of the guanine residues and the "quasi equatorial" hydrogens of the *cis* diamine in the 1,2-d(GpG) intrastrand cross-link.[22]

Experimental Section

Starting Materials: Ethylenediamine, K_2PtCl_4, and Ag_2SO_4 were purchased from Fluka, and acyclovir (acv) was a gift of LEK, Pharmaceutical Works, Slovenia. [PtCl(dmso)(en)]Cl was prepared following the method by Romeo et al.[23]

Preparation of the Complex: $[Pt(en)(acv)_2](SO_4)\cdot 2.5H_2O$ was synthesized by mixing 0.50 mmol of Ag_2SO_4 and 0.50 mmol of [PtCl(dmso)(en)]Cl in 10 mL of water and stirring the solution for 24 h at 60 °C. After filtration 1.00 mmol of acv was added. This mixture was stirred at 50 °C for 24 h and then the solvents evaporated in the open air. Colourless crystals suitable for X-ray analysis were obtained from the solution in a few days. – $C_{18}H_{35}N_{12}O_{12.5}PtS$: calcd. C 25.5, H 4.2, N 19.9; found C 26.0, H 3.9, N 20.1.

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 were recorded on a Bruker Avance DPX 300 (^1H at 300.131 MHz, ^{195}Pt at 64.325 MHz) spectrometer. Sample concentration was 18 mg in 0.6 mL 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]. ^{195}Pt chemical shifts are referenced to H_2PtCl_6 which was recorded separately. The sample temperature was set at 302 K and controlled to approximately ±0.5 K. *ID spectra:* ^1H: 10 ppm sweep width, 32 k time domain, zero filling to 64 k; ^{195}Pt: 64.4 kHz sweep width, 1368 time domain, 100 k scans, line broadening of 50 Hz prior to FT.

X-ray Structure Analysis[24]

Data Collection: A colourless needle of **1** of dimensions 0.30 × 0.10 × 0.05 mm was selected under a polarising microscope, and then mounted on a glass fibre. The data were collected with a Siemens P4 automatic four-circle diffractometer. Graphite-monochromatized Mo-K_α radiation ($\lambda = 0.71073$ Å) was employed. Accurate cell constants (Table 3) were determined by full-matrix least-squares refinement of the values of 28 carefully centred randomly selected reflections in the range $10 \leq 2\theta \leq 33°$. The data were collected at 295 K and then corrected for Lorentz-polarization and absorption effects (ψ-scan technique based on at least three reflections). The collected reflections totalled 4751, 3365 of which were independent with $I > 2\sigma(I)$. The space group (*C*2/*c*, no. 15) is in agreement with the systematic extinctions. Three standard reflections were monitored periodically (97 reflections) during the data collection; no appreciable decay was observed.

Table 3. Selected crystal data and structure refinement for $[Pt(en)(acv)_2]SO_4\cdot 2.5H_2O$ **(1)**

Parameters	Value
Empirical formula	$C_{18}H_{35}N_{12}O_{12.50}PtS$
Formula weight	846.73
Temperature/K	293(2)
Wavelength/Å	0.71073
Crystal system, space group	Monoclinic, *C*2/*c* (no. 15)
Unit cell dimensions	
a/Å	23.479(2)
b	11.2710(10)
c	22.691(3)
β/deg	101.16(1)
Volume /Å^3	5891.2(11)
Z, Calculated density /Mg·m^{-3}	8, 1.909
Absorption coefficient/mm^{-1}	4.916
Reflections collected/unique	4475/4355 [*R*(int) = 0.0106]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4355/9/442
Final *R* indices [$I > 2\sigma(I)$, 3365 refls.]	*R*1, 0.0414; *wR*2, 0.0993
R indices (all data)	*R*1, 0.0613; *wR*2, 0.1095

Structure Solution and Refinement: The structure was solved with the Patterson and Fourier techniques. The difference-Fourier map computed after a twelve-cycles refinement at the isotropic level showed three new peaks in the proximity of three atoms of the exocyclic chains of both the acyclovir molecules. This was interpreted as a statistical disorder and the six new peaks were assigned as oxygen and carbon atoms, namely O(1′B), C(1′B) and C(2′B), and O(1′C), O(3′C) and C(2′C). On the basis of the peak height, the occupancies of the new atoms were fixed at 0.4 and 0.3, respectively, whereas those of the atoms O(1′1), C(1′1), and C(2′1) and O(1′2), O(3′2), and C(2′2) were fixed at 0.60 and 0.70, respectively. At the same stage of refinement four new peaks appeared close to the oxygen atoms [O(1*S*)–O(4*S*)] of the sulfate anion in agreement with a statistical disorder also for this part of the structure. The new peaks were assumed as possible positions for oxygen atoms [whose symbols were assigned as O(5*S*)–O(8*S*)]. The occupancies of the two sets of oxygen atoms were fixed at 0.5 each.

Three broad peaks from the Fourier-difference map were assigned to oxygen atoms of three water molecules whose occupancies are 1, 1, and 0.5, respectively, in agreement with the elemental analysis of the sample and with the analysis of the crystal packing and the hydrogen bonding scheme. The bond lengths for the atoms of the exocyclic chains of acyclovir were restrained as follows: C–O = 1.45 ± 0.02 Å; C–C = 1.52 ± 0.02 Å. The hydrogen atoms for the whole structure were included through the HFIX and AFIX options of SHELX97,[25] excluding the hydrogen atoms for the exocyclic chain of acyclovir and those of the water molecules, which were not included at all. The hydrogen atoms were allowed to ride on the atoms to which they are linked. At the final refinement stage the hydrogen atoms and all the atoms of the disordered chain from acyclovir(1) were treated as isotropic. All the other atoms were refined anisotropically. The thermal parameters for the H-atoms were restrained to be 1.2 times the U_{eq} values of the atoms to which they are bound. All the calculations were carried out with the SHELX 97,[25] PARST 97[26] and XPMA-ZORTEP[27] and ORTEP 3[28] computer programs implemented on Pentium machines.

Molecular Orbital Analysis and Computational Methods: All the calculations were performed with the GAUSSIAN94/DFT package[29] implemented on an Origin 2000 SG machine located at CINECA (Interuniversity Computing Center), Bologna, Italy. Geometry optimizations and energy calculations were obtained by using the B3LYP method[30] and the LANL2DZ basis set.[29] This consists of 6–31G-like functions for nontransition metal atoms, excluding the Cl atom for which the basis set 6–31G**[20] was used, and a valence double-zeta basis set for 3*s*, 3*p*, 3*d* and 4*s* electrons and orbitals along with an effective core potential (Hay and Wadt[31]) for the metal. All the geometrical parameters were fully optimized without symmetry constraints, unless otherwise specified. Other details are as those reported in ref.[32]. The systems investigated were CH_2O, $[Pt(NH_3)_4]^{2+}$, $[Pt(NH_3)_4(CH_2O)]^{2+}$, $[PtCl_4]^{2-}$ and $[PtCl_4]^{2-}\cdots CH_2O$. The starting structures for the metal-containing molecules have planar coordination geometries.

Finally, a single-point DFT calculation was carried out for the molecule *HT cis*-$[Pt(NH_3)_2\{N(=CH_2)-C(=CH_2)-C(=O)-NH_2\}_2]^{2+}$ as a model for *HT cis*-$[Pt(NH_3)_2$-(Guanine)$_2]^{2+}$. The coordinates for the nonhydrogen atoms were those from the *HT cis*-$[Pt(NH_3)_2(acv)_2]^{2+}$ complex reported in ref.[18a]. The hydrogen atoms were introduced in calculated positions by using the HyperChem 5.0 package;[33] whereas molecular drawings were obtained through XPMA-ZORTEP.[27] and ORTEP 32.[28] packages. All graphic calculations were performed on Pentium machines.

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