Synthesis and Characterization of Platinum Complexes with Acyclovir and Some Acetylated Derivatives: Crystal and Molecular Structure of *trans*-[9-(2-Acetoxyethoxymethyl)guanine-κN^7]dichloro(η-ethylene)platinum(II)†

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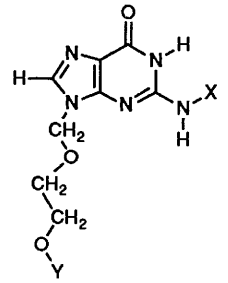
By reaction of Zeise's salt with selected, N(9)-alkylated, guanine derivatives L [9-(2-hydroxyethoxymethyl)guanine, acyclovir, L^1; 9-(2-acetoxyethoxymethyl)guanine, monoacetylacyclovir, L^2; or 9-(2-acetoxyethoxymethyl)-*N*(2)-acetylguanine, diacetylacyclovir, L^3] the complexes *trans*-[$PtCl_2(\eta^2$-$C_2H_4)L$] (L = L^1, **1**; L^2, **2**; or L^3, **3**) have been prepared. Crystals of complex **2** were obtained from 1,2-dichloroethane solution and characterized by X-ray crystallography: monoclinic, space group *C*2/*c*, *a* = 41.290(6), *b* = 4.896(3), *c* = 18.285(2) Å, β = 112.02(1)° and *Z* = 8. The refinement converged to *R* and *R'* values of 0.0204 and 0.0240, respectively. The metal co-ordination is square planar, involving the ethylene ligand, the two *trans* chloride ions, and the N(7) atom of the guanine ligand. The Pt···O(6) distance of 3.672(2) Å excludes any bonding interaction between these two atoms. The bond lengths and angles are normal. In methanol solution the NMR spectra of complexes **1**–**3** are consistent with exchange of L with solvent. In chloroform solution the spectra are consistent with N(7) co-ordination of the purine ligand. For **2** the NH_2 signal splits into two resonances on lowering the temperature, consistent with restricted rotation of this group about the C(2)–NH_2 bond. The N(1)H signal for complex **3** is relatively downfield, suggesting a hydrogen-bond interaction with the carbonyl oxygen of the C(2)NHCOMe group. Only one rotational isomer for this latter group appears to be present. The complexes [$PtCl_2$(dmso)L] (dmso = dimethyl sulphoxide; L = L^1, **4**; L^2, **5**; or L^3, **6**), [$PtCl_2L_2$] (L = L^2, **7**; or L^3, **8**) and [$PtCl(NH_3)_2L^1$]NO_3 **9** were also synthesized and characterized.

Of all the recognized metal binding sites on DNA nucleobases, N(7) of guanine is the site preferred by most metal species at neutral pH based on thermodynamic and/or kinetic evidence.[1–4] The most extensive studies of metal complexes of guanine derivatives have involved platinum(II) species since N(7) of guanine is the site of preferential attack by platinum anticancer drugs on DNA, the likely molecular target of the drugs.[3,4] The reasons for the preferential attack at guanine N(7) are not fully understood but may be due to favourable interaction of the 6-oxo group either with the platinum(II) centre or with hydrogen-bond-donating ligands in the complexes.[5] Moreover, since nucleobase complexes with platinum(II) centres are kinetically inert, it is not clear whether the kinetically formed species is also the thermodynamically favoured species.

The primary aim of the study reported here was to examine the complexes formed with ethylene in the co-ordination sphere. The ethylene can play two roles. First it favours the formation of five-co-ordinate species allowing an excellent opportunity for 6-oxo group–platinum(II) interaction.[6,7] Secondly, it renders the *trans* position kinetically labile, circumventing the problem of kinetic control of complex formation.[8] To simplify the system further we wanted to avoid hydrogen-bond-donating ligands on platinum(II) and to prepare complexes soluble in non-hydrogen-bonding solvents.

Our aims have been achieved using acyclovir [9-(2-hydroxyethoxymethyl)guanine, L^1] and two of its acetylated derivatives. Acyclovir, a guanine derivative which mimics guanosine, is a highly specific inhibitor of herpes virus replication with a much higher efficacy and much lower host-cell toxicity than previously available compounds.[9,10] Various forms of this drug have been in clinical use since 1982 and research on these and related compounds effective against more resistant viruses is of much current interest also in relation to the treatment of patients with autoimmune deficiency syndrome (AIDS).[11] Moreover, complexes formed between nucleosides and nucleoside analogues and platinum(II) species can exhibit antiviral or anticancer activity different from those of the constituents.



	X	Y
L^1	H	H
L^2	H	MeCO
L^3	MeCO	MeCO

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† acyclovir = 9-(2-Hydroxyethoxymethyl)guanine.

Supplementary data available: see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1991, Issue 1, pp. xviii–xxii.

Experimental

Starting Materials.—Zeise's salt K[$PtCl_3(\eta^2-C_2H_4)$] was prepared according to the method of Cramer *et al.*[12] from potassium tetrachloroplatinate(II) and ethylene gas. The complexes *cis*-[$PtCl_2(dmso)_2$] (dmso = dimethyl sulphoxide) and *cis*-[$PtCl_2(NH_3)_2$] were prepared from $K_2[PtCl_4]$ by published methods.[13,14] 9-(2-Hydroxyethoxymethyl)guanine (acyclovir, L^1), 9-(2-acetoxyethoxymethyl)guanine (monoacetylacyclovir, L^2) and 9-(2-acetoxyethoxymethyl)-*N*(2)-acetylguanine (diacetylacyclovir, L^3) were prepared by the method of Matsumoto *et al.*[15]

Preparation of Complexes.—*trans*-[$PtCl_2(\eta^2-C_2H_4)L$] (L = L^1, **1**; L^2, **2**; *or* L^3, **3**). These complexes were prepared by a slight modification of the method of Schmidt and Orchin.[16] To a rapidly stirred solution of Zeise's salt (0.20 g, 0.5 mmol) in the minimum volume of methanol at 0 °C, was added the stoichiometric amount of finely ground ligand. In the case of L^1 the yellow solid which separated from the solution was collected, washed with a small amount of cold methanol, and dried in a stream of dry air. Yield 70% (Found: C, 23.0; H, 3.0; Cl, 13.4; N, 13.2. Calc. for $C_{10}H_{15}Cl_2N_5O_3Pt$: C, 23.1; H, 2.9; Cl, 13.6; N, 13.5%). In the cases of L^2 and L^3 the reaction products were quite soluble in methanol; therefore, after 2 h of stirring at 0 °C the reaction mixtures were taken to dryness by evaporation of the solvent *in vacuo*. The solid residues were dissolved in the minimum amount of dichloromethane, the resulting yellow solutions were filtered, and the solvent slowly evaporated *in vacuo* to leave yellow solids of the desired products. Yield *ca.* 70% (Found: C, 25.6; H, 3.0; Cl, 12.9; N, 12.4. Calc. for $C_{12}H_{17}Cl_2N_5O_4Pt$, **2**: C, 25.7; H, 3.0; Cl, 12.6; N, 12.5. Found: C, 27.9; H, 3.1; Cl, 11.6; N, 11.6. Calc. for $C_{14}H_{19}Cl_2N_5O_5Pt$, **3**: C, 27.9; H, 3.2; Cl, 11.7; N, 11.6%).

[$PtCl_2(dmso)L$] (L = L^1, **4**; L^2, **5**; *or* L^3, **6**). These compounds were obtained by reaction of *cis*-[$PtCl_2(dmso)_2$] and L in a molar ratio of 1:1. Typically, a suspension of *cis*-[$PtCl_2(dmso)_2$] (0.42 g, 1 mmol) in methanol (50 cm^3) was treated with the stoichiometric amount of ligand and the mixture left to stir for 1 d. In the cases of L^1 and L^2 the yellow solid which separated from the solution was collected, washed with methanol, then with diethyl ether and dried in a stream of dry air. The yield was *ca.* 65% (Found: C, 21.1; H, 3.0; Cl, 12.2; N, 12.2. Calc. for $C_{10}H_{17}Cl_2N_5O_4PtS$, **4**: C, 21.1; H, 3.0; Cl, 12.4; N, 12.3. Found: C, 23.9; H, 3.2; Cl, 11.2; N, 11.4. Calc. for $C_{12}H_{19}Cl_2N_5O_5PtS$, **5**: C, 23.6; H, 3.1; Cl, 11.6; N, 11.5%). In the case of L^3 the reaction product was soluble in methanol; therefore, after reduction of the volume to 1/10 of its initial value, the solution was filtered and treated with excess of diethyl ether. The light yellow solid which separated was collected, washed with diethyl ether, and dried in the air. Yield 65% (Found: C, 25.8; H, 3.2; Cl, 11.0; N, 10.2. Calc. for $C_{14}H_{21}Cl_2N_5O_6PtS$, **6**: C, 25.7; H, 3.2; Cl, 10.8; N, 10.7%). The reaction procedure described above afforded mostly the *trans* isomer of **4**–**6** containing a small amount of the *cis* isomer. In the case of **6**, which is soluble in methanol, it was possible to convert the *trans* isomer into the *cis* species. A solution of *trans*-**6** (0.6 mmol) in aqueous methanol (1:1, v/v, 50 cm^3) containing a few drops of dmso was stirred at 70 °C for 1 h. The solvent was evaporated under vacuum and the resulting pale yellow solid of the *cis* isomer was washed with diethyl ether and dried.

[$PtCl_2L_2$] (L = L^2, **7**; *or* L^3, **8**). The complexes were prepared by reaction of $K_2[PtCl_4]$ and L in 1:2 molar ratio. Thus $K_2[PtCl_4]$ (0.20 g, 0.5 mmol) in water (50 cm^3) was treated with L (1 mmol) and the suspension was left to stir at room temperature for 3 d. The yellow precipitate was collected, washed with water, then methanol, and finally with ether. Yield 80% (Found: C, 30.6; H, 3.3; Cl, 9.0; N, 17.6. Calc. for $C_{20}H_{26}Cl_2N_{10}O_8Pt$, **7**: C, 30.0; H, 3.3; Cl, 8.9; N, 17.5. Found: C, 32.3; H, 3.3; Cl, 8.3; N, 16.0. Calc. for $C_{24}H_{30}Cl_2N_{10}O_{10}Pt$, **8**: C, 32.6; H, 3.4; Cl, 8.0; N, 15.8%).

[$PtCl(NH_3)_2L^1$]NO_3 **9**. This complex was prepared from *cis*-[$PtCl_2(NH_3)_2$] and L^1 according to the method of Hollis *et al.*[17] Thus *cis*-[$PtCl_2(NH_3)_2$] (0.30 g, 1 mmol) and $AgNO_3$ (0.15 g, 0.9 mmol) were stirred in dimethyl formamide (dmf) (30 cm^3) for 1 d. The resulting mixture was filtered and the stoichiometric amount of L^1 (0.22 g, 1 mmol) was added to the filtrate. Stirring was resumed and continued for 1 d. After a second filtration, the solution was taken to dryness and the residue crystallized from water. Yield 70% (Found: C, 17.4; H, 3.1; Cl, 6.7; N, 20.2. Calc. for $C_8H_{17}ClN_8O_6Pt$, **9**: C, 17.4; H, 3.1; Cl, 6.4; N, 20.3%).

Physical Measurements.—Infrared spectra in the range 4000–400 cm^{-1} were recorded as KBr pellets; spectra in the range 400–200 cm^{-1} were recorded as Polythene pellets on Perkin-Elmer 283 and FT 1600 spectrophotometers. Proton NMR spectra were obtained with Varian XL200 and Nicolet NT-360 spectrometers.

Molecular Mechanics Calculations.—Calculations were performed with the MacroModel V2.5 (MMOD) package implemented on a Vax 11/780 computer.[18] The force field used for all the atoms but Pt was that reported in the AMBER version contained in MMOD.[19]

Calculation of $\Delta G^‡$.—The free energy of activation was calculated by using the expression $\Delta G_{T_c}{}^‡ = -RT\ln[\pi(\Delta\nu)h/2^{\frac{1}{2}}kT]$, where $\Delta\nu$ represents the chemical shift difference ($\Delta\delta$ in Hz) of the coalescing peaks in the absence of exchange, *T* the coalescence temperature, and *R*, *k* and *h* have their usual thermodynamic significance.[20]

X-Ray Crystallography.—A yellow needle with approximate dimensions of 0.05 × 0.05 × 0.150 mm was used. Crystal data and data collection and processing parameters are reported in Table 1.

Structure analysis and refinement. Heavy-atom method. Anisotropic full-matrix least-squares refinement on *F* for all non-hydrogen atoms; all H atoms isotropic with *U* fixed at 0.06 Å^2. Final refinement of 268 parameters gave $R = 0.0204$, $R' = 0.0240$, weighting scheme $w = 1/[\sigma^2(F) + 0.0011F^2]$. Maximum $\Delta/\sigma = 0.255$ for the *X*/*a* coordinate of H(1′A). Two maxima in the final $\Delta\rho$ map with 0.83 e Å^{-3} were found at 0.91 and 1.28 Å from Pt; minimum,maximum of −0.76,0.83 e Å^{-3}.

Absorption corrections were introduced by applying the DIFABS program.[21] Scattering factors for neutral atoms including *f*′ and *f*″ were from ref. 22. Calculations were performed with the SHELX 76 and 86 packages[23,24] on a VAX/750 computer. The final atomic coordinates are listed in Table 2.

Additional material available from the Cambridge Crystallographic Data Centre comprises thermal parameters.

Results and Discussion

The structure of acyclovir (L^1) is strikingly similar to that of guanosine but the rigid ribofuranosyl ring has been substituted by the more flexible 2-hydroxyethoxymethyl acyclic chain C(1′)H_2OC(2′)H_2C(3′)H_2OH. Moreover, two derivatives acetylated at the 2-hydroxyethoxy position (L^2) and at both the 2-hydroxyethoxy and the 2-amino positions (L^3) have also been prepared. The acetyl groups confer different solubility characteristics to the ligands and related complexes, but should not modify N(7) co-ordination.

The reaction of acyclovir ligands with Zeise's salt, K[$PtCl_3(\eta^2-C_2H_4)$], in a 1:1 ratio leads to formation of [$PtCl_2(\eta^2-C_2H_4)L$] (L = L^1, **1**; L^2, **2**; or L^3, **3**). The compounds are soluble in methanol; **2** and **3** also dissolve in chlorinated solvents. By slow crystallization from 1,2-dichloroethane, yellow crystals of **2** suitable for X-ray structure analysis were obtained.

X-Ray Structure.—The crystal structure of compound **2** con-

Table 1 Experimental details for the crystallographic analysis

Formula	$C_{12}H_{17}Cl_2N_5O_4Pt$
M	561.29
Crystal system	Monoclinic
Space group	$C2/c$ (no. 15)
Unit-cell determination	25, randomly selected, high θ reflections
a/Å	41.290(6)
b/Å	4.896(3)
c/Å	18.285(2)
β/°	112.02(1)
U/Å^3	3427
D_c/g cm^{-3}	2.18
Z	8
F(000)	2144
μ(Mo-Kα)/cm^{-1}	86.15
Diffractometer	Enraf-Nonius, CAD4
λ/Å	0.710 69, graphite monochromatized
Scan range/°	$5 < 2\theta < 50$
Scan type	ω–2θ
ω Scan width/°	0.80 + 0.35tanθ
Prescan speed/° min^{-1}	8.2
Prescan acceptance σ(I)/I	0.5
Required σ(I)/I for measured reflections	0.02
Maximum allowed scanning time/s	60
Reflections collected	$\pm h\,k\,l$
Intensity-control parameter	Three standard reflections periodically measured, 2 h ($\overline{16}\,0\,2$, $\overline{19}\,1\,4$, $\overline{19}\,1\,0$); no significant change
No. of data collected at 22 °C	3492
Data reduction	Lorentz polarization and empirical absorption corrections (DIFABS)
No. of independent observed reflections with $F > 3\sigma(F)$	2438
Structure solution	Patterson and Fourier methods
Refinement	Pt, Cl, O, N, C atoms anisotropic; H atoms isotropic

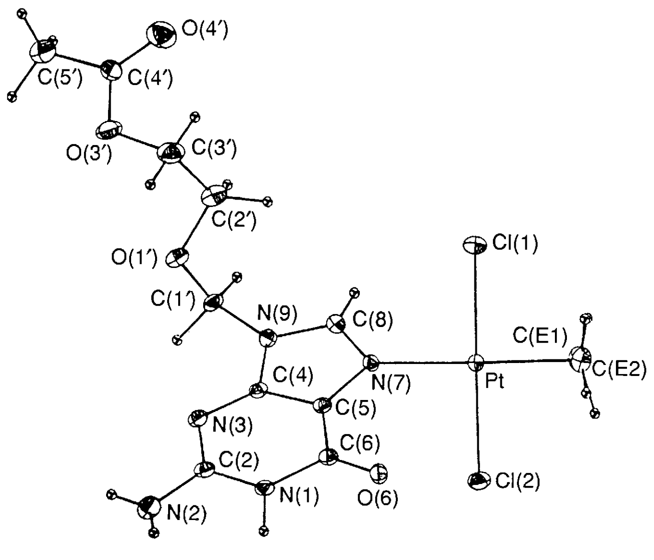


Fig. 1 View of $[PtCl_2(\eta^2\text{-}C_2H_4)L^2]$ **2** along the perpendicular to the co-ordination plane, with the atomic labelling scheme. The ellipsoids enclose 30% probability

tains discrete molecules with the metal centre co-ordinated to N(7) of the guanine moiety, to two *trans* chloride ions and to an ethylene molecule (Fig. 1). Bond lengths and angles are reported in Tables 3 and 4, respectively.

The square-planar co-ordination around platinum is regular with N(7)–Pt–Cl(1), N(7)–Pt–Cl(2), C_E–Pt–Cl(1) and C_E–Pt–Cl(2) angles (C_E = midpoint of ethylene ligand) of 89.2(1), 91.9(1), 89.2(2) and 89.6(2)°, respectively. The Pt atom and C_E deviate from the N(7),Cl(1),Cl(2),C_E plane by only −0.0487(5) and −0.011(6) Å, respectively.

The Pt–N(7) distance of 2.078(3) Å is longer than corresponding values in other purine complexes, *e.g.* (ethylenediamine)diguanosineplatinum(II) [1.96(2) Å],[33] *cis*-diamminebis(inosine 5′-monophosphato)platinate(2−) (2.02 Å),[34] and *cis*-diammine(2′-deoxyguanylyl-5′,3′-guanylyl)platinum(II) [1.99(2) Å],[35] as a consequence of the greater *trans* influence of C_2H_4.[36] The Pt–Cl distances average 2.296(1) Å and are in full agreement with literature values, *e.g.* 2.304(2) Å for $[PtCl(C_2H_4)(tmen)]^+$ [37] (tmen = *NNN′N′*-tetramethylethylenediamine) and 2.302(2) Å for Cl *cis* to C_2H_4 in Zeise's anion.[38]

The ethylene ligand. The C=C bond of the ethylene ligand is perpendicular [88.8(4)°] to the co-ordination plane. The Pt–C bond lengths [2.150(5) and 2.143(6) Å] are midway between corresponding values found in cationic $[PtCl(C_2H_4)(tmen)]^+$ [2.184(5) and 2.166(5) Å] and in Zeise's anion [2.135(3) and 2.128(3) Å].[37,38] The C–C distance is 1.353(8) Å in the present case, 1.376(3) and 1.375(4) Å in $[PtCl(C_2H_4)(tmen)]^+$ and $[PtCl_3(C_2H_4)]^-$ respectively,[37,38] and 1.337(2) Å in free ethylene.[39]

The hydrogen atoms of the ethylene group are slightly bent away from the central platinum atom and the angle between the normals to the H–C–H planes is 30(2)°. The corresponding value in both $[PtCl(C_2H_4)(tmen)]^+$ and $[PtCl_3(C_2H_4)]^-$ is 32°.[37,38] These values indicate that the metal–ethylene back bonding is similar in the three cases and suggest that the purine N(7) atom behaves as a comparable electron donor to the amine and chlorine ligands.

The purine ligand. The atoms of the purine moiety are coplanar, with a maximum deviation of 0.066(5) Å for C(6). Atoms O(6), N(2), H(2A) and H(2B), which were not included in the least-squares calculation, deviate from the purine plane by −0.189(3), 0.127(6), 0.01(7) and 0.02(7) Å, respectively. This suggests that the N(2) atom has a high sp^2 character, with the NH_2 group coplanar with the aromatic system. The C(2)–N(2) distance of 1.353(7) Å is also in agreement with a high percentage of double-bond character. Representative C(2)–NH_2 distances recently found in guanine derivatives are all in the range 1.34–1.36 Å, *e.g.* refs. 1, 26 and 40.

The C(6)–O(6) distance of 1.219(6) Å is consistent with significant double-bond character. The C(5)–C(6)–O(6) bond angle of 129.7(4)° is in agreement with other relatively high values found in platinum complexes of 6-oxopurines co-ordinated exclusively through N(7).[1,26,30,32] It is to be noted that for the bis(η-cyclopentadienyl)(3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dionato)titanium complex,[41] in which the metal is co-ordinated to both the N(7) and O(6) atoms, the C(5)–C(6)–O(6) angle is only 122.7(3)°.

Other bond lengths and angles in the guanine moiety have normal values.

The aliphatic chain linked to N(9) points away from the co-ordination sphere and it does not have any intramolecular interaction with the N(2)H_2 and N(1)H groups of the guanine moiety. The value of the glycosidic dihedral angle [C(4)–N(9)–C(1′)–O(1′), χ = 74.2(6)°] is very close to those found in free acyclovir [74.4(5)–90.5(6)°].[42] The N(9)–C(1′)–O(1′)–C(2′) torsion angle, φ, is 77.0(5)° corresponding to a *gauche* conformation; in accord with this conformation is the N(9)–C(1′) bond distance of 1.469(6) Å which is longer than that usually found in the opposite *trans* conformation [electron donation from the nitrogen atom N(9) p_z orbital to the antibonding orbital of C(1′)–O(1′) (σ*) has been suggested to be responsible for the lengthening of this bond in the *gauche* conformation].[42] The C(1′)–O(1′)–C(2′)–C(3′) torsion angle of −178.5(5)° corresponds to a *trans* conformation as also found in free

Table 2 Atomic coordinates (× 10^4) with estimated standard deviations (e.s.d.s) for $[PtCl_2(\eta^2\text{-}C_2H_4)L^2]$ **2**

Atom	X/a	Y/b	Z/c
Pt	1 046.4(0)	479.6(4)	3 907.9(1)
Cl(1)	1 632.5(3)	−352(3)	4 577.7(8)
Cl(2)	470.0(3)	1 430(4)	3 199.5(7)
C(E1)	1 114(2)	−328(12)	2 818(3)
C(E2)	1 034(2)	−2 698(13)	3 092(3)
N(1)	300.7(9)	2 452(9)	5 559(2)
C(2)	421(1)	4 536(10)	6 086(3)
N(2)	204(1)	5 281(13)	6 451(3)
N(3)	719(1)	5 778(8)	6 238(2)
C(4)	882(1)	4 875(9)	5 779(3)
C(5)	785(1)	2 871(9)	5 213(2)
C(6)	475(1)	1 334(11)	5 099(3)
O(6)	357.7(9)	−669(7)	4 689(2)
N(7)	1 038.0(9)	2 633(8)	4 880(2)
C(8)	1 277(1)	4 421(10)	5 241(3)
N(9)	1 197(1)	5 855(7)	5 793(2)
C(1′)	1 413(1)	7 962(10)	6 325(3)
O(1′)	1 582.9(8)	6 975(7)	7 085(2)
C(2′)	1 880(2)	5 316(14)	7 162(4)
C(3′)	2 038(2)	4 293(15)	7 996(4)
O(3′)	2 182(1)	6 462(11)	8 552(2)
C(4′)	2 515(1)	7 118(12)	8 716(3)
O(4′)	2 698(1)	6 027(11)	8 427(3)
C(5′)	2 632(2)	9 357(17)	9 317(5)
H(E1A)	1 353(20)	50(131)	2 868(42)
H(E1B)	872(19)	464(128)	2 269(43)
H(E2A)	846(18)	−3 239(155)	2 949(39)
H(E2B)	1 205(18)	−4 125(136)	3 430(38)
H(1)	55(17)	1 943(138)	5 428(34)
H(2A)	39(20)	4 263(140)	6 403(40)
H(2B)	279(17)	6 316(149)	6 817(40)
H(8)	1 466(20)	4 758(130)	5 127(41)
H(1′A)	1 581(17)	8 482(152)	6 099(35)
H(1′B)	1 241(19)	9 489(135)	6 366(39)
H(2′A)	1 826(16)	3 392(143)	6 753(35)
H(2′B)	1 989(17)	6 477(154)	6 907(39)
H(3′A)	2 211(17)	3 245(135)	8 025(38)
H(3′B)	1 842(18)	3 852(146)	8 138(36)
H(5′A)	2 394(19)	9 896(133)	9 418(39)
H(5′B)	2 740(18)	10 716(134)	9 075(41)
H(5′C)	2 797(18)	8 958(136)	9 799(42)

Table 3 Bond lengths (Å) with e.s.d.s for $[PtCl_2(\eta^2\text{-}C_2H_4)L^2]$ **2**

Pt–Cl(1)	2.302(1)	C(5)–N(7)	1.398(5)
Pt–Cl(2)	2.291(1)	C(6)–O(6)	1.219(6)
Pt–C(E1)	2.150(5)	C(6)–N(1)	1.406(6)
Pt–C(E2)	2.143(6)	N(7)–C(8)	1.298(6)
Pt–N(7)	2.078(3)	C(8)–N(9)	1.368(6)
C(E1)–C(E2)	1.353(8)	N(9)–C(1′)	1.469(6)
N(1)–C(2)	1.363(6)	C(1′)–O(1′)	1.387(6)
C(2)–N(2)	1.353(7)	O(1′)–C(2′)	1.434(7)
C(2)–N(3)	1.307(7)	C(2′)–C(3′)	1.502(10)
N(3)–C(4)	1.333(6)	C(3′)–O(3′)	1.435(9)
C(4)–C(5)	1.372(6)	O(3′)–C(4′)	1.329(7)
C(4)–N(9)	1.376(6)	C(4′)–O(4′)	1.199(8)
C(5)–C(6)	1.431(6)	C(4′)–C(5′)	1.498(10)
H(E1A)–C(E1)	0.97(8)	H(1′B)–C(1′)	1.05(7)
H(E1B)–C(E1)	1.19(7)	H(2′A)–C(2′)	1.17(7)
H(E2A)–C(E2)	0.77(7)	H(2′B)–C(2′)	0.95(7)
H(E2B)–C(E2)	1.02(7)	H(3′A)–C(3′)	0.86(6)
H(1)–N(1)	0.99(7)	H(3′B)–C(3′)	0.97(6)
H(2A)–N(2)	0.82(7)	H(5′A)–C(5′)	1.10(8)
H(2B)–N(2)	0.80(7)	H(5′B)–C(5′)	0.99(7)
H(8)–C(8)	0.90(8)	H(5′C)–C(5′)	0.91(7)
H(1′A)–C(1′)	0.96(6)		

acyclovir.[42] Finally the O(1′)–C(2′)–C(3′)–O(3′) and C(2′)–C(3′)–O(3′)–C(4′) torsion angles of −65.9(7) and −89.6(7)°, respectively, are both in accord with a *gauche* conformation. The reason for this is the presence of a hydrogen bond between O(4′) and C(3′). The O(4′) ··· H(3′A) distance is 2.31(7) Å compared to the sum of the van der Waals radii of 2.70 Å.[43–45] The C(3′)–H(3′A) ··· O(4′) angle is 109°, well above 90°, as usually required to consider a short H ··· X contact a hydrogen bond.[45]

A consequence of the *gauche* conformation around χ is the 2.76(7) Å distance between N(3) of the guanine and one hydrogen atom of C(1′), namely H(1′B) [N(3) ··· H(1′B)–C(1′) 94°]. If a hydrogen-bond interaction arises this could stabilize the conformation. However, it must be pointed out that the sum of the van der Waals radii for N and H is 2.75 Å.[43,44] Notwithstanding, the C(1′) atom is adjacent to N(9) and O(1′), which may decrease its electron density and enhance the facility with which it participates in C–H ··· X hydrogen bonds.[45] In metal nucleotide complexes the corresponding distances range from 2.61 to 2.91 Å,[1,46] consistent with the acyclovir species being a useful nucleoside/nucleotide mimic.

A molecular-mechanics energy calculation for the isolated complex molecule as a function of the rotation around the N(9)–C(1′) bond shows a local minimum at χ = 74° [observed value = 74.2(6)°]. However, the absolute minimum for the gas phase occurs at about −106° and the calculated energy difference between the two minima is *ca.* 8 kJ mol^{-1}.

The co-ordination of purine to platinum. We also wished to assess whether O(6) interacts with Pt, since the ethylene ligand should stabilize five-co-ordination around the metal relative to platinum complexes lacking such a π-bonding ligand.[6,7]

Two parameters can be used to asses the interaction. First, the Pt ··· O interatomic distance: this is 3.672(2) Å in the present case, compared to the sum of the van der Waals radii of only 3.3 Å.[43] Secondly, the relative magnitude of the Pt–N(7)–C angles: if a Pt–O(6) interaction occurs the Pt–N(7)–C(5) angle should become smaller than Pt–N(7)–C(8); however, the opposite situation is found with Pt–N(7)–C(5) 132.1(3)° against Pt–N(7)–C(8) 121.6(3)°. On this basis we can conclude that no bonding interaction between Pt and O(6) takes place and it appears to us very unlikely that Pt–O(6) interactions have anything other than a very transitory role in the interaction of platinum drugs with guanine residues.

Furthermore, when we examined several structures, a tendency was found to a linear relationship between the difference in the Pt–N(7)–C angles and the dihedral angle between the purine and the metal co-ordination planes (Fig. 2).[25–32] In the present case, a Pt–N(7)–C difference of 10° is consistent with a dihedral angle of 38°. Therefore it appears that the major determinant of the difference in Pt–N(7)–C angles is the interligand steric repulsion between the 6-oxo group and the contiguous *cis* ligand, which increases as the purine plane approaches the metal co-ordination plane. Any intra- or intermolecular interaction which would decrease the dihedral angle between these two planes will also increase the Pt–N(7)–C(5) angle over that of Pt–N(7)–C(8). In our case, packing forces appear to be responsible for the 38° value of the dihedral angle between the purine and the metal co-ordination plane, particularly the hydrogen bonding between O(6) and N(1)($\bar{x}, \bar{y}, \bar{z} + 1$) [O(6) ··· N(1)($\bar{x}, \bar{y}, \bar{z} + 1$) 2.73(7) Å, O(6) ··· H–N(1)($\bar{x}, \bar{y}, \bar{z} + 1$) 171(2)°] (Fig. 3).[47] It has also been suggested that intermolecular hydrogen bonds can cause deviations from

Table 4 Bond angles (°) with e.s.d.s for $[PtCl_2(\eta^2\text{-}C_2H_4)L^2]$ **2**

Cl(1)–Pt–Cl(2)	177.3(0)	C(4)–C(5)–C(6)	118.6(4)
Cl(1)–Pt–N(7)	89.2(1)	C(4)–C(5)–N(7)	109.5(4)
Cl(1)–Pt–C(E1)	89.1(2)	C(6)–C(5)–N(7)	131.8(4)
Cl(1)–Pt–C(E2)	89.3(2)	C(5)–C(6)–N(1)	109.8(4)
Cl(2)–Pt–N(7)	91.9(1)	C(5)–C(6)–O(6)	129.7(4)
Cl(2)–Pt–C(E1)	89.0(2)	O(6)–C(6)–N(1)	120.5(4)
Cl(2)–Pt–C(E2)	90.3(2)	C(5)–N(7)–C(8)	105.8(4)
N(7)–Pt–C(E1)	159.3(2)	N(7)–C(8)–N(9)	112.0(4)
N(7)–Pt–C(E2)	163.8(2)	C(8)–N(9)–C(4)	107.1(4)
C(E1)–Pt–C(E2)	36.8(2)	C(8)–N(9)–C(1′)	126.5(4)
Pt–N(7)–C(5)	132.1(3)	C(4)–N(9)–C(1′)	126.3(4)
Pt–N(7)–C(8)	121.6(3)	N(9)–C(1′)–O(1′)	111.8(4)
C(2)–N(1)–C(6)	125.6(4)	C(1′)–O(1′)–C(2′)	112.9(4)
N(1)–C(2)–N(2)	114.7(5)	O(1′)–C(2′)–C(3′)	108.6(6)
N(1)–C(2)–N(3)	124.3(3)	C(2′)–C(3′)–O(3′)	112.3(6)
N(2)–C(2)–N(3)	121.0(5)	C(3′)–O(3′)–C(4′)	117.2(5)
C(2)–N(3)–C(4)	111.6(4)	O(3′)–C(4′)–O(4′)	124.1(6)
N(3)–C(4)–C(5)	129.7(4)	O(3′)–C(4′)–C(5′)	111.6(6)
N(3)–C(4)–N(9)	124.6(4)	O(4′)–C(4′)–C(5′)	124.3(6)
C(5)–C(4)–N(9)	105.7(4)		

H(E1A)–C(E1)–C(E2)	121(4)	H(2′A)–C(2′)–C(3′)	107(3)
H(E1A)–C(E1)–H(E1B)	121(6)	H(2′A)–C(2′)–H(2′B)	100(6)
H(E1B)–C(E1)–C(E2)	110(3)	H(2′B)–C(2′)–O(1′)	99(4)
H(E2A)–C(E2)–C(E1)	122(6)	H(2′B)–C(2′)–C(3′)	126(4)
H(E2A)–C(E2)–H(E2B)	111(6)	H(3′A)–C(3′)–C(2′)	107(4)
H(E2B)–C(E2)–C(E1)	127(4)	H(3′A)–C(3′)–O(3′)	106(4)
H(1)–N(1)–C(6)	118(4)	H(3′A)–C(3′)–H(3′B)	127(6)
H(1)–N(1)–C(2)	116(4)	H(3′B)–C(3′)–C(2′)	105(4)
H(8)–C(8)–N(7)	125(4)	H(3′B)–C(3′)–O(3′)	98(4)
H(8)–C(8)–N(9)	123(4)	H(5′A)–C(5′)–C(4′)	104(3)
H(1′A)–C(1′)–N(9)	105(4)	H(5′A)–C(5′)–H(5′B)	119(5)
H(1′A)–C(1′)–O(1′)	110(4)	H(5′A)–C(5′)–H(5′C)	106(5)
H(1′A)–C(1′)–H(1′B)	117(6)	H(5′B)–C(5′)–C(4′)	104(4)
H(1′B)–C(1′)–N(9)	107(4)	H(5′B)–C(5′)–H(5′C)	106(6)
H(1′B)–C(1′)–O(1′)	106(4)	H(5′C)–C(5′)–C(4′)	118(4)
H(2′A)–C(2′)–O(1′)	116(3)		

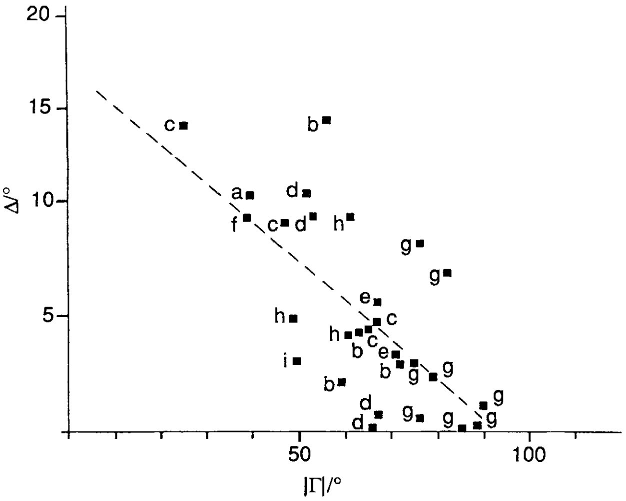


Fig. 2 Plot of the difference between the angles Pt–N(7)–C(5) and Pt–N(7)–C(8) against the absolute value of the torsion angle Γ = L(*cis*)–Pt–N(7)–C(5) for a number of 6-oxopurine complexes of platinum. For |Γ| > 90°, the value of 180 − |Γ| is plotted. The dotted line results from linear regression of the experimental values: correlation coefficient, −0.707; slope, −0.188; level of significance less than 0.000 05: **a**, this work; **b**, ref. 25; **c**, ref. 26; **d**, ref. 27; **e**, ref. 28; **f**, ref. 29; **g**, ref. 30; **h**, ref. 31 and **i**, ref. 32

planarity of the nucleobases.[42] Indeed both N(2) and O(6) atoms deviate significantly from the purine plane by 0.127(6) and −0.189(3) Å, respectively.

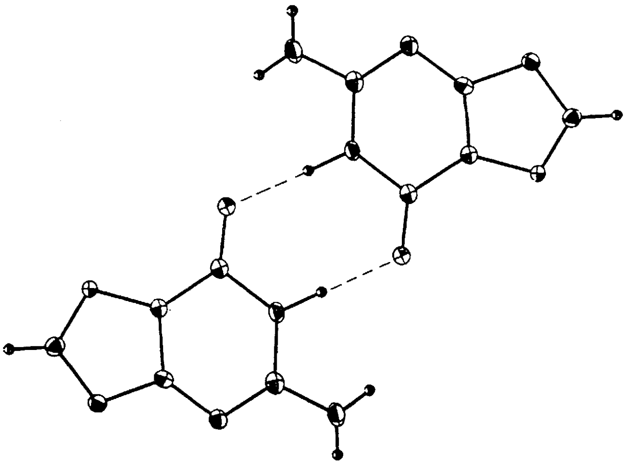


Fig. 3 Hydrogen-bond interactions (dotted lines) between the guanine moieties of two symmetrically related molecules of compound **2**

NMR Data.—The ^1H NMR spectra of compounds **1**–**3** in deuteriomethanol exhibit, on lowering the temperature, a definite broadening of the C(8)H and ethylene proton signals, which reached its maximum between +20 and +10 °C. Below this temperature the signals of C(8)H sharpened and shifted downfield by *ca.* 0.20 ppm at −60 °C, and the signal of ethylene first sharpened then broadened again. A broadening of the $C(1')H_2$ resonance was also apparent at −60 °C.

In deuteriochloroform compounds **2** and **3** (**1** is not soluble in this solvent) did not undergo any broadening of the C(8)H and ethylene signals between 20 and 0 °C. On the other hand, the resonance of the $C(2)NH_2$ protons of **2**, which was rather sharp and centred at δ 6.3 at +20 °C, broadened as the temperature was lowered and then split into two resonances at δ 7.6 and 5.0 (the latter overlaps with the signal of the ethylene protons). Similarly, the resonance of the C(2)N*H*COMe proton of **3** broadened and shifted to lower field as the temperature was lowered (δ 9.15, 9.75 and 10.05 at 35, −30 and −60 °C, respectively). At −60 °C a broadening of the ethylene and of the $C(1')H_2$ signals was observed for both **2** and **3**.

Concerning the C(8)H and ethylene resonances, the data in deuteriomethanol can be explained on the basis of a dissociation equilibrium of the nucleobase which is favoured by the strong *trans*-labilizing effect of ethylene and by the co-ordinating ability of methanol. The downfield shift of the C(8)H signal also indicates that the solvation equilibrium was shifted towards the undissociated species as the temperature was lowered. To test this hypothesis, the NMR spectrum of a solution of compound **1** and free acyclovir, in a molar ratio of 1:1, in deuteriomethanol was recorded between +35 and −60 °C. At +35 °C a single resonance was observed for each type of proton, indicating fast exchange between free and co-ordinated ligand. On lowering the temperature the single set of resonances split into two sets, one belonging to free and the other to complexed ligand.

In a non-co-ordinating solvent such as chloroform no broadening or shifting of the signals was observed over a comparable range of temperature. Therefore no dissociation of the nucleobase *trans* to ethylene occurred.

The non-equivalence of the NH_2 protons observed for compound **2** in chloroform at low temperature can originate from hindered rotation of the amino group about the C(2)–N bond. The $\Delta G^{\ddagger}$ of this process was estimated to be *ca.* 48 kJ mol^{-1} on the basis of the coalescence temperature. In the absence of significant steric interactions, only a delocalization of the lone pair of electrons of the amino group into the guanine π system can account for the observed phenomenon. The X-ray data give full support to this explanation.

In previous studies, even with acetylated guanosine derivatives, more polar solvents (dmso, dmf) were necessarily used to dissolve the guanine derivatives and, even at low temperatures, only one C(2)NH$_2$ signal was observed.[48] Indeed, even in the interior guanine–cytosine base pairs of oligonucleotides, only one C(2)NH$_2$ signal per base pair is found.[49] To our knowledge, this is the first time that such a splitting has been observed and the only suggestion we can offer is that the lower polarity of chloroform might lead to an increase in the rotation barrier if the double-bond character of the C–N bond is greater in a non-polar environment.

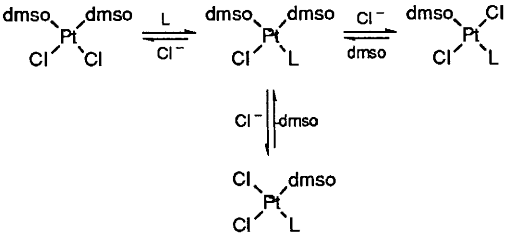
The signal of the corresponding C(2)NHCOMe proton in compound **3** was shifted downfield (from δ 9.15 to 10.05) as the temperature was lowered (from +35 to −60 °C). Also in this case, as in **2**, it is expected that the rotation rate about the C(2)–N bond is diminished as the temperature is lowered; however, only one of the two possible stereoisomers is formed. The most likely explanation is that the formation of only one rotamer is dictated by the possibility of forming a strong hydrogen bond between the carbonyl oxygen of the N-acetyl group and N(1)H. A favourable six-membered ring structure is built in this way. The downfield position of the N(1)H signal and the insensitivity of this signal to the different solvents are also consistent with internal hydrogen-bond formation.

In all cases examined (compounds **1**–**3**, in CD$_3$OD and **2**–**3** in CDCl$_3$) a broadening of the C(1′)H$_2$ and ethylene signals was observed on lowering the temperature to −60 °C, while the C(8)H signal remained sharp. The broadening could originate from a decrease in one of the dynamic rotational processes, *i.e.* of the ethylene, or of the 2-hydroxy- or 2-acetoxy-ethoxymethyl groups. The similar behaviour in the two solvents suggests that the hydrogen-bonding interaction with the solvent plays a minimal role in the binding and dynamic processes, except for ligand dissociation in methanol at the higher temperatures.

The reaction of acyclovir ligands with *cis*-[PtCl$_2$(dmso)$_2$] in a 1:1 molar ratio leads to formation of [PtCl$_2$(dmso)L] (L = L^1, **4**; L^2, **5**; or L^3, **6**). Two different isomers, *cis* and *trans*, can be formed; however, under the experimental conditions used here, the *trans* isomer was obtained in far greater yield. In the case of **6**, which is soluble in common organic solvents, heating of a solution of the *trans* isomer in methanol–water containing a small amount of dmso at 70 °C caused isomerization of the *trans* to the *cis* isomer which could be isolated from the solution. The assignment of the *trans* and *cis* structure to the two isomers of **6** was performed on the grounds that the spectrum of only one of the two isomers exhibits diastereotopic splitting of the methyl signals of dmso. Only the *cis* isomer can have an asymmetric metal centre. This is possible if the L^3 ligand does not rotate freely about the Pt–N bond and if the purine plane is not coincident with the co-ordination plane.

The NH signals of the C(2)-amino and C(2)-acetylamino groups in compounds **5** and **6** are shifted to lower field with respect to the corresponding protons in compounds **2** and **3** (by 0.7 and 1.8 ppm, respectively). We attribute this difference to a solvent effect (dmso and acetone in **5** and **6**, chloroform in **2** and **3**) since chloroform cannot accept a hydrogen bond from the NH group. This hypothesis is supported by the observation that the peak of the non-cyclic amine proton, in the free L^3 ligand, undergoes a surprisingly large downfield migration from δ 8.24 in CDCl$_3$ to δ 11.80 in dmso. The downfield migration begins when 5% (v/v) dmso is added to the CDCl$_3$ solution, thus indicating that dmso is directly responsible for such a shift due to hydrogen bonding involving its oxygen (Table 5).

The preferred formation of the *trans* isomer in the reaction of L with *cis*-[PtCl$_2$(dmso)$_2$] is a consequence of the greater *trans* effect of Cl$^-$ compared to the nitrogen atom of the nucleobase. The reaction occurs in two steps: Cl$^-$ substitution by L, followed by substitution of the dmso *trans* to Cl by the chloride ion displaced in the first step. The overall reaction, Scheme 1, allows also for the formation of the *cis* isomer under suitable experimental conditions.



Scheme 1

The compounds [PtCl$_2$L$_2$] (L = L^2, **7**; or L^3, **8**) and [PtCl(NH$_3$)$_2$L^1]NO$_3$ **9** have also been prepared and fully characterized. For all complexes the NMR spectra revealed that

Table 5 Proton chemical shift (δ, downfield from SiMe$_4$) for the free ligands and compounds **1**–**9**

Compound	Solvent	T/°C	C(1′)H$_2$	C(2′)H$_2$	C(3′)H$_2$	OH or OCOCH$_3$	C(2)NH$_2$ or C(2)NHR	NCOCH$_3$	N(1)H	C(8)H	C$_2$H$_4$* or dmso
L^1	(CD$_3$)$_2$SO		5.33	3.45		4.66	6.48		10.60	7.80	
L^2	(CD$_3$)$_2$SO		5.34	4.06	3.64	1.95	6.50		10.62	7.81	
L^3	(CD$_3$)$_2$SO		5.46	4.06	3.67	1.93	11.80	2.16	12.07	8.13	
	CDCl$_3$		5.44	4.23	3.71	2.04	8.24	2.28	11.88	7.76	
	5% (CD$_3$)$_2$SO 95% CDCl$_3$		5.48	4.19	3.70	2.04	11.23	2.26	12.23	7.81	
1	CD$_3$OD	+35	5.57	3.67						8.30	4.70
		−60	5.60	3.65						8.52	4.76
2	CD$_3$OD	+35	5.56	4.17	3.83	1.99				8.31	4.75
		−60	5.55	4.15	3.83	2.00				8.56	4.73
	CDCl$_3$	+35	5.52	4.25	3.83	2.09	6.30		11.33	8.10	4.85
		−60	5.55	4.25	3.86	2.16	7.60, 5.00		11.28	8.10	4.88
3	CD$_3$OD	+35	5.65	4.17	3.85	1.99		2.24		8.60	4.70
	CDCl$_3$	+35	5.48	4.23	3.80	2.08	9.15	2.33	12.35	8.15	4.83
		−60	5.59	4.20	3.81	2.13	10.05	2.42	12.47	8.24	4.84
trans-**4**	(CD$_3$)$_2$SO	+20	5.40	3.46			6.75		11.03	8.43	3.13
trans-**5**	(CD$_3$)$_2$SO	+20	5.40	4.04	3.66	1.93	6.78		11.16	8.51	3.26
trans-**6**	(CD$_3$)$_2$CO	+20	5.69	4.16	3.86	1.96	10.92	2.34	12.30	8.54	3.45, 3.40
cis-**6**	(CD$_3$)$_2$CO	+20	5.68	4.18	3.85	2.00	10.95	2.36	12.42	8.65	3.58
7	(CD$_3$)$_2$SO	+20	5.33	4.05	3.65	1.95	6.53		10.66	7.84	
8	(CD$_3$)$_2$SO	+20	5.46	4.03	3.66	1.93	11.77	2.15	12.06	8.12	
9	D$_2$O	+20	5.58	3.70						8.43	

* J(PtH) for ethylene protons always in the range 60–62 Hz.

the H(8) signal was downfield and that, except for **1** and **9** which were studied only in protic solvents, the N(1)H signal could be observed. These results confirm that in all the complexes N(7) co-ordination occurs regardless of the hydrogen-bonding and *trans* effect ability of the non-leaving ligands. No evidence for direct Pt••• O(6) interaction was obtained and, in systems with ethylene ligands, the thermodynamic product contained N(7)-bonded species.

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