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FULL PAPER

Synthesis and structural characteristics of metal–acyclovir (ACV) complexes: [Ni(or Co)$(ACV)_2(H_2O)_4]Cl_2\cdot 2ACV$, [Zn(ACV)-$Cl_2(H_2O)]$, $[Cd(ACV)Cl_2]\cdot H_2O$ and $[\{Hg(ACV)Cl_2\}_x]$. Recognition of acyclovir by Ni–ACV

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The monomeric $[M(ACV)_2(H_2O)_4]Cl_2\cdot 2ACV$ (M = Ni^{II} **1** or Co^{II} **2**), $[Zn(ACV)Cl_2(H_2O)]$ **3** and the polymeric $[Cd(ACV)Cl_2]\cdot H_2O$ **4** [ACV = acyclovir = 9-(2-hydroxymethoxymethyl)guanine] complex have been prepared and characterised by X-ray diffraction and IR data; ^1H and ^{13}C NMR have been used to interpret the structural characteristics of the complexes in solution. Compounds **1** and **2** exist as octahedral complexes with four H_2O ligands in the basal plane [Ni–OW 2.053(2) and 2.057(7) Å] and two axial ACV molecules linked to Ni through N(7) [Ni–N(7) 2.160(2) Å]. Two additional ACV molecules are included in the outer sphere of the complex, interacting by means of hydrogen bonds with the co-ordinated ACVs. This reveals the unprecedented recognition of free acyclovir molecules by Ni(or Co)-ACV (**1** and **2**). The monomeric zinc(II) complex **3** exhibits a distorted-tetrahedral geometry, involving two chlorides, the N(7) of the ACV ligand [Zn–N(7) 2.009(2) Å] and a water molecule. The hydrogen bonding of two guanine bases *via* NH_2 and N(3) (unit 1) with N(3) and NH_2 (unit 2) represents a novel type of interaction between nucleobases. In the case of the cadmium(II) complex **4** the structure is built by polymeric $(CdCl_2)_n$ chains which are held together by ACV ligands. The cadmium cation is octahedrically coordinated by four chlorides, the N(7) from an ACV molecule and the hydroxylic oxygen from another ACV molecule, the latter two atoms being placed in *cis* disposition. On the other hand, the complex $[\{Hg(ACV)Cl_2\}_x]$ **5** can be tentatively assigned as a polymer by comparison with analogous guanosine systems and spectroscopic and conductometric data.

Acyclovir (ACV), 9-[(2-hydroxyethoxy)methyl]guanine, an analogue of 2′-deoxyguanosine is an efficient topically active acyclic nucleoside with inhibitory activity towards several herpes viruses, especially HSV-1 and HSV-2.[1] Several studies have shown that the antiviral action of acyclovir involves its enzymatic conversion into the triphosphate of acycloguanosine {9-[(2-hydroxyethoxy)methyl]guanine}.[2] It is converted into the monophosphate in herpes-infected cells (yet only to a very limited extent in uninfected cells) by viral-induced thymidine kinase. It is further phosphorylated by the host cell guanosine monophosphate kinase to acyclovir diphosphate, which in turn is phosphorylated to the triphosphate by unidentified cellular enzymes. The triphosphate of acycloguanosine is more inhibitory to the viral DNA polymerase than to the α-DNA polymerase of the cell.[3] As a result, acyclovir is much more toxic to herpes viruses in an HSV-infected cell than to the cell itself. Metals can play an important role in both the mechanism of action and toxic side effects of organic drugs and their metabolites.[4] Although several acyclovir complexes and derivatives have been described[5–8] very little structural information is available.[8–10] Thus in the present work studies of several metal(II) complexes with acyclovir have been carried out.

Experimental

Reagents were used as received from Roig Farma (acyclovir) and Aldrich (metallic salts).

Syntheses

$[M(ACV)_2(H_2O)_4]Cl_2\cdot 2ACV$ (M = Ni^{II} 1 or Co^{II} 2). To an aqueous solution (20 ml of water at 70 °C) of 12 mmol of $MCl_2\cdot 6H_2O$ (M = Ni or Co), 6 mmol of acyclovir were added. The resulting solution was stirred for 2–3 h. After several days crystals were obtained.

Complex **1** exhibits a mass decrease (Found: 28.5. Calc.: 29.0%) between 30 and 335 °C corresponding to the loss of 4 H_2O + 4 CH_2OH–CH_2OH per formula unit (Found: C, 34.78; H, 4.84; N, 25.19. Calc. for $C_{32}H_{52}Cl_2N_{20}NiO_{16}$: C, 34.83; H, 4.72; N, 25.37%). Selected IR bands (cm^{-1}): 1123s, 1182m, 1403m, 1462m, 1490s, 1537m, 1574s, 1637vs, 1670vs and 1682 (sh). UV/VIS (DMSO): λ 786 (ε 5.4), 720 (sh), 425 (13) and 259 nm (7.2×10^4 dm^3 mol^{-1} cm^{-1}). The complex undergoes solvation in solution and $Ni(DMSO)_6^{2+}$ seems to be formed. Λ_M/Ω^{-1} cm^2 mol^{-1} (10^{-3} mol dm^{-3} in DMSO, 25 °C) = 63.7.

Complex **2** exhibits a first mass decrease (Found: 3.4. Calc.: 3.3%) between 40 and *ca.* 150 °C corresponding to the loss of two water molecules per formula unit and a second mass decrease (Found: 25.0. Calc.: 25.9%) between 150 and 330 °C corresponding to the loss of 2 H_2O + 4 CH_2OH–CH_2OH per formula unit (Found: C, 34.76; H, 4.80; N, 25.19. Calc. for $C_{32}H_{52}Cl_2CoN_{20}O_{16}$: C, 34.84; H, 4.72; N, 25.41%). Selected IR bands (cm^{-1}): 1122s, 1186m, 1404m, 1460m, 1488s, 1539m, 1574s, 1635vs, 1669vs and 1683 (sh). UV/VIS (DMSO): λ 678 (ε 90), 610 (sh) and 259 nm (8.2×10^4 dm^3 mol^{-1} cm^{-1}). The complex undergoes solvation in solution and $Co(DMSO)_6^{2+}$ seems to be formed. Λ_M/Ω^{-1} cm^2 mol^{-1} (10^{-3} mol dm^{-3} in DMSO, 25 °C) = 47.7.

$[Zn(ACV)Cl_2(H_2O)]$ 3, $[Cd(ACV)Cl_2]\cdot H_2O$ 4 and $[\{Hg(ACV)-Cl_2\}_x]$ 5. To an aqueous solution (20 ml of water at 70 °C) of 12 mmol of MCl_2 (M = Zn or Hg) or $CdCl_2\cdot 2.5\ H_2O$, 6 mmol of

acyclovir were added. The resulting solution was stirred for 2–3 h. The complex precipitated during the reaction and was filtered off, washed with water and air dried. Crystals of **3** and **4** were obtained by slow evaporation of mother-liquors.

Complex **3** exhibits a mass decrease (Found: 4.9. Calc.: 4.7%) between 30 and 190 °C corresponding to the loss of the water molecule per formula unit (Found: C, 24.99; H, 3.42; N, 18.29. Calc. for $C_8H_{13}Cl_2N_5O_4Zn$: C, 25.30; H, 3.42; N, 18.44%). Selected IR bands (cm^{-1}): 1130s, 1188m, 1403m, 1461w, 1494m, 1548m, 1587vs, 1651vs and 1690vs. UV (DMSO): λ 259 nm (ε 1.4 × 10^4 dm^3 mol^{-1} cm^{-1}). ^{1}H NMR (DMSO-d_6): δ 10.86 [s, 1 H, H(1)], 8.04 [s, 1 H, H(8)], 6.68 (s, 2 H, NH_2), 5.48 [s, 2 H, C(10)H], 4.79 (br t, 1 H, OH, J = 3.6 Hz) and 3.56 [s, 4 H, C(11)H and C(12)H]. ^{13}C NMR (DMSO-d_6): δ 160.5 [C(6)], 158.0 [C(2)], 155.3 [C(4)], 142.4 [C(8)], 119.7 [C(5)], 76.2 [C(10)], 74.5 [C(12)] and 63.9 [C(11)]. Λ_M/Ω^{-1} cm^2 mol^{-1} (10^{-3} mol dm^{-3} in DMSO, 25 °C) = 6.8.

Complex **4** exhibits a mass decrease (Found: 16.7. Calc.: 16.7%) between 40 and 280 °C corresponding to the loss of two chlorine atoms per formula unit (Found: C, 22.45; H, 3.07; N, 16.20. Calc. for $C_8H_{13}CdCl_2N_5O_4$: C, 22.50; H, 3.05; N, 16.41%). Selected IR bands (cm^{-1}): 1118m, 1190m, 1398w, 1456 (sh), 1471m, 1539m, 1571 (sh), 1635vs and 1676s. UV (DMSO): λ 259 nm (ε 1.4 × 10^4 dm^3 mol^{-1} cm^{-1}). ^{1}H NMR (DMSO-d_6): δ 10.75 [s, 1 H, H(1)], 7.93 [s, 1 H, H(8)], 6.62 (s, 2 H, NH_2), 5.45 [s, 2 H, C(10)H], 4.78 (br t, 1 H, OH, J = 2.4 Hz) and 3.56 [s, 4 H, C(11)H and C(12)H]. ^{13}C NMR (DMSO-d_6): δ 160.5 [C(6)], 158.1 [C(2)], 155.2 [C(4)], 142.1 [C(8)], 119.4 [C(5)], 76.4 [C(10)], 74.6 [C(12)] and 64.0 [C(11)]. Λ_M/Ω^{-1} cm^2 mol^{-1} (10^{-3} mol dm^{-3} in DMSO, 25 °C) = 17.3.

Complex **5** is thermally stable until 230 °C (Found: C, 19.22; H, 2.16; N, 13.83. Calc. for $C_8H_{11}Cl_2HgN_5O_3$: C, 19.33; H, 2.22; N, 14.10%). Selected IR bands (cm^{-1}): 1112s, 1183m, 1396 (sh), 1463 (sh), 1485m, 1539m, 1585s, 1624s, 1666 (sh) and 1694vs. UV (DMSO): λ 260 nm (ε 1.6 × 10^4 dm^3 mol^{-1} cm^{-1}). ^{1}H NMR (DMSO-d_6): δ 10.85 [s, 1 H, H(1)], 8.01 [s, 1 H, H(8)], 6.67 (s, 2 H, NH_2), 5.48 [s, 2 H, C(10)H], 4.78 (br s, 1 H, OH) and 3.58 [s, 4 H, C(11)H and C(12)H]. ^{13}C NMR (DMSO-d_6): δ 160.6 [C(6)], 158.3 [C(2)], 155.1 [C(4)], 142.9 [C(8)], 119.4 [C(5)], 76.7 [C(10)], 74.7 [C(12)] and 64.0 [C(11)]. Λ_M/Ω^{-1} cm^2 mol^{-1} (10^{-3} mol dm^{-3} in DMSO, 25 °C) = 2.6.

Physical measurements

Elemental analyses were carried out using a Carlo Erba model 1106 microanalyser. The infrared spectra in the solid state (KBr pellets) were recorded on a PE 683 spectrometer with a PE 1600 infrared data station and electronic spectra on a PE 552 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 spectrometer. Proton and carbon chemical shifts in DMSO-d_6 were referenced to DMSO-d_6 [^{1}H, δ(DMSO) 2.60; ^{13}C, δ(DMSO) 43.5]. The ^{1}H NMR temperature studies were referenced to tetramethylsilane [δ(DMSO) 2.50 relative to TMS]. Thermogravimetric data in the range from 30 to 900 °C were obtained in air (heating rate 10 °C min^{-1}) on a PE TGA-2 thermobalance.

Crystallography

Crystal of compounds **1**, **3** and **4** were mounted in a Siemens P4 diffractometer equipped with Mo-Kα radiation. The unit cell was determined in each case from 40 random reflections in the range $4 < \theta < 25°$. The number of independent reflections measured and the ranges of θ, h, k and l are indicated together with other procedural data in Table 1. Three standards reflections were measured every 100, showing slight decomposition of samples **1** and **3** (around 5%). Data were corrected for Lorentz-polarisation effects and empirically (ψ scans) for absorption in compounds **3** and **4** (not for **1**); the transmission ranges were 0.333–0.503 and 0.462–0.516 respectively.

The structures were solved by the heavy atom method and refined by full-matrix least squares on F^2. Extinction was corrected for compound **4** by means of the method implemented in SHELXTL-V5,[11] the corresponding parameter reaching the value χ = 0.0482(13). Hydrogen atoms were introduced in their ideal positions, except those of water molecules and the hydroxyl group of the ligand that were found in ΔF maps and refined with fixed (0.86 Å) O–H distances; thermal parameters 1.2 times those of their parent atoms were applied to all H atoms.

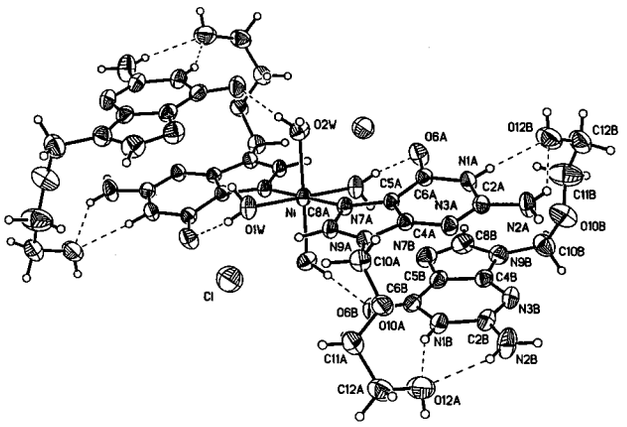

Fig. 1 Molecular structure of $[Ni(ACV)_2(H_2O)_4]Cl_2 \cdot 2ACV$ **1**.

Final residuals as well as crystal data are in Table 1. The program package SHELXTL-V5 was used for structure solution and refinement and for the drawings.

CCDC reference number 186/1242.

Powder X-ray diffraction diagrams were collected on a Siemens D5000 diffractometer with secondary graphite-monochromated Cu-Kα radiation (λ = 1.54056 Å). Reflections were placed in the range $2 < 2\theta < 60$.

Results and discussion

Crystal structures

Nickel(II) and cobalt(II) complexes (1 and 2). The structure of complex **1** consists of elongated centrosymmetric octahedral molecules with H_2O ligands in the basal plane [Ni–OW 2.053(2) and 2.057(7) Å] and two ACV molecules bound to Ni through N(7) [Ni–N(7) 2.160(2) Å] (Table 2). In order to complete the structural unit, two other ACV molecules are included in the outer sphere of the complex, interacting by means of hydrogen bonds with the co-ordinated ACVs [N(1A)···O(12B) 2.803(3); N(2A)···O(12B) 3.001(3); O(12A)···N(1B) 2.776(3); O(12A)···N(2B) 2.885(3) Å; O(1W)···O(6A) 2.634(2); O(2W)···O(6B) 2.696(2) Å] (Fig. 1). The oxygen atom of the carbonyl group of both co-ordinated and secondary ACV are involved in hydrogen bonds to the co-ordinated water molecules [O(1W)···O(6A) 2.634(2); O(2W)···O(6B) 2.696(2) Å] as observed in several Cu–ACV complexes.[8,9] Values of Ni–OW and Ni–N(7) are similar to those in other structurally related complexes such as $[Ni(IMP)(H_2O)_5]$,[12] $[Ni(en)(IMP)_2(H_2O)_2]$,[13] $[Ni(GMP)(H_2O)_5]$,[14] $[Ni(GMP)_2(H_2O)_4]^{2-}$,[15] $[Ni(en)_{0.7}(dGMP)_2(H_2O)_{0.6}(H_2O)_2]^{2-}$ [15] and $[Ni(dGMP)(H_2O)_5]$.[16]

The guanine moiety, of all ACV molecules presented in complex **1**, is essentially planar. The bond lengths and angles of guanine conform well to those found in the three molecules of the asymmetric unit of crystalline ACV·$\frac{2}{3}H_2O$ [17] and those corresponding to $[Cu(ACV)_2Cl_2(H_2O)_2]$,[9] $[Cu(ACV)_2(H_2O)_x]^{2+}$ (x = 2 [10a] or 3 [10b]), $[Cu(ACVP)_2(H_2O)_2]$ [8] (ACVP = acyclovir monophosphate) and $[Pt(ACVA)Cl_2(\eta^2\text{-}C_2H_4)]$ [7] (ACVA = acyclovir monoacetate). In previously described complexes the C(10) is coplanar to the plane of guanine however in **1** a noticeable distortion {τ[N(7)–C(8)–N(9)–C(10)] = 171.04° (8.9° up to plane)} appears. The Ni bonded to N(7) is placed 11.2° below the plane of guanine {τ[N(9)–C(8)–N(7)–Ni] = 168.78°}. This

Table 1 Crystal data and structure refinement for $[Ni(ACV)_2(H_2O)_4]Cl_2 \cdot 2ACV$ **1**, $[Zn(ACV)Cl_2(H_2O)]$ **3** and $[Cd(ACV)Cl_2] \cdot H_2O$ **4**

	1	**3**	**4**
Empirical formula	$C_{32}H_{52}Cl_2N_{20}NiO_{16}$	$C_8H_{13}Cl_2N_5O_4Zn$	$C_8H_{13}CdCl_2N_5O_4$
M	1102.55	379.50	426.53
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
Crystal dimensions/mm	0.45 × 0.3 × 0.25	0.5 × 0.4 × 0.2	0.2 × 0.3 × 0.4
a/Å	12.6672(8)	7.7878(7)	7.2653(5)
b/Å	15.1340(12)	8.6616(6)	7.9452(6)
c/Å	12.8273(11)	10.9133(10)	12.5441(10)
α/°		97.841(7)	84.702(6)
β/°	111.077(5)	106.910(7)	75.186(6)
γ/°		94.220(6)	78.932(5)
U/Å^3	2294.5(3)	692.74(10)	686.30
D_c/g cm^{-3}	1.596	1.819	2.064
Z	2	2	2
μ(Mo-Kα)/cm^{-1}	6.31	21.78	20.00
T/K	293(2)	293(2)	293(2)
θ Range/°	1.94–25.00	1.98–30.0	1.68–30.00
hkl Ranges	−1 to 15, −1 to 17, −15 to 14	−1 to 10, −12 to 12, −15 to 15	−1 to 10, −11 to 11, −17 to 17
No. reflections collected	4999	4815	4879
No. independent reflections	4035	4001	4008
(R_{int})	(0.0241)	(0.0171)	(0.0175)
F(000)	1148	384	420
Data/restraints/parameters	4035/6/340	3999/3/190	4008/3/191
Goodness of fit on F^2	1.027	1.087	1.141
Final $R1$, $wR2$ [$I > 2\sigma(I)$]	0.0383, 0.0973	0.0327, 0.0873	0.0220, 0.0580
(all data)	0.0443, 0.1019	0.0385, 0.0928	0.0225, 0.0584
Largest difference peak, hole/e Å^{-3}	1.051, −0.374	0.455, −0.940	0.514, −0.562

value is higher than those of the corresponding Pt[7] (8.2°) and Cu[9] (5.2°) complexes. The acyclic chains of the two different ACVs present in the structural unit of **1** are folded, with C(11)–C(12) bonds in *gauche* conformation, but a *syn* conformation between N(7) and O(12) appears† which permits five hydrogen bonds to stabilise the non-co-ordinated ACVs in the complex structure. On the other hand, stacking between co-ordinated and non-co-ordinated ACVs is present (average distance between the two rings = 3.4 Å; this distance is essentially the same as that found between adjacent base pairs in DNA[17]). These subtle changes in the lateral chains could be responsible for the recognition of non-co-ordinated ACV by Ni–ACV. The powder X-ray diffraction diagrams of the nickel **1** and cobalt **2** complexes clearly demonstrate that the compounds are isostructural, diffraction peaks changing only slightly in position and intensity from one diagram to the other.

Zinc(II) complex 3. The co-ordination geometry about the Zn^{II} in complex **3** is approximately tetrahedral with an ACV molecule [Zn–N(7) 2.009(2) Å], two chlorine atoms [Zn–Cl(1) 2.2544(6) and Zn-Cl(2)=2.1976(6) Å] and a water molecule [Zn–OW 1.996(2) Å] [Table 2 and Fig. 2(a)]. The crystal structure is formed by three types of hydrogen bonds between ACVs [$N(2)H_2$(unit 1)···N(3)(unit 2) 3.041(2) Å], between acyclovir and the chlorine atom [N(1)(unit 1)···Cl(1)(unit 3) 3.255(2) and $N(2)H_2$(unit 1)···Cl(1)(unit 3) 3.473(2) Å] and between the hydroxyl group of the lateral chain of ACV and the water molecule [O(12)(unit 2)···OW(unit 3) 2.690(2)]. The hydrogen bond scheme of two guanine bases *via* NH_2 and N(3) (unit 1) with N(3) and NH_2 (unit 2) could represent a novel type of interaction between nucleobases as described by Lippert and co-workers.[18] The value of Zn–N(7) is similar to that of polymeric Zn(5′-IMP)[19] [Zn–N(7)(distorted tetrahedral co-ordination) 1.99 Å] but lower than those corresponding of $[Zn(H_2O)_4$(Me-5′-IMP)] and $[Zn(H_2O)_4$(Me-5′-GMP)][20] [Zn–N(7)(octahedral co-ordination) 2.158 and 2.143 Å] [Fig. 2(b)].

† A similar C(11)–C(12) *gauche* conformation but an *anti* conformation between N(7) and C(12) is present in units A and B of free ACV (see ref. 16).

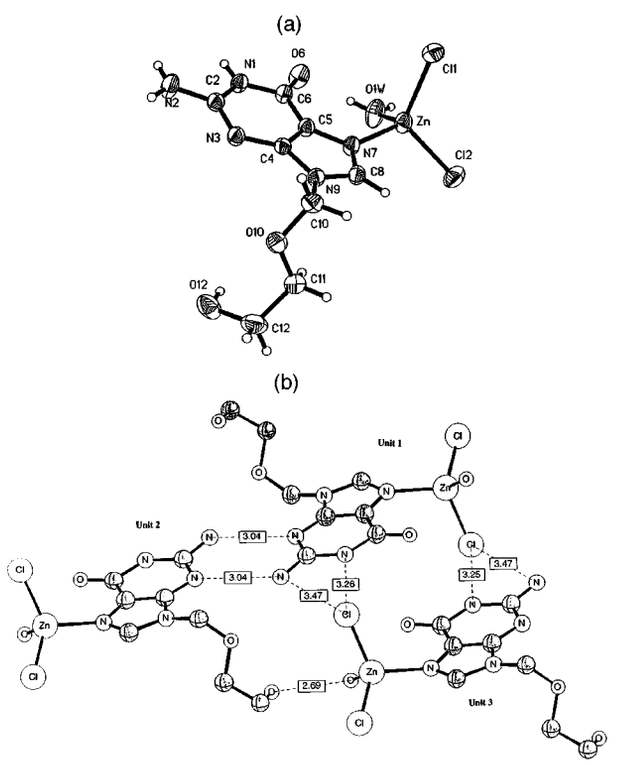

Fig. 2 (a) Molecular structure of $[Zn(ACV)Cl_2(H_2O)]$ **2**. (b) Packing of three complex units showing the hydrogen bonds and the novel type of interaction between two guanine nucleobases [NH_2 and N(3) (unit 1) with N(3) and NH_2 (unit 2)].

Like in the other complexes, the guanine moiety of ACV in **3** is essentially planar and bond lengths and angles are similar.[7–10,17] Nevertheless, this complex presents an important non-coplanarity of C(10) {τ[N(7)–C(8)–N(9)–C(10)] = 190.90°} and Zn{τ[N(9)–C(8)–N(7)–Zn] = 164.17°} with these two atoms placed on the same side of the plane of guanine [C(10) 10.9° and Zn 15.8°]. As in **1**, the acyclic chain of ACV in **3** is folded

Table 2 Bond lengths (Å) and angles (°)

Nickel complex **1**							
Ni–O(1W)	2.053(2)	Ni–O(2W)	2.057(7)	Ni–N(7A)	2.160(2)		
N(1A)–C(2A)	1.369(3)	N(1B)–C(2B)	1.371(3)	C(6A)–O(6A)	1.237(3)	C(6B)–O(6B)	1.238(3)
N(1A)–C(6A)	1.389(3)	N(1B)–C(6B)	1.387(3)	N(7A)–C(8A)	1.313(3)	N(7B)–C(8B)	1.304(4)
C(2A)–N(3A)	1.324(3)	C(2B)–N(3B)	1.319(3)	C(8A)–N(9A)	1.369(3)	C(8B)–N(9B)	1.375(4)
C(2A)–N(2A)	1.331(3)	C(2B)–N(2B)	1.333(3)	N(9A)–C(10A)	1.471(3)	N(9B)–C(10B)	1.464(3)
N(3A)–C(4A)	1.349(3)	N(3B)–C(4B)	1.356(3)	C(10A)–O(10A)	1.387(3)	C(10B)–O(10B)	1.390(3)
C(4A)–N(9A)	1.372(3)	C(4B)–N(9B)	1.371(3)	O(10A)–C(11A)	1.428(3)	O(10B)–C(11B)	1.386(4)
C(4A)–C(5A)	1.382(3)	C(4B)–C(5B)	1.384(3)	C(11A)–C(12A)	1.498(4)	C(11B)–C(12B)	1.482(5)
C(5A)–N(7A)	1.400(3)	C(5B)–N(7B)	1.383(3)	C(12A)–O(12A)	1.418(3)	C(12B)–O(12B)	1.398(3)
C(5A)–C(6A)	1.422(3)	C(5B)–C(6B)	1.416(3)				
Hydrogen bonds present in the molecular unit							
N(1A)···O(12B)	2.803(3)	N(1B)···O(12A)	2.776(3)	N(2A)···O(12B)	3.001(3)	N(2B)–O(12A)	2.885(3)
O(1W)–Ni–N(7A)	87.23(7)	O(2W)–Ni–N(7A)	90.76(7)	C(8A)–N(7A)–Ni	121.0(2)	C(5A)–N(7A)–Ni	133.38(14)
O(1W)–Ni–O(2W)	91.51(8)						
C(2A)–N(1A)–C(6A)	126.2(2)	C(2B)–N(1B)–C(6B)	125.7(2)	O(6A)–C(6A)–C(5A)	129.2(2)	O(6B)–C(6B)–C(5B)	129.7(2)
N(3A)–C(2A)–N(2A)	120.7(2)	N(3B)–C(2B)–N(2B)	120.9(2)	C(5A)–C(6A)–N(1A)	111.7(2)	C(5B)–C(6B)–N(1B)	111.5(2)
N(3A)–C(2A)–N(1A)	122.7(2)	N(3B)–C(2B)–N(1B)	123.6(2)	C(8A)–N(7A)–C(5A)	104.4(2)	C(8B)–N(7B)–C(5B)	104.1(2)
N(2A)–C(2A)–N(1A)	116.6(2)	N(2B)–C(2B)–N(1B)	115.6(2)	N(7A)–C(8A)–N(9A)	113.1(2)	N(7B)–C(8B)–N(9B)	113.8(2)
C(2A)–N(3A)–C(4A)	112.4(2)	C(2B)–N(3B)–C(4B)	112.1(2)	C(8A)–N(9A)–C(4A)	106.6(2)	C(8B)–N(9B)–C(4B)	105.7(2)
N(3A)–C(4A)–N(9A)	124.7(2)	N(3B)–C(4B)–N(9B)	125.9(2)	C(8A)–N(9A)–C(10A)	127.6(2)	C(8B)–N(9B)–C(10B)	128.4(2)
N(3A)–C(4A)–C(5A)	129.2(2)	N(3B)–C(4B)–C(5B)	128.3(2)	C(4A)–N(9A)–C(10A)	125.3(2)	C(4B)–N(9B)–C(10B)	125.9(2)
N(9A)–C(4A)–C(5A)	106.0(2)	N(9B)–C(4B)–C(5B)	105.7(2)	O(10A)–C(10A)–N(9A)	113.0(2)	O(10B)–C(10B)–N(9B)	112.9(2)
C(4A)–C(5A)–N(7A)	109.9(2)	C(4B)–C(5B)–N(7B)	110.7(2)	C(10A)–O(10A)–C(11A)	114.4(2)	C(10B)–O(10B)–C(11B)	115.7(3)
C(4A)–C(5A)–C(6A)	117.6(2)	C(4B)–C(5B)–N(7B)	118.8(2)	O(10A)–C(11A)–C(12A)	108.6(2)	O(10B)–C(11B)–C(12B)	110.9(3)
N(7A)–C(5A)–C(6A)	132.2(2)	N(7B)–C(5B)–C(6B)	130.5(2)	O(12A)–C(12A)–C(11A)	109.4(2)	O(12B)–C(12B)–C(11B)	110.6(3)
O(6A)–C(6A)–N(1A)	119.1(2)	O(6B)–C(6B)–N(1B)	118.8(2)				
Zinc complex **3**							
Zn–O(1W)	1.996(2)	Zn–N(7)	2.009(2)	Zn–Cl(1)	2.2544(6)	Zn–Cl(2)	2.1976(6)
N(1)–C(2)	1.379(2)	C(4)–N(9)	1.378(2)	C(6)–O(6)	1.236(2)	C(10)–O(10)	1.389(2)
N(1)–C(6)	1.389(2)	C(4)–C(5)	1.382(2)	N(7)–C(8)	1.316(2)	O(10)–C(11)	1.426(2)
C(2)–N(2)	1.329(2)	C(5)–N(7)	1.385(2)	C(8)–N(9)	1.364(2)	C(11)–C(12)	1.501(3)
C(2)–N(3)	1.331(2)	C(5)–C(6)	1.416(2)	N(9)–C(10)	1.470(2)	C(12)–O(12)	1.421(3)
N(3)–C(4)	1.350(2)						
O(1W)–Zn–Cl(1)	108.49(7)	O(1W)–Zn–Cl(2)	111.58(6)	C(2)–N(3)–C(4)	112.37(14)	C(8)–N(9)–C(4)	106.84(13)
N(7)–Zn–Cl(1)	110.92(5)	N(7)–Zn–Cl(2)	106.96(5)	N(3)–C(4)–N(9)	126.36(14)	C(8)–N(9)–C(10)	125.09(14)
Zn–N(7)–C(8)	123.08(12)	Zn–N(7)–C(5)	129.50(12)	N(3)–C(4)–C(5)	128.01(14)	C(4)–N(9)–C(10)	127.06(14)
O(1W)–Zn–N(7)	104.53(7)			N(9)–C(4)–C(5)	105.62(14)	O(10)–C(10)–N(9)	113.0(2)
C(2)–N(1)–C(6)	125.42(14)	O(6)–C(6)–C(5)	127.6(2)	C(4)–C(5)–N(7)	109.99(14)	C(10)–O(10)–C(11)	113.2(2)
N(3)–C(2)–N(2)	120.0(2)	C(5)–C(6)–N(1)	111.38(14)	C(4)–C(5)–C(6)	119.5(2)	O(10)–C(11)–C(12)	108.6(2)
N(2)–C(2)–N(1)	116.7(2)	C(8)–N(7)–C(5)	105.16(14)	N(7)–C(5)–C(6)	130.4(2)	O(12)–C(12)–C(11)	112.9(2)
N(3)–C(2)–N(1)	123.3(2)	N(7)–C(8)–N(9)	112.4(2)	O(6)–C(6)–N(1)	121.0(2)		
Cadmium complex **4**							
Cd–Cl(1)	2.6631(5)	Cd–Cl(1′)	2.5993(5)	Cd–N(7)	2.402(2)	Cd–O(12*)	2.3050(13)
Cd–Cl(2)	2.5654(5)	Cd–Cl(2″)	2.6884(5)				
N(1)–C(2)	1.374(2)	C(4)–N(9)	1.374(2)	C(6)–O(6)	1.243(2)	C(10)–O(10)	1.405(2)
N(1)–C(6)	1.386(2)	C(4)–C(5)	1.385(2)	N(7)–C(8)	1.313(2)	O(10)–C(11)	1.443(2)
C(2)–N(2)	1.351(2)	C(5)–N(7)	1.393(2)	C(8)–N(9)	1.369(2)	C(11)–C(12)	1.496(2)
C(2)–N(3)	1.323(2)	C(5)–C(6)	1.419(2)	N(9)–C(10)	1.458(2)	C(12)–O(12)	1.433(2)
N(3)–C(4)	1.344(2)						
O(12*)–Cd–N(7)	83.11(5)	Cd–Cl(2)–Cd[3]	94.66(2)	N(7)–Cd–Cl(2)	88.52(4)	Cl(1)–Cd–Cl(1)[2]	83.18(2)
O(12*)–Cd–Cl(2)	163.99(4)	Cd–Cl(1)–Cd[2]	96.82(2)	N(7)–Cd–Cl(1)[2]	165.91(4)	Cl(2)–Cd–Cl(1)[2]	101.02(2)
O(12*)–Cd–Cl(1)[2]	89.87(3)	Cd–N(7)–C(8)	115.94(12)	N(7)–Cd–Cl(1)	84.43(4)	Cl(2)–Cd–Cl(2)[3]	85.34(2)
O(12*)–Cd–Cl(1)	88.45(4)	Cd–N(7)–C(5)	138.97(11)	N(7)–Cd–Cl(2)[3]	91.29(4)	Cl(1)[2]–Cd–Cl(2)[3]	99.73(2)
O(12*)–Cd–Cl(2)[3]	81.25(4)			Cl(1)–Cd–Cl(2)[3]	169.26(2)		
C(2)–N(1)–C(6)	125.2(2)	N(9)–C(4)–C(5)	105.66(14)	O(6)–C(6)–C(5)	128.4(2)	O(10)–C(10)–N(9)	111.70(14)
N(3)–C(2)–N(2)	119.5(2)	C(4)–C(5)–N(7)	110.2(2)	C(5)–C(6)–N(1)	112.15(14)	C(10)–O(10)–C(11)	113.58(14)
N(2)–C(2)–N(1)	117.1(2)	C(4)–C(5)–C(6)	118.0(2)	C(8)–N(7)–C(5)	104.45(14)	O(10)–C(11)–C(12)	107.56(14)
N(3)–C(2)–N(1)	123.4(2)	N(7)–C(5)–C(6)	131.8(2)	N(7)–C(8)–N(9)	113.0(2)	O(12)–C(12)–C(11)	109.27(14)
C(2)–N(3)–C(4)	112.4(2)	O(6)–C(6)–N(1)	119.4(2)	C(8)–N(9)–C(4)	106.64(14)	C(12)–O(12)–O(6)[4]	107.24(11)
N(3)–C(4)–N(9)	125.4(2)	Cd[4]–O(12)–O(6)[4]	108.76(6)	C(8)–N(9)–C(10)	125.8(2)	C(12)–O(12)–Cd[4]	123.22(10)
N(3)–C(4)–C(5)	128.9(2)			C(4)–N(9)–C(10)	127.2(2)		

[a] Superscripts represent other different monomeric units.

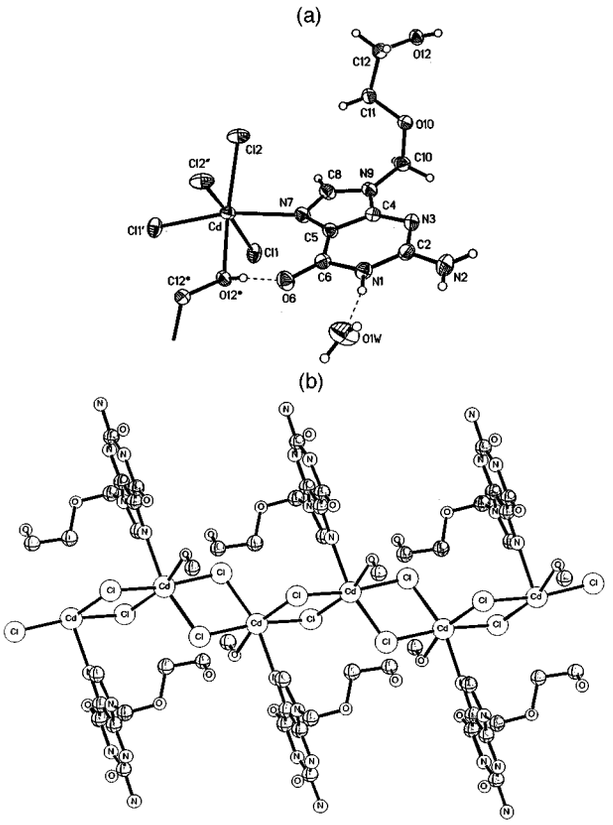

Fig. 3 (a) Molecular structure of $[Cd(ACV)Cl_2]\cdot H_2O$ **3**. (b) Drawing of the polymeric chain $(CdCl_2)_n$.

with C(11)–C(12) bonds in *gauche* conformation and *syn* conformation between N(7) and O(12).

Cadmium(II) complex 4. The Cd^{II} in the polymeric complex **4** presents a distorted octahedral co-ordination with four chlorine atoms, N(7) from an ACV molecule and O(12) from another ACV molecule [Cd–Cl between 2.5654(5) and 2.6884(5), Cd–N(7) 2.402(2), Cd–O(12) 2.3050(13) Å] (Table 2). These two ACVs are placed in *cis* disposition [Fig. 3(a)]. The value of the distance Cd–N(7) is slightly higher than that of the octahedral monomeric structure of Cd(5′-GMP)[21] [Cd–N(7) 2.37 Å]. The guanine moiety of ACV in **4** is also essentially planar. As in **3**, C(10) and Cd atoms of the complex are placed on the same side of the plane of guanine [C(10) 6.8° and Cd 7.7°] and although the acyclic chain of ACV is folded with C(11)–C(12) bonds in *gauche* conformation a *trans* conformation between N(7) and O(12) can be observed. To our knowledge, this is the first example where the hydroxyl group of the lateral chain of ACV interacts directly with the metal.

The structure is built by polymeric $(CdCl_2)_n$ chains linked by ACV ligands [Fig. 3(b)]. The chains run along the *a* axis and cadmium atoms alternate in them with pairs of bridging chlorine ligands. Four-membered Cd_2Cl_2 centrosymmetric rings are generated in this way, which considerably deviate from a perfect square-planar geometry as far as the angles are concerned. Consecutive Cd_2Cl_2 rings are almost perpendicular (average dihedral angle = 81.52°) and therefore the polymeric chain is twisted.[22] The chains are linked to each other by the acyclovir ligands which are co-ordinated *via* N(7) to a cadmium atom of one chain and *via* the terminal hydroxyl group O(12) to a cadmium atom of another chain. This latter bond is reinforced by a hydrogen bond formed with the carbonyl oxygen atom O(6) of the ACV molecule co-ordinated *via* N(7) [O(12)···O(6) 2.636(2) Å], yielding a two-dimensional polymer perpendicular to the *c* axis. An interstitial water molecule completes the asymmetric unit, being strongly attached to the structure *via* hydrogen bonds [N(1)···OW 2.801(2), O(6)···OW 2.893(2) and O(10)···OW 2.841(2) Å].

The Ni–ACV **1**, Zn–ACV **3**, Cd–ACV **4**, Cu–ACV[8–10] and Pt–ACV[7] complexes present a lateral chain with a global conformation type: *gauche* [N(9)–C(10)], *gauche* [C(10)–O(10)], *trans* [O(10)–C(11)] and *gauche* [C(11)–C(12)] which is equivalent to those observed in the A and B molecules of free acyclovir[17] (Table 3). The *gauche* conformation of the glycosidic bond N(9)–C(10) is consistent with the observed distances [from 1.459(2) to 1.471(3) Å] which are longer than those usually found in the opposite *trans* conformation [1.441(5) Å].[7]

Infrared spectra

The IR spectra of the obtained complexes were compared with that of acyclovir.[23,24] The more relevant features are: (a) shift to lower frequencies of the strong band at 1718 cm^{-1} (1682, 1670 for **1**; 1683, 1669 for **2**; 1690 for **3**; 1676 for **4** and 1694, 1666 cm^{-1} for **5**) which is assigned to the vibration ν[C(6)=O(6)] in free ACV. This is consistent with the C=O group involved in hydrogen bonds. In some Cu–ACV complexes[8,9] it has been observed that short hydrogen bonds involving O(6) significantly diminish the carbonyl stretching frequency in the IR spectra. The 1634 cm^{-1} band related to $\delta(NH_2)$ is not appreciably shifted for **1**, **2,** **4** and **5**, although for **3** it is shifted to 1651 cm^{-1}, possibly due to the double interaction of the NH_2 group present [N(3)···H_2N, Cl···H_2N]. (b) Splitting of the 1487 cm^{-1} band[23] (1490, 1462 for **1**; 1488, 1460 for **2**; 1494, 1461 for **3**; 1471, 1456 for **4** and 1485, 1463 for **5**) assigned to δ[C(8)–H] + ν[C(8)–N(7)] and these variations, related to the five-membered ring, have been observed in the spectra of several structurally known N(7)-metallated complexes.[23,25] The far-IR spectra of the complexes show a new band at 312 **1** and 313 cm^{-1} **2** assigned as essentially ν(M–N).[26] The low frequency band at 332 cm^{-1}, found for compound **3**, may be attributed to the Zn–Cl stretching mode of the terminal chlorides.[27]

NMR spectra

Unequivocal assignments of ^{1}H and ^{13}C NMR spectra of compounds **3**, **4** and **5** are shown in Table 4. As can be appreciated, the spectra of the compounds of Zn^{II}, Cd^{II} and Hg^{II} show small differences with regards to the ACV ligand, but are similar to those of other equivalent guanosine complexes,[28] which can be explained by the practically no modification of the structural features of the guanine ring and the lateral chain (see X-ray section). Thus, at room temperature, in the ^{1}H NMR only slight modifications (Zn +0.12, Cd +0.01 and Hg +0.09 ppm) of H(8) of the guanine ring can be observed. On the other hand, the ^{13}C NMR of these complexes show a slight general upfield shift of C(5) (Zn −0.7, Cd −1.0 and Hg −1.0 ppm) and downfield shift of C(8) (Zn +0.7, Cd + 0.4 and Hg +1.2 ppm), which can be explained by the formation of the metal(II)–N(7) bond.

Although we cannot discard the substitution of the remaining ligands by DMSO molecules, the existence in solution of ACV–metal interaction has been studied between 20 and 60 °C (internal reference: tetramethylsilane). In the Zn–ACV **3** and Hg–ACV **5** complexes the resonance of the aromatic H(8) proton shows an upfield shift when the temperature is increased (*ca.* 0.04 ppm per 10 °C) compared with free ACV which remains practically unaltered. A possible explanation is the reversible labilisation of the N(7)–M bond which diminishes the non-shielding effect of the metal over H(8). The H(8) of the Cd–ACV complex **4** shows similar behaviour to that of ACV and we cannot conclude whether in solution the N(7)–M bond remains unaltered.

Conclusion

The compound ACV presents a general N(7)–M interaction

Table 3 Dihedral angles (°) corresponding to the lateral chain in ACV and ACV complexes

	ACV Molecule								
Dihedral angle	A	B	C	Ni–ACV		Zn–ACV	Cd–ACV	Cu–ACV	Pt–ACV
C(4)–N(9)–C(10)–O(10)	−76.5	−74.4	−90.5	−73.8	(−72.7)[a]	74.6	−82.7	92.5	74.2
N(9)–C(10)–O(10)–C(11)	−76.9	−66.3	−173.3	−82.8	(−103.2)	73.2	−71.2	−88.7	77.0
C(10)–O(10)–C(11)–C(12)	173.2	−176.2	−171.9	−179.5	(172.5)	178.8	−170.8	−178.2	−178.4
O(10)–C(11)–C(12)–O(12)	60.6	73.5	−174.4	−66.6	(−60.8)	59.3	63.2	−69.1	−65.9

[a] Non-co-ordinated ACV.

Table 4 Proton and ^{13}C NMR (selected peaks, at 294 K) of ACV and complexes **3**–**5**

					$\Delta\delta$		
	ACV	**3**	**4**	**5**	$[Hg(Guo)Cl_2]$	$[Hg(Guo)Br_2]$	$[Hg(Guo)(SCN)_2]$
H(1)	10.77	10.86(+0.09)	10.75(−0.02)	10.85(+0.08)	(+0.21)	(+0.06)	(+0.21)
H(8)	7.92	8.04(+0.12)	7.93(+0.01)	8.01(+0.09)	(+0.08)	(+0.11)	(+0.21)
NH_2	6.62	6.68	6.62	6.67			
C(6)	160.8	160.5(−0.3)	160.5(−0.3)	160.6(−0.2)	(−0.4)	(−0.4)	(−0.5)
C(2)	157.8	158.0(+0.2)	158.1(+0.3)	158.3(+0.5)	(+0.1)	(+0.1)	(+0.3)
C(4)	155.4	155.3(−0.1)	155.2(−0.2)	155.1(−0.3)	(−0.3)	(−0.6)	(−0.7)
C(8)	141.7	142.4(+0.7)	142.1(+0.4)	142.9(+1.2)	(0.0)	(+0.3)	(+0.8)
C(5)	120.4	119.7(−0.7)	119.4(−1.0)	119.4(−1.0)	(−0.6)	(0.0)	(−0.4)
C(10)	76.0	76.2(+0.2)	76.4(+0.4)	76.7(+0.7)			
C(12)	74.4	74.5(+0.1)	74.6(+0.2)	74.7(+0.3)			
C(11)	63.9	63.9(0.0)	64.0(+0.1)	64.0(+0.1)			

which is accompanied by hydrogen bonds, stabilising a monomeric unit and/or the crystal structure. Although all heteroatoms of the ligand constitute potential sites to form hydrogen bonds in metal chloride complexes of Co, Ni, Cu, Zn, Cd and Hg with ACV, there is a preference of the guanidine moiety of the guanine ring [N(1), N(2) and N(3)] for ACV · · · ACV interactions, whereas oxygens [O(6), O(10) and O(12)] are normally involved in ACV · · · H_2O interactions. On the other hand, Ni (and Co)–ACV constitute examples of recognition of ACV for Ni(or Co)–ACV.

The Cd–ACV complex is the first example where an oxygenated group [O(12)H] of the lateral chain of ACV interacts directly with the metal.

In the Zn–ACV complex the hydrogen bonding of two guanine bases *via* NH_2 and N(3) (unit 1) with N(3) and NH_2 (unit 2) represents a novel type of interaction between nucleobases. Based on X-ray and spectral data we can conclude that Co–, Ni–, Cu–[9] and Zn–ACV are monomeric complexes and Cd–ACV is a polymeric structure (Figs. 1–3). The complex Hg–ACV could be tentatively assigned as a $[\{Hg(ACV)Cl_2\}_x]$ polymer based on spectral data which show direct N(7)–Hg interaction, conductometric measurements (no electrolyte) and comparison with other similar structures $[\{Hg(Guo)X_2\}_x]$ (X = Cl, Br or SCN).[28]

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