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The first examples of platinum amine hydroxamate complexes: structures and biological activity

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Two novel benzohydroxamate complexes of anticancer active Pt(II)–diamine moieties have been synthesised in which Pt–C bonds are present in the dinuclear structures. The complexes, $[\{Pt(en)\}_2(\mu\text{-bha})]ClO_4\cdot H_2O$ (en = ethane-1,2-diamine) and $[\{Pt(R,R\text{-chxn})\}_2(\mu\text{-bha})]NO_3\cdot 2H_2O$ (chxn = cyclohexane-1,2-diamine), have two platinum centres that are bridged through the bha ligand *via* (O,O) and (C,N) coordination modes, the latter mode occurring through deprotonation of the *ortho* carbon of the phenyl ring. The cytotoxicities of the complexes were tested against a panel of cell lines based on the A2780 ovarian cancer cell line and revealed that both dinuclear complexes were less active than their corresponding dichloro parent complexes. It is likely that they act in a similar manner to the parent complexes, but with the cytotoxicity mediated by factors influencing cellular uptake, such as the charge and lipophilicity of the compounds.

Introduction

Cisplatin (*cis*-dichlorodiammineplatinum(II)) and its congeners are the most widely used class of anticancer drugs but are limited in effectiveness by toxicity related side-effects and resistance. Consequently considerable research has been directed toward finding analogues of these drugs that are less toxic and circumvent cross-resistance whilst maintaining potent anticancer activity.[1,2] Traditionally this has been attempted by modifications of the am(m)ine carrier ligands and to a lesser extent by employing alternative *cis* leaving groups. Attempts to selectively target Pt drugs to tumour cells over healthy cells using biologically active ligands, particularly those that have an affinity for tumour cells or have increased cellular uptake, have not met with great success.[3–5]

Recent approaches to anticancer therapy have involved agents that target specific cellular processes that are enhanced or altered in tumours. In particular, the discovery of matrix metalloproteinases (MMPs) as enzymes critically linked to metastasising tumours has prompted development of a class of drugs that have the potential to not only be potent, but act selectively on tumours as well.[6] MMP inhibitors have reached later phase clinical trials and have much promise not only as anticancer drugs but as treatments for arthritis and other such pathological states.[7] Most of these inhibitors are based on the hydroxamate functional group which binds to and ultimately deactivates the Zn atom of the active site of MMPs. Hydroxamates have also been employed as inhibitors of the nickel enzyme urease[8,9] and are the basis of the biological iron transport agents, siderophores.[10,11]

In light of their biological importance we sought to investigate hydroxamates as leaving groups in anticancer active complexes of Pt(II). By employing them as leaving groups it was envisaged that platinum based cytotoxic agents could eventually be combined with tumour selective, hydroxamate based MMP inhibitors. However, we have recently shown that hydroxamates do not usually form stable complexes with Pt(II) amines[12] and no such complexes have been reported in the literature. Hydroxamate binding to Pt(II) can be stabilised by the presence of softer ligands such as phosphines and sulfoxides, evidently as a result of stabilisation of the dinegative hydroximate form (Fig. 1).[12,13] Here, we report the synthesis, characterisation, and cytotoxicity of the first two diamine Pt(II) complexes of hydroxamate ligands.

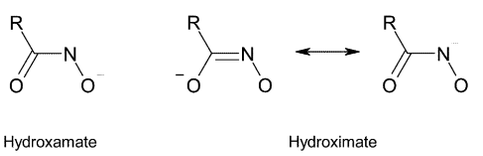

Fig. 1 Representation of the canonical structures of the hydroxamate and hydroximate forms of ionised hydroxamic acids.

Experimental

$[PtCl_2(en)]$ (en = ethane-1,2-diamine) and $[PtCl_2(R,R\text{-chxn})]$ (chxn = cyclohexane-1,2-diamine) were prepared by reaction of a 1 : 1 mixture of the diamine with $K_2[PtCl_4]$ in water overnight. Yields were approximately 95%. Benzohydroxamic acid (bhaH) was obtained from Aldrich and used as supplied without further purification. Microanalysis (C, H, N) was conducted by the Microanalytical Service of the Australian National University.

Synthesis of $[\{Pt(en)\}_2(\mu\text{-bha})]ClO_4\cdot H_2O$ (1)

A suspension of $[PtCl_2(en)]$ (0.50 g, 1.5 mmol) in water (15 mL) was treated with an aqueous solution of $AgNO_3$ (0.52 g, 1.98 equivalents) and stirred in the dark overnight. The precipitate of AgCl was filtered off and benzohydroxamic acid (0.32 g, 2.3 mmol) was added to the filtrate. The solution was stirred at 70 °C for 5 h whilst maintaining the pH at 5.5 by addition of aqueous NaOH (1 M). $NaClO_4$ (0.28 g, 2.3 mmol) was then added and the solution concentrated to yield the product $[\{Pt(en)\}_2(\mu\text{-bha})]ClO_4\cdot H_2O$ (**1**) as a yellow precipitate that was filtered off, washed with a little water and air dried. Yield: 0.36 g (63%). The product was recrystallised from hot water giving crystals suitable for X-ray diffraction. Anal. Calc. for $C_{11}H_{22}ClN_5O_7Pt_2$: C, 17.3; H, 2.9; N, 9.2. Found: C, 17.2; H, 3.0; N, 9.1%. **CAUTION:** Perchlorate salts are potentially hazardous and should not be excessively heated or scraped in glass frits.

Synthesis of $[\{Pt(R,R\text{-chxn})\}_2(\mu\text{-bha})]NO_3\cdot 2H_2O$ (2)

The *R*,*R*-*trans*-cyclohexane-1,2-diamineplatinum(II) complex of bha was synthesised by the corresponding procedure to that described for **1**, up to the addition of the hydroxamic acid, using $[PtCl_2(R,R\text{-chxn})]$ as the starting material. The reaction mixture from this step was stirred for two days at approximately 40 °C whereupon a pale yellow solid precipitated that was

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filtered off, washed with water and air dried affording [{Pt(*R*,*R*-chxn)}$_2$(μ-bha)]NO_3·$2H_2O$ (**2**). Yield: 0.23 g (63%). The product was recrystallised from an aqueous ethanol solution (50%) giving yellow crystals. Anal. Calc. for $C_{19}H_{36}N_6O_7Pt_2$: C, 26.8; H, 4.3; N, 9.9. Found: C, 26.2; H, 4.0; N, 9.4%.

Crystallography

X-Ray crystallographic analyses were performed on suitable crystals mounted on thin glass fibres. The data were obtained at either room temperature or 150 K with a Bruker SMART 1000 CCD diffractometer using graphite-monochromated Mo-Kα radiation generated from a sealed tube. The low-temperature collection was performed with an Oxford Systems Cryostream. An empirical absorption correction determined with SADABS[14,15] was applied to the data. The data integration and reduction were undertaken with SAINT and XPREP,[16] and subsequent computations were carried out with the WinGX[17] graphical user interface. The data reduction included the application of Lorentz and polarisation corrections. The structures were solved either by direct methods with SHELXS-86[18] or SHELXS-97,[19] and extended and refined with SHELXL-97.[19] The structures were refined on F^2 by full-matrix least squares with anisotropic thermal parameters for all non-H atoms and calculated (riding model) positions for H atoms with U_{ij} set at 1.5 of that of the parent atom. Final *R* indices and weighting schemes are as quoted in the corresponding crystal data tables. ORTEP[20] representations of the structures were plotted with thermal ellipsoids at the 30% probability level.

CCDC reference numbers 200413 and 203671.

See http://www.rsc.org/suppdata/dt/b2/b212553f/ for crystallographic data in CIF or other electronic format.

In vitro cytotoxicity assays

Cell lines. The parental human ovarian carcinoma cell line A2780 and two resistant A2780 cell lines; A2780 cisR (cisplatin) and A2780 473R (AMD473) were used in this study.[21,22] Cells were maintained in exponential growth as monolayers at 37 °C in 5% CO_2 in RPMI 1640 medium (TRACE Bioscience) supplemented with 2 mM glutamine and 10% fetal calf serum.

MTT Assay. The complexes tested were dissolved in water to make 0.5 mM solutions immediately prior to the assay. Cytotoxicity was assessed using the MTT assay as previously described.[23] The MTT assay is dependent on the cellular reduction of MTT by the mitochondrial dehydrogenase of viable cells to a purple formazan product. The water-insoluble MTT-formazan can be measured spectrophotometrically when dissolved in DMSO. Single-cell suspensions were obtained by trypsinisation of monolayer cultures, with cell counts performed using a heamocytometer counter (Weber). Approximately 5×10^4 cells were seeded onto each well of flat bottom 96-well plates (Corning) and allowed to attach overnight. Serial dilutions of the platinum complex solutions were added to quadruplicate wells for 72 h, and following incubation of cells the culture medium was removed and MTT (0.05 mg in 50 μL growth medium) was added to each well and incubated for a further 4 h. The culture medium was then removed from each well and DMSO (150 μL) (Sigma) was added, the plate was shaken for 5 seconds and the absorbance measured immediately at 540 nm using a microplate reader (SpectraCount, PACKARD). IC_{50} values were determined as the drug concentration that reduced the absorbance to 50% of that in untreated control wells.

Results and discussion

Syntheses

The two dinuclear complexes were synthesised using typical procedures[24] for the preparation of Pt(II) complexes with anionic O-donor ligands. This involved treating the starting materials with silver nitrate in aqueous media to remove the halide ligands thereby creating an aqua hydroxo intermediate expected to facilitate the coordination of the hydroxamate ligand. In the case of **1** the final product was isolated as a less soluble salt by addition of the appropriate counter anion. In the procedure described above, sodium perchlorate was used, but the complex was obtained as the hexafluorophosphate salt in the same manner for use in the biological assays. Complex **2** precipitated as the sparingly soluble nitrate salt; all further work was performed on this form of the complex.

The complexes form as dinuclear species with Pt(en) moieties bridged through the hydroximate ligand, involving the formation of a (C,N) chelate to one Pt atom. The mechanism of formation of this chelate is unclear but presumably involves initial coordination of the Pt(en) moiety to N(1) followed by ring closure to C(3). This type of platinum coordination has been previously reported but its observation in this case is of considerable interest given the mild reaction conditions. Typically, platinum–aryl complexes are prepared by oxidative addition reactions involving starting materials with the Pt^0 oxidation state—there is no indication here of such a reaction taking place. Furthermore, platinum–aryl complexes are normally stabilised by soft ligands such as tertiary phosphines.

Attempts at obtaining the desired mononuclear species $[Pt(bha)(diamine)]^+$ by other synthetic pathways were unsuccessful with the dinuclear complexes forming preferentially. Similarly, only benzohydroxamate complexes were able to be prepared; complexes of simple alkyl hydroxamates, such as acetohydroxamate, were not obtained using the above procedure. In both complexes the benzohydroxamato ligand has adopted the doubly deprotonated hydroximate form which has been observed in all of the other reported Pt(II)–hydroxamate complexes.[12,13] The evidence from those cases suggests that ligands with soft base donor atoms *trans* to the hydroximate ligand stabilise this form. In the complexes of this study it is likely the additional Pt(amine) moieties similarly confer stability to the benzohydroximate ligand and thereby stability to the Pt–hydroximate interaction.

Description of crystal structures

Figs. 2 and 3 show thermal ellipsoid representations of the crystal structures of **1** and **2**, respectively. Crystallographic and

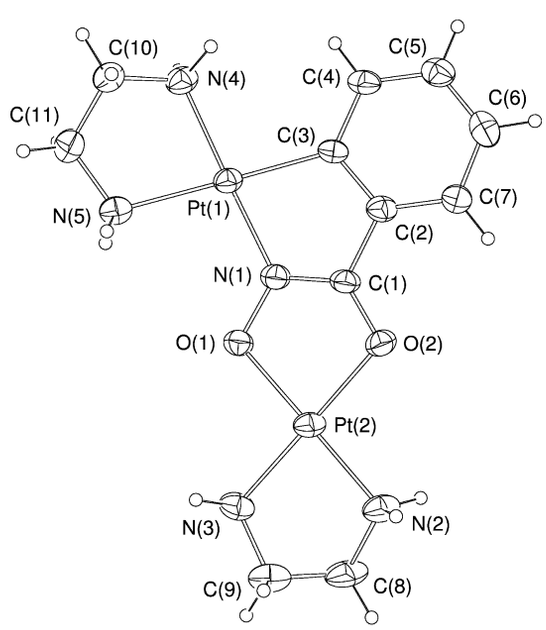

Fig. 2 Thermal ellipsoid representation of **1** showing crystallographic atom numbering. Perchlorate and water molecules omitted for clarity. Ellipsoids at 30% probability.

Table 1 Crystal data and refinement details for **1** and **2**

	1	**2**
Empirical formula	$C_{11}H_{22}ClN_5O_7Pt_2$	$C_{38}H_{72}N_{12}O_{14}Pt_4$
M_r	761.97	1693.37
T/K	293(2)	150(2)
λ/Å	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	$C2/c$	$P2_1$
a/Å	24.038(5)	7.704(3)
b/Å	9.838(2)	23.505(8)
c/Å	17.166(4)	15.251(5)
β/°	103.438(3)	99.141(6)
V/Å^3	3948.3(14)	2726.7(15)
Z	8	2
D_c/Mg m^{-3}	2.557	2.062
μ/mm^{-1}	14.334	10.296
$F(000)$	2800	1600
θ range for data collection/°	2.25–28.28	1.35–28.31
Index ranges	$-31 \le h \le 31$	$-10 \le h \le 9$
	$-12 \le k \le 12$	$-31 \le k \le 31$
	$-22 \le l \le 22$	$-20 \le l \le 20$
Reflections collected	17757	24663
Independent reflections (R_{int})	4626 (0.0638)	6601 (0.0563)
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/parameters	4626/244	6601/614
Goodness-of-fit on F^2	1.082	1.079
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0428$	$R_1 = 0.0563$
	$wR_2 = 0.1134$	$wR_2 = 0.1383$
R indices (all data)	$R_1 = 0.0494$	$R_1 = 0.0860$
	$wR_2 = 0.1243$	$wR_2 = 0.1587$
Flack parameter		0.44(6)
Largest diff. peak and hole/e Å^{-3}	2.070 and −1.656	4.890 and −1.452

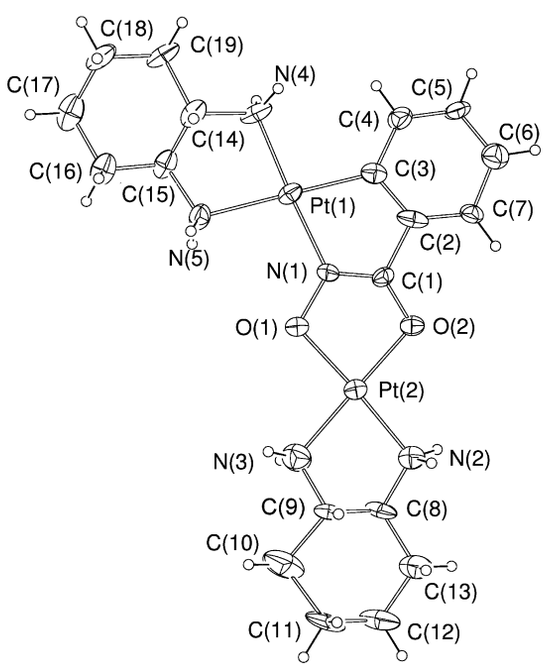

Fig. 3 Thermal ellipsoid representation of **2** showing one of the independent molecules with crystallographic atom numbering. Nitrate and water molecules omitted for clarity. Ellipsoids at 30% probability.

refinement details of the two complexes are listed in Table 1. Selected bond lengths and angles of both are given in Tables 2 and 3. In **1**, the Pt is chelated by an en ligand and by the benzohydroxamato ligand in an [O,O] fashion as expected. Unexpectedly though, a second Pt(en) moiety is bound to the hydroxamate—through the deprotonated N(1) atom and a deprotonated C(3) on the phenyl ring. The unipositive charge of the complex supports this observed yet unexpected deprotonation. The overall structure of the complex is close to planar with slight bends toward the en ligands. Two disordered solvent water molecules are observed and each refined to half occupancy.

Both platinum centres of **1** display distorted square planar coordination geometries—the chelate angles being 83.2(3)° for the en, and 82.6(2)° for O,O in Pt(1) and 80.8(3)° for en and 79.4(3)° for C,N in Pt(2). Pt(1) lies close (0.05 Å) to the plane of the hydroxamate group, the mean plane being defined by O(1)–N(1)–C(1)–O(2). However, Pt(2) deviates by 0.21 Å from the mean plane defined as C(3)–C(2)–C(1)–N(1), the other chelating group of the hydroxamato ligand. This distortion is possibly due to the canting of the phenyl ring (containing C(3) and C(2)) with respect to the hydroxamate group (containing C(1) and N(1)).

The Pt(2)–O(1) and Pt(2)–O(2) bond lengths to the hydroxamato ligand are 2.001(5) and 2.003(6) Å respectively, which are consistent with the bond lengths in other platinum(II) complexes with oxygen donors. Of interest are the bond lengths of the coordinated benzohydroxamato ligand relative to those of the free hydroxamate;[25] these are O(1)–N(1) +0.039, C(1)–N(1) −0.031 and C(1)–O(2) +0.055. The contraction of the C–N bond and elongation of the C–O bond are indicators of delocalisation of additional negative charge in the ionised form of the hydroxamic acid which in turn is consistent with the ligand adopting the doubly deprotonated hydroximate form. The Pt(1)–C(3) bond length was found to be 2.010(7) Å, similar to other reported platinum–aryl complexes.[26]

The asymmetric unit of **2** consists of two independent molecules of $[\{Pt(R,R\text{-chxn})\}_2(\mu\text{-bha})]^+$ with four waters of crystallisation refined to half occupancies and two nitrate anions. The complex is structurally analogous to **1** with two Pt(chxn) moieties bridged through the benzohydroxamate ligand. The second Pt similarly binds through a deprotonated C atom on the phenyl ring of the bha. The complex displays an essentially planar overall structure with the cyclohexane rings adopting the chair conformation. The two molecules are situated side-by-side in the asymmetric unit and stack in the lattice with a sheet like formation with the 'layers' separated by nitrate anions. The large magnitude of the Flack parameter is possibly indicative of a high level of twinning of the crystal; also of note is the large anisotropy seen from the thermal ellipsoids that is not consistent throughout the molecule.

Table 2 Selected bond lengths (Å) for **1** and selected average bond lengths (Å) for **2**

1		**2**	
C(1)–N(1)	1.292(10)	C(1)–N(1)	1.30
C(1)–O(2)	1.305(9)	C(1)–O(2)	1.32
C(3)–Pt(1)	2.010(7)	C(3)–Pt(1)	1.98
N(1)–O(1)	1.408(8)	N(1)–O(1)	1.40
N(1)–Pt(1)	1.982(7)	N(1)–Pt(1)	2.00
N(2)–Pt(2)	2.019(7)	N(2)–Pt(2)	2.01
N(3)–Pt(2)	2.042(7)	N(3)–Pt(2)	2.03
N(4)–Pt(1)	2.039(7)	N(4)–Pt(1)	2.09
N(5)–Pt(1)	2.140(7)	N(5)–Pt(1)	2.14
O(1)–Pt(2)	2.001(5)	O(1)–Pt(2)	2.016
O(2)–Pt(2)	2.003(6)	O(2)–Pt(2)	2.003

Table 3 Selected bond angles (°) for **1** and selected average bond angles (°) for **2**

1		**2**	
N(1)–C(1)–O(2)	123.8(7)	N(1)–C(1)–O(2)	123
N(1)–C(1)–C(2)	112.7(7)	N(1)–C(1)–C(2)	113
O(2)–C(1)–C(2)	123.3(7)	O(2)–C(1)–C(2)	124
C(3)–C(2)–C(1)	113.4(7)	C(3)–C(2)–C(1)	113
C(2)–C(3)–Pt(1)	113.6(5)	C(2)–C(3)–Pt(1)	115
C(4)–C(3)–Pt(1)	129.8(6)	C(4)–C(3)–Pt(1)	131
C(9)–C(8)–N(2)	111.5(9)	C(9)–C(8)–N(2)	104
C(8)–C(9)–N(3)	108.0(8)	C(8)–C(9)–N(3)	109
C(11)–C(10)–N(4)	107.8(8)	C(15)–C(14)–N(4)	106
C(10)–C(11)–N(5)	110.2(8)	C(14)–C(15)–N(5)	108
C(1)–N(1)–O(1)	116.0(6)	C(1)–N(1)–O(1)	117
C(1)–N(1)–Pt(1)	120.0(5)	C(1)–N(1)–Pt(1)	119
O(1)–N(1)–Pt(1)	124.0(5)	O(1)–N(1)–Pt(1)	124
C(8)–N(2)–Pt(2)	108.8(6)	C(8)–N(2)–Pt(2)	111
C(9)–N(3)–Pt(2)	109.6(6)	C(9)–N(3)–Pt(2)	107
C(10)–N(4)–Pt(1)	111.4(6)	C(14)–N(4)–Pt(1)	111
C(11)–N(5)–Pt(1)	110.0(5)	C(15)–N(5)–Pt(1)	109
N(1)–O(1)–Pt(2)	108.8(4)	N(1)–O(1)–Pt(2)	108
C(1)–O(2)–Pt(2)	108.8(5)	C(1)–O(2)–Pt(2)	109
N(1)–Pt(1)–C(3)	79.4(3)	N(1)–Pt(1)–C(3)	80
N(1)–Pt(1)–N(4)	178.1(3)	N(1)–Pt(1)–N(4)	177
C(3)–Pt(1)–N(4)	99.2(3)	C(3)–Pt(1)–N(4)	98
N(1)–Pt(1)–N(5)	100.5(3)	N(1)–Pt(1)–N(5)	102
C(3)–Pt(1)–N(5)	173.2(3)	C(3)–Pt(1)–N(5)	177
N(4)–Pt(1)–N(5)	80.8(3)	N(4)–Pt(1)–N(5)	80
O(1)–Pt(2)–O(2)	82.6(2)	O(1)–Pt(2)–O(2)	83
O(1)–Pt(2)–N(2)	178.2(3)	O(1)–Pt(2)–N(2)	178
O(2)–Pt(2)–N(2)	97.6(3)	O(2)–Pt(2)–N(2)	98
O(1)–Pt(2)–N(3)	96.7(3)	O(2)–Pt(2)–N(3)	178
O(2)–Pt(2)–N(3)	178.2(3)	N(2)–Pt(2)–N(3)	83
N(2)–Pt(2)–N(3)	83.2(3)	O(1)–Pt(2)–N(3)	96

The geometries of all the Pt centres are distorted square planar with the same trends as observed for **1**. The structural parameters of the chxn ligands are consistent with reported structures.[27] The average lengths of the Pt–O bonds corresponding to Pt(1)–O(1) and Pt(1)–O(2) are 2.016 and 2.003 Å, respectively, which are in agreement with the equivalent bonds in **1**. The average hydroxamate bond lengths are also in accord with this structure: N(1)–O(1) 1.40 Å, C(1)–N(1) 1.30 Å, C(1)–O(2) 1.32 Å. Also consistent with the previous complex is the average Pt–C bond length of 1.98 Å.

In-vitro cytotoxicity assays

In the present study the two dinuclear Pt(II) complexes were tested along with the corresponding parent mononuclear dichloro complexes to compare their relative cytotoxicity against the A2780 ovarian cancer cell lines. Two A2780 cell lines were selected for their resistance to cisplatin and AMD473. The IC_{50} values for the complexes are listed in Table 4.

The results demonstrate that the dinuclear complexes display lower cytotoxicity than the related mononuclear complexes. Despite this, **2** displays a significant degree of activity. The parent [$PtCl_2$(*R*,*R*-chxn)] complex has the highest activity across all the cell lines as shown by the low IC_{50} values. This is consistent with values determined for other cell lines tested in studies with this complex where it generally displays higher cytoxicity than cisplatin and little or no cross-resistance.[28,29] The IC_{50} values for **2** are approximately five times higher than those for the parent complex. As expected from the results of previous studies, the complex [$PtCl_2$(en)] displays higher IC_{50} values than the corresponding chxn complex and shows cross-resistance with the A2780cisR cell line.

Table 4 Inhibition of growth (IC_{50}) of A2780 human cancer cell lines determined by the MTT growth inhibition assay

	IC_{50}[a]/μM		
Compound	A2780	A2780 cisR	A2780 473R
[$PtCl_2$(en)]	4.1	12.1	6.4
[$PtCl_2$(chxn)]	0.90	0.82	0.77
1	79	80	86
2	4.8	5.1	4.1

[a] Values are mean for data from two or three independent experiments with four values for each. Standard deviations were within the range 5–40%.

As observed for the dinuclear chxn complex, **2**, the dinuclear en complex, **1**, is less active than the dichloro complex, in this case by more than an order of magnitude, with the IC_{50} values roughly 80 μM. However, unlike the corresponding parent complex, **1** appears not to be cross-resistant with cisplatin.

While no direct information about the mechanism of action of drugs can be obtained from this type of assay it would appear that the dinuclear complexes exhibit a similar mode of action to that conventionally ascribed to Pt drugs. In this instance the hydroximate ligands would act as leaving groups with the Pt–diamine moiety as the active agent. In early studies[30] investigating the drug oxaliplatin ((*R*,*R*-cyclohexane-1,2-diamineoxalato)platinum(II)), Kidani *et al.* found a range of activity when leaving groups with two oxygen donors were employed in chxn complexes, and the IC_{50} value of **2** falls into this range. However, it is unclear whether one or both of the Pt–diamine moieties contribute to the cytotoxic action. Counter to this argument is the observed lack of cross-resistance to the A2780cisR cell line for **1**. In this case the dinuclear complex is substantially less active than the parent complex, [$PtCl_2$(en)], which suggests that the complex is very stable or that cellular uptake is poor—nevertheless it is probable that the ultimate cytotoxic mechanism is unchanged.

Conventional structure–activity rules for Pt-drugs dictate that only neutral species are active,[31,32] in order for the drug to by taken up efficiently by cells, yet recently new drugs such as the multinuclear BBR-3464 have demonstrated that charged species can exhibit high anticancer activity. This is partly due to other factors such as the lipophilicity of the drug which would increase passive diffusion across the cell membrane. In the case of the present complexes the charge may account for some of the reduced activity relative to the parent complexes. In particular **1** should be less lipophilic than **2** and so would be less likely to be taken up by the cells.

Conclusions

A number of interesting points emerge from this first study of the properties of Pt(II)–hydroxamate complexes as potential anticancer agents. From a synthetic viewpoint we have obtained a novel type of dinuclear Pt complex with a (C,N) coordination mode that was unexpected given the reaction conditions employed. Additionally, the formation of these complexes is consistent with the findings of our previous studies where it appears that only the subset of aryl hydroxamates will readily

bind to Pt(II). Furthermore, hydroxamates preferentially bind in the hydroximate form that evidently is stabilised in these complexes by the binding of the second Pt centre bridged through the benzohydroximato ligand. These may be limiting factors in creating a Pt complex of an MMP inhibitor since these inhibitors are generally peptide based hydroxamates.

Nevertheless, the complex $[\{Pt(R,R\text{-chxn})\}_2(\mu\text{-bha})]NO_3\cdot 2H_2O$ displays a promising activity profile against the panel of A2780 ovarian cancer cell-lines. The complex has a lower activity than the precursor complex $[PtCl_2(chxn)]$ but could prove amenable to therapeutic application. The related Pt(IV) complex tetraplatin (tetrachloro(*R*,*R*-cyclohexane-1,2-diamine)platinum(IV)) whilst highly active was also highly neurotoxic resulting in its abandonment from further development[33]—the lesser activity of **2** might reduce this toxicity related problem. Furthermore the higher solubility of this complex is a distinct advantage. The mechanism of action of the dinuclear complexes is unclear from this study—it seems likely that the Pt(amine) moieties effect the activity but the presence of the hydroxamate bridge possibly modifies the rate of aquation and DNA binding of these species. Further investigation to elucidate this could lead to use of other amine carrier ligands and hence tailoring of the properties of the complex.

References

1 R. B. Weiss and M. C. Christian, *Drugs*, 1993, **46**, 360.
2 L. R. Kelland, S. Y. Sharp, C. F. O'Neill, F. I. Raynaud, P. J. Beale and I. R. Judson, *J. Inorg. Biochem.*, 1999, **77**, 111.
3 W. Beck, B. Purucker, M. Girnth, H. Schoenenberger, H. Seidenberger and G. Ruckdeschel, *Z. Naturforsch., Teil B*, 1976, **31**, 832.
4 E. Bersanetti, A. Pasini, G. Pezzoni, G. Pratesi, G. Savi, R. Supino and F. Zunino, *Inorg. Chim. Acta*, 1984, **93**, 167.
5 Y.-P. Ho, K. K. W. To, S. C. F. Au-Yeung, X. Wang, G. Lin and X. Han, *J. Med. Chem.*, 2001, **44**, 2065.
6 M. Whittaker, C. D. Floyd, P. Brown and A. J. H. Gearing, *Chem. Rev.*, 1999, **99**, 2735.
7 M. Hidalgo and S. G. Eckhardt, *J. Natl. Cancer Inst.*, 2001, **93**, 178.
8 A. J. Stemmler, J. W. Kampf, M. L. Kirk and V. L. Pecoraro, *J. Am. Chem. Soc.*, 1995, **117**, 6368.
9 S. Ciurli, S. Benini, W. R. Rypniewski, K. S. Wilson, S. Miletti and S. Mangani, *Coord. Chem. Rev.*, 1999, **190–192**, 331.
10 J. R. Telford and K. N. Raymond, in *Comprehensive Supramolecular Chemistry*, Elsevier Science, Oxford, 1996, vol. 1, pp. 245–266.
11 K. N. Raymond, G. Muller and B. F. Matzanke, *Top. Curr. Chem.*, 1984, **123**, 49.
12 M. D. Hall, T. W. Failes, D. E. Hibbs and T. W. Hambley, *Inorg. Chem.*, 2002, **41**, 1223.
13 P. L. Bellon, S. Cenini, F. Demartin, M. Manassero, M. Pizzotti and F. Porta, *J. Chem. Soc., Dalton Trans.*, 1980, 2060.
14 R. H. Blessing, *Acta Crystallogr., Sect. A*, 1995, **51**, 33.
15 G. M. Sheldrick, SADABS, Empirical absorption correction program for area detector data, University of Gottingen, 1996.
16 Bruker Analytical X-ray Instruments Inc, SMART, SAINT and XPREP, Area detector control and data integration and reduction software, Madison, WI, 1995.
17 L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837.
18 G. M. Sheldrick, SHELXS86, Program for crystal structure solution, University of Göttingen, Germany, 1986.
19 G. M. Sheldrick, SHELX97, Programs for crystal structure analysis (Release 97–2), University of Göttingen, Germany, 1998.
20 C. K. Johnson, ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.
21 B. C. Behrens, T. C. Hamilton, H. Masuda, K. R. Grotzinger, J. Whang-Peng, K. G. Louie, T. Knutsen, W. M. McKoy, R. C. Young and R. F. Ozols, *Cancer Res.*, 1987, **47**, 414.
22 J. Holford, P. J. Beale, F. E. Boxall, S. Y. Sharp and L. R. Kelland, *Eur. J. Cancer*, 2000, **36**, 1984.
23 J. Carmichael, W. G. DeGraff, A. F. Gazdar, J. D. Minna and J. B. Mitchell, *Cancer Res.*, 1987, **47**, 936.
24 A. A. Grunberg, *Helv. Chim. Acta*, 1931, **14**, 455.
25 J. Podlaha, I. Cisarova, L. Soukupova and J. Schraml, *Collect. Czech. Chem. Commun.*, 2000, **65**, 1273.
26 D. P. Arnold and M. A. Bennett, *Inorg. Chem.*, 1984, **23**, 2117.
27 B. Spingler, D. A. Whittington and S. J. Lippard, *Inorg. Chem.*, 2001, **40**, 5596.
28 Y. Kidani, K. Inagaki and S. Tsukagoshi, *Am. J. Pathol.*, 1976, **67**, 921.
29 T. Yamashita, J. Hirose, M. Noji, R. Saito, H. Tomida and Y. Kidani, *Biol. Pharm. Bull.*, 1993, **16**, 1014.
30 Y. Kidani and K. Inagaki, *J. Med. Chem.*, 1978, **21**, 1315.
31 T. W. Hambley, *Coord. Chem. Rev.*, 1997, **166**, 181.
32 M. J. Cleare and J. D. Hoeschele, *Bioinorg. Chem.*, 1973, **2**, 187.
33 M. C. Christian, *Abstracts, 7th International Symposium on Platinum and other Metal Coordination Compounds in Cancer Chemotherapy*, Amsterdam, 1995, S128.