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Synthesis, Characterization and Cytotoxicity of New Platinum(IV) Axial Carboxylate Complexes: Crystal Structure of Potential Antitumor Agent [Pt^{IV}(*trans*-1*R*,2*R*-Diaminocyclohexane)*trans*(acetate)$_2Cl_2$]

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Abstract—A series of new platinum(IV) complexes of the type [Pt^{IV}(DACH)*trans*(L)$_2Cl_2$] (where DACH = *trans*-1*R*,2*R*-diaminocyclohexane, and L = acetate, propionate, butyrate, valerate, hexanoate, or heptanoate) bearing the carboxylate groups in the axial positions have been synthesized and characterized by elemental analysis, IR, and ^{195}Pt NMR spectroscopy. The crystal structure of the analogue [Pt^{IV}(DACH)*trans*(acetate)$_2Cl_2$] was determined by single crystal X-ray diffraction method. There were two crystallographically independent molecules, both of which lie on crystallographic two-fold axes. The bond lengths and bond angles of both the molecules were the same within the experimental error. The compound crystallizes in the monoclinic space group C2, with $a = 11.180(2)$ Å, $b = 14.736(3)$ Å, $c = 10.644(2)$ Å, $\beta = 112.38(3)°$, $Z = 4$ and $R = 0.0336$, based upon a total of 1648 collected reflections. In this complex, the platinum had a slightly distorted octahedron geometry owing to the presence of a geometrically strained five-member ring. The two adjacent corners of the platinum plane were occupied by the two amino nitrogens of DACH, whereas the other two equatorial positions were occupied by two chloride ions. The remaining two axial positions were occupied by the oxygens of acetate ligands. The DACH ring was in a chair configuration. An intricate network of intermolecular hydrogen bonds held the crystal lattice together. These analogues were evaluated in vitro and demonstrated cytotoxic activity against the human ovarian 2008 tumor cell line ($IC_{50} = 0.001$–0.06 μM). Structure–activity study revealed that activity was highest for the analogue where L = butyrate.

Introduction

Cisplatin is one of the most active antitumor agents in clinical use today especially because of its activity against testicular, ovarian, head and neck, cervical and bladder cancers.[1–4] However, its spectrum of antitumor activity is narrow, and its clinical use is limited by severe dose toxicities such as nephrotoxicity, ototoxicity, neurotoxicity, nausea, vomiting, and myelosuppression.[5,6] Therefore, researchers in many laboratories around the world have been actively engaged in synthesizing and studying cisplatin and its analogues, hoping to discover a better antitumor drug, that is less toxic, has better antitumor activity, and is fairly soluble in water. In this light, efforts were directed at developing new platinum drugs with higher or equal antitumor activity but less toxicity by modifying the chemical structure and altering the pharmacokinetics of cisplatin. The result was carboplatin, which is in clinical use today.[7,8] On the other hand, it was found that platinum complexes of 1,2-diaminocyclohexane (1,2-DACH)[9–13] retain activity against cisplatin-resistant tumors.[14–16] As a result, a number of drugs containing different isomers of 1,2-DACH, including oxaliplatin [Pt^{II}(*trans-l*-1,2-DACH)(oxalate)][17] and LNDDP (liposome entrapped [Pt^{II}(*trans*-1*R*,2*R*-DACH)(neodecanoate)$_2$][18] are currently under study in clinical trails.

Conversion of platinum(II) complexes to platinum(IV) analogues is another approach to moderate the toxicity of platinum(II) complexes.[19,20] In fact, much has been

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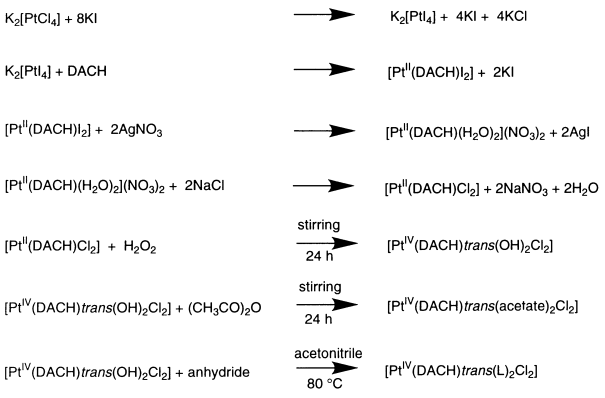
done to develop more stable Pt(IV) analogues[21] that would facilitate clinical evaluation and also from the view point of modulating favorable interactions with target DNA,[22] increase the spectrum of antitumor activity. These Pt(IV) complexes, such as tetraplatin [Pt^{IV}(*trans-d,l*-1,2-DACH)Cl_4][23] and JM216 [Pt^{IV}(NH_3)(cyclohexylamine)*trans*(acetate)$_2Cl_2$][24] have entered in clinical trials. The complex JM216 is particularly interesting in that it has axial acetate ligands, which increases its lipophilicity and allows it to be administered orally.

In our continuing efforts to develop new platinum-based antitumor agents, we have reported the synthesis, characterization, and antitumor activity of Pt(II) and Pt(IV) complexes with various isomers of 1,2-DACH.[25–29] In this paper, we now report the synthesis, characterization, and cytoxicity of a series of new axial carboxylate complexes along with the crystal structure of the analogue, [Pt^{IV}(DACH)*trans*(acetate)$_2Cl_2$] (where DACH = *trans*-1*R*,2*R*-diaminocyclohexane).

Results and Discussion

Synthesis of platinum complexes

The synthesis of Pt(IV) complexes is shown in Scheme 1. [Pt^{II}(DACH)Cl_2] was prepared according to Dhara's method.[30] This method was adopted because it is rapid and gives a much higher yield than when K_2PtCl_4 is treated directly with DACH. Reaction of K_2PtCl_4 with an excess of KI produced K_2PtI_4 in solution. K_2PtI_4 was then reacted with one equivalent of DACH to precipitate [Pt^{II}(DACH)I_2]. The reaction of [Pt^{II}(DACH)I_2] with $AgNO_3$ led to the formation of [Pt^{II}(DACH)(H_2O)](NO_3)$_2$, which was converted to [Pt^{II}(DACH)Cl_2] with the treatment of excess of NaCl. [Pt^{II}(DACH)Cl_2] was then oxidized with 30% H_2O_2 to form [Pt^{IV}(DACH)*trans*(OH)$_2Cl_2$]. The [Pt^{IV}(DACH)*trans*(OH)$_2$$Cl_2$] was reacted directly with acetic anhydride to get complex 1. Complexes **2**–**6** were prepared by refluxing *trans*-hydroxy complex with corresponding carboxylic acid anhydrides in acetonitrile at 80 °C. This method was proved to be the best, especially for the carboxylation of DACH-Pt^{IV}*trans*-hydroxy complexes with longer chain anhydrides, and would be cost-effective if the anhydrides are expensive.[31]



Scheme 1. L = Propionate, butyrate, valerate, hexanoate, or heptanoate.

All platinum(IV) complexes were chromatographically pure, and the theoretical and actual composition of each complex as determined by elemental analysis showed good agreement (Table 1).

The complexes were characterized by IR, ^{13}C NMR and ^{195}Pt NMR spectroscopy (Table 2). The formation of axial-carboxylate complexes from their axial-hydroxy analogues can be seen by prominent changes in IR spectra.[32] The IR spectra of *trans*-dihydroxy-platinum(IV) complexes showed characteristic PtO–H stretches in the range 3490–3540 cm^{-1} and Pt–O stretches in the range between 550 and 570 cm^{-1}. After carboxylation, PtO–H stretches disappeared and a strong C=O stretch of the carboxylate appeared in the range 1635–1670 cm^{-1}. The presence of a signal in the range 184–186 ppm in the ^{13}C NMR spectra of the complexes also confirmed the carboxylation. In ^{195}Pt NMR spectra, the singlet observed in the range 1022–1036 ppm was assignable to the $PtN_2O_2Cl_2$ system and was close to the related platinum(IV) complexes having two nitrogen, two oxygen, and two chloride atoms as donor ligand[33–35] (Fig. 1).

Crystal structure

The crystal structure and atomic numbering scheme of the two crystallographically independent [Pt^{IV}(DACH)-*trans*(acetate)$_2Cl_2$] molecules is shown in Figure 2.

Table 1. Elemental analysis of [Pt^{IV}(DACH)*trans*(L)$_2Cl_2$]

		Found (calculated)			
Complex no.	L	%C	%H	%N	Yield (%)
1	Acetate	24.17 (24.08)	4.19 (4.01)	5.49 (5.62)	70
2	Propionate	27.58 (27.36)	4.66 (4.56)	5.23 (5.32)	72
3	Butyrate	30.39 (30.31)	5.14 (5.05)	5.01 (5.05)	69
4	Valerate	32.78 (32.98)	5.53 (5.50)	4.72 (4.80)	65
5	Hexanoate	35.19 (35.40)	5.75 (5.90)	4.57 (4.59)	75
6	Heptanoate	37.49 (37.60)	6.23 (6.27)	4.51 (4.39)	70

Table 2. Spectroscopic data for platinum(IV) complexes

	IR, cm^{-1}				NMR, ppm	
No.	ν(N–H)	ν_a(C=O)	ν_s(C–O)	ν(Pt–Cl)	$^{13}C(>C=O)^a$	$^{195}Pt^b$
1	3215	1650	1390	330	183	1022
2	3230	1640	1375	320	184	1013
3	3225	1655	1380	320	184	1036
4	3200	1635	1350	330	184	1032
5	3200	1640	1375	345	186	1034
6	3220	1670	1400	365	185	1033

[a]Recorded in methanol-d_4.
[b]Recorded in acetone.

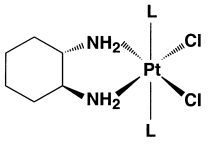


Figure 1. Structure of [Pt^{IV}(DACH)*trans*(L)$_2$Cl$_2$], where DACH = 1*R*,2*R*-diaminocyclohexane, and L = acetate, propionate, butyrate, valerate, hexanoate, or heptanoate group.

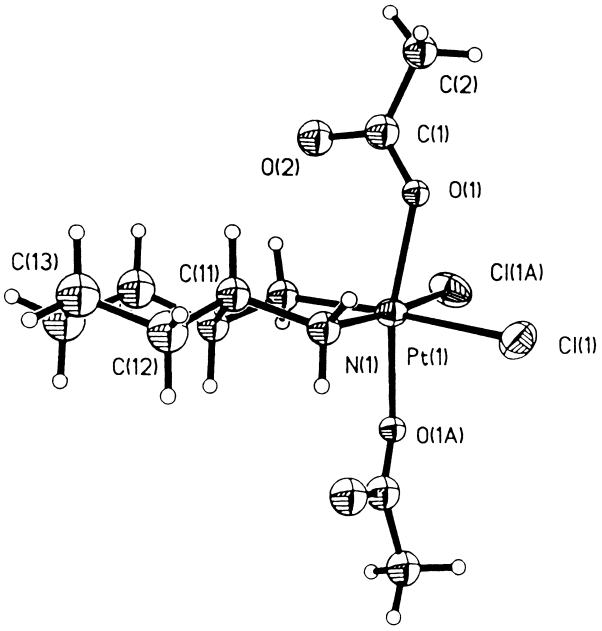


Figure 2. ORTEP representation of the structure of [Pt^{IV}(DACH)-*trans*(acetate)$_2$Cl$_2$] molecule with atom numbering scheme. The thermal ellipsoids are 50% equiprobability envelopes, with hydrogens as spheres of arbitrary diameter.

Because the two independent molecules are so similar, only one is pictured (Fig. 2). Data collection and structural refinement parameters are given in Table 3. Selected bond lengths and bond angles are summarized in Table 4. There are only minor differences in bond lengths and bond angles between the two independent molecules, both of which lie on the 2-fold axes. The bond lengths and bond angles of both the molecules were within the experimental error. As the data show, the coordination around the platinum atom in this complex has slightly distorted octahedron geometry. The distortion appears to be caused by a longer bite distance in the chelating ligand, DACH. The two adjacent corners of the platinum plane are occupied by two nitrogens of the DACH, and the remaining two equatorial positions are bound to two chloride ions. The axial positions in the complex are occupied by two oxygens of acetate ligands. The DACH ring is in a chair configuration, which is usually found in the platinum complexes of *trans*-1*R*,2*R*-DACH.[36–38] DACH forms a five-member chelate ring with the platinum atom, with the average N−Pt−N bond angle of (82.2(1.9)°,[39]) which is typical of five-member rings that have similar donor atoms such as 85(1)° in [Pt(*trans-d,l*-DACH)(9-methylguanine)$_2$Cl$_2$](NO$_3$)$_2$.11 H$_2$O,[40] 82.7(6)° in [Pt(*trans-R,R*-DACH)(N-Me-IDA)Cl]Cl,[41] 83.3° in [Pt(*trans-d,l*-DACH)(N-Me-IDA)],[36] and 82.9° in [Pt(*trans-d,l*-1,2-DACH)Cl$_4$].[42] The average C–N–Pt angle is (111.2(6)°,[39]) which is close to the values seen in 1,2-DACH platinum complexes.[42]

Table 3. Crystallographic data and structure refinement parameters for [Pt^{IV}(DACH)*trans*(acetate)$_2$Cl$_2$]

Molecular formula	$C_{10}H_{20}Cl_2N_2O_4Pt$
Formula weight	498.27
Temperature	293(2) K
Crystal system	monoclinic
Space group	C2
Cell constants	
a, Å	11.180(2)
b, Å	14.736(3)
c, Å	10.644(2)
α (°)	90.00
β (°)	112.38(3)
γ (°)	90.00
Volume Å^3	621.5(6)
Formula units per cell, *Z*	4
Density, ρ (mg m^{-3})	2.041
Absorption coefficient, μ (mm^{-1})	8.992
F(000)	952
Crystal size (mm)	0.1 0.1 0.5
θ range for data collection (°)	2.07-19.99
Index ranges	$-9\leq h\leq 10$, $-14\leq k\leq 14$, $-10\leq l\leq 10$
Reflections collected	1648
Independent reflections	1465 [R(int) = 0.0435]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1465/1/93
Goodness-of-fit on F^2	1.321
Radiation (Mo K$_\alpha$), λ (Å)	0.71073
Final *R* indices [I > 2σ(1)][a]	$R_1 = 0.0336$, $R_w = 0.0968$
R indices (all data)[a]	$R_1 = 0.0375$, $R_w = 0.1073$
Absolute structure parameter	0.07(3)
Largest difference peak and hole (e Å^{-3})	1.930 and −0.732

[a] $R_1 = \Sigma||Fo|-|Fc||/\Sigma|Fo|$. $R_w = [\Sigma w(Fo^2 - Fc^2)^2]/\Sigma[w(Fo^2)^2]^{1/2}$. $w = [\sigma^2(Fo^2) + (aP)^2 + bP]^{-1}$. $P = (Fo^2 + 2Fc^2)/3$.

The average Pt–N bond length of (2.03(3)[39] Å) seen in [Pt^{IV}(DACH)*trans*(acetate)$_2$Cl$_2$] is comparable with the average Pt–N bond distances observed in other 1,2-DACH or 1,4-DACH platinum complexes.[43–46] For example, [Pt(*trans-R,R*-DACH)(N-Me-IDA)Cl]Cl, (2.038 Å),[41] [Pt(*trans-d,l*-1,2-DACH)Cl$_4$] (2.06 Å),[42] [Pt(*trans-d,l*-DACH)(9-methylguanine)$_2$Cl$_2$](NO$_3$)$_2$.11 H$_2$O (2.04 Å)[40] and [Pt(*cis*-1,4-DACH)(*trans*-Cl$_2$)(CBDCA)].1/2 MeOH (2.03 Å).[46] The average Pt−Cl bond length of (2.323(12)[39] Å) is also consistent with those found in structurally related complexes such as [Pt(*cis*-1,4-DACH)*trans*(acetate)$_2$Cl$_2$] (2.318 Å),[31] [Pt(*trans-d,l*-DACH)(9-methylguanine)$_2$Cl$_2$](NO$_3$)$_2$.11 H$_2$O (2.31 Å),[40] [Pt(*trans-R,R*-DACH)(N-Me-IDA)Cl]Cl (2.289 Å),[41] [Pt(*trans-d,l*-1,2-DACH)Cl$_4$] (2.31 Å)[42] and [Pt(NH$_3$)(cyclohexylamine)*trans*(acetate)Cl$_2$] (2.319 Å).[47] The average axial Pt−O bond length of (2.028(14)[39] Å) is also consistent with the average axial Pt−O bond distance of 2.035(3) Å reported for [Pt(NH$_3$)(cyclohexylamine)*trans*(acetate)Cl$_2$],[47] and is slightly longer than the average axial Pt–O bond distance of 2.009(2) Å reported for [Pt(*cis*-1,4-DACH)*trans*(acetate)$_2$Cl$_2$].[31] Figure 3 shows a stereoscopic view of the molecular packing. The molecules in this crystal are held together by a system of N–H···Cl hydrogen bonds.

Table 4. Selected bond lengths (Å) and bond angles (°) for [Pt^{IV}(DACH)*trans*(acetate)$_2$Cl$_2$][a]

Molecule 1		Molecule 2	
Pt(1)- N(1)	2.01(2)	Pt(2)-N(2)	2.05(2)
Pt(1)-O(1)	2.036(11)	Pt(2)-O(3)	2.019(12)
Pt(1)-Cl(1)	2.331(9)	Pt(2)-Cl(2)	2.315(9)
N(1)-Pt(1)-N(1)#1	84.0(14)	N(2)#2-Pt(2)-N(2)	80.4(14)
N(1)-Pt(1)-O(1)#1	98.6(8)	O(3)-Pt(2)-N(2)	92.5(8)
N(1)-Pt(1)-O(1)	90.5(8)	O(3)#2-Pt(2)-N(2)	86.6(8)
N(1)#1-Pt(1)-O(1)	98.6(8)	O(3)-Pt(2)-N(2)#2	86.6(8)
O(1)#1-Pt(1)-O(1)	167.9(9)	O(3)-Pt(2)-O(3)#2	178.8(10)
N(1)-Pt(1)-Cl(1)	91.0(6)	N(2)-Pt(2)-Cl(2)	93.7(6)
N(1)#1-Pt(1)-Cl(1)	174.6(8)	N(2)#2-Pt(2)-Cl(2)	174.1(8)
O(1)#1-Pt(1)-Cl(1)	88.4(4)	O(3)-Pt(2)-Cl(2)	93.4(5)
O(1)-Pt(1)-Cl(1)	83.3(4)	O(3)#2-Pt(2)-Cl(2)	87.4(5)
N(1)-Pt(1)-Cl(1)#1	174.6(8)	N(2)-Pt(2)-Cl(2)#2	174.1(8)
O(1)-Pt(1)-Cl(1)#1	88.4(4)	O(3)-Pt(2)-Cl(2)#2	87.4(5)
Cl(1)-Pt(1)-Cl(1)#1	94.1(5)	Cl(2)#2-Pt(2)-Cl(2)	92.2(4)
C(1)-O(1)-Pt(1)	125.6(13)	C(4)-O(3)-Pt(2)	121.2(12)
C(11)-N(1)-Pt(1)	110.7(13)	C(21)-N(2)-Pt(2)	111.7(14)

[a]Symmetry transformations used to generate equivalent atoms: #1$-x+1$, y, $-z-2$; #2 $-x+1$, y, $-z-1$.

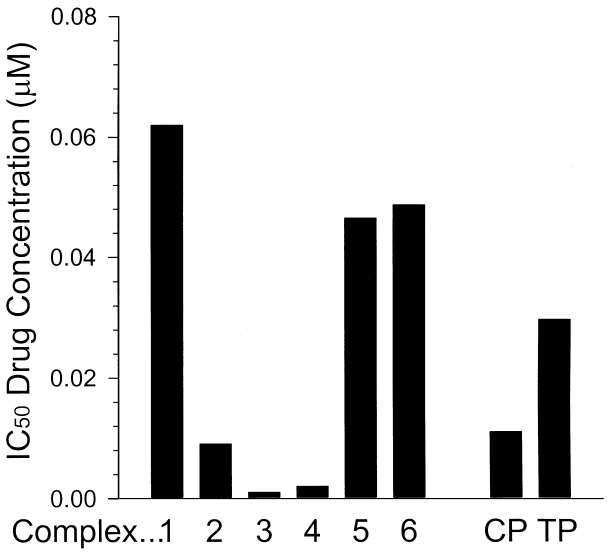


Figure 4. Cytotoxicity of platinum complexes against human ovarian 2008 tumor cell line in vitro.

Cytotoxicity

Biological activities of DACH-platinum complexes with axial carboxylato ligands were evaluated in vitro, and the data are presented in Figure 4. Reference compounds cisplatin (CP) and tetraplatin (TP) are included for comparison. Against 2008 tumor cells, cisplatin was very cytotoxic with an IC_{50} of 0.01 μM. Tetraplatin, on the other hand, was 3-fold less active with an IC_{50} of 0.03 μM. In comparison, the carboxylato analogues displayed cytotoxicity with IC_{50} in the range 0.001–0.06 μM. Examination of the structure–activity relationships (SAR) indicates that ascending the homologous series results in an initial decrease in IC_{50} and then an increase (Fig. 4).[48] The lowest IC_{50} observed was that for complex **3**, which was about 10- and 30-fold more cytotoxic than cisplatin and tetraplatin, respectively. Since, lipophilic character increases with increasing size of the carboxylate group in the axial position, the observed SAR indicates that cytotoxicity is unrelated to the lipophilicity of the molecule. However, such parabolic relationship between structure and activity in a homologous series is well known,[48] and we have previously reported a similar relationship for mixed amine platinum(II) analogues in mouse tumor models in vivo.[49]

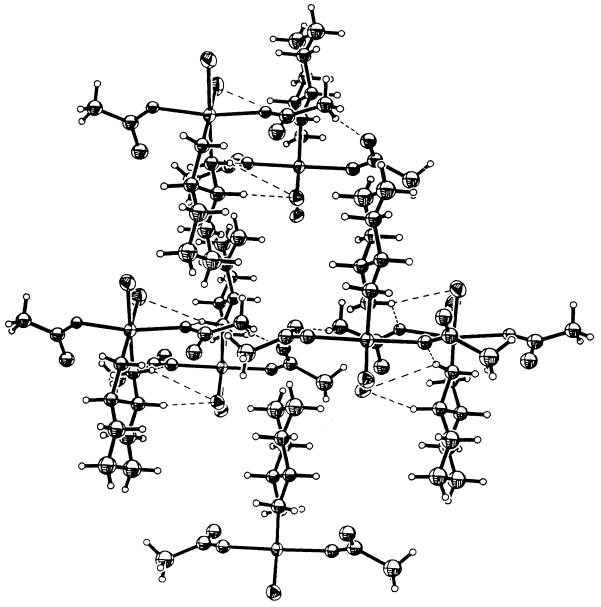


Figure 3. A stereoscopic view of the molecular packing. Hydrogen bonds are indicated by dashed lines.

Conclusion

In conclusion, a series of axial dicarboxylatoplatinum(IV) complexes were synthesized and characterized by elemental analysis and spectroscopic techniques such as IR, ^{13}C NMR and ^{195}Pt-NMR spectroscopy. The crystal structure of the complex [Pt^{IV}(DACH)*trans*(acetate)$_2$Cl$_2$] was determined by X-ray crystallography. These cisplatin analogues were effective cytotoxic agents against the human ovarian 2008 tumor cell line. Further investigations of these compounds are in progress to explore their clinical potential.

Experimental

Chemicals

K_2PtCl_4 was purchased from Johnson Matthey, Seabrook, NH. DACH was purchased from Morton Thiokol, Inc., Danver, MA. Acetic anhydride, propionic anhydride, butyric anhydride, valeric anhydride, hexanoic anhydride, and heptanoic anhydride were purchased from Aldrich Chemical Company, Milwaukee, WI. Silver nitrate and 30% H_2O_2 were obtained from Fisher Scientific Co., Pittsburgh, PA. All chemicals obtained from commercial sources were used as supplied.

Physical measurements

Elemental analysis was performed by Robertson Laboratory Inc., Madison, NJ. IR spectra were recorded in KBr pellets using a Beckman 250 MX spectrometer. ^{195}Pt NMR spectra were recorded on a Bruker 200/AF spectrometer using a 10-mm tunable probe. The spectra were recorded at 43.055 MHz, and the shifts were measured relative to an external standard of 2.2 M Na_2PtCl_6 in D_2O at 0.00 ppm. The purity of the complexes was evaluated by high-pressure liquid chromatography (HPLC) using a Water's Nova-Pack C18 column (3.9×300 mm), with methanol as the mobile phase, at a flow rate 1 mL/min. This confirmed the presence of only a single complex in the purified product.

Preparation of platinum complexes

Synthesis of [Pt^{IV}(DACH)*trans*(acetate)$_2$Cl$_2$] (1). K_2PtCl_4 (20.76 g, 50 mmol) was dissolved in 250 mL of deionized water and filtered. KI (83.0 g, 0.5 mol) in 100 mL of water was added to it and stirred for 10 min. An aqueous solution of DACH (5.7 g, 50 mmol) was added slowly, while stirring, to get a yellow precipitate, [Pt^{II}(DACH)I$_2$]. The precipitate was then filtered, washed with a small amount of dimethylformamide, water, ethanol and acetone and dried under vacuum. (Yield: 80%). [Pt^{II}(DACH)I$_2$] (11.25 g, 20 mmol) was suspended in 250 mL of an aqueous solution of silver nitrate (3.31 g, 19.6 mmol). The reaction mixture was stirred for 24 h at room temperature in the dark. The AgI precipitate was filtered off, and a solution of NaCl was added dropwise to the filtrate with constant stirring until a yellow precipitate of [Pt^{II}(DACH)Cl$_2$] formed. The precipitate was filtered, washed with water and acetone, and dried under vacuum (yield: 85%). To a suspension of [Pt^{II}(DACH)Cl$_2$] (4.14 g; 10 mmol) in 300 mL of water was added 15 mL of 30% H_2O_2. The reaction mixture was stirred for 1 h at 70 °C and continuously thereafter for 1 day at room temperature. As a result, the color of the solid was changed from yellow to light yellow. The mixture was then evaporated to dryness under reduced pressure at 35 °C. A light yellow solid of [Pt^{IV}(DACH)-*trans*(OH)$_2$Cl$_2$] was obtained, which was isolated and washed with acetone and dried under vacuum (yield: 80%). [Pt^{IV}(DACH)*trans*(OH)$_2$Cl$_2$] (2.08 g; 5 mmol) in 25 mL of acetic anhydride was stirred overnight. Then, 200 mL of methanol was added, and stirring was continued for another day at room temperature until a clear yellow solution was obtained. The solvent was removed, and the resulting yellow residue was redissolved in acetone and filtered. The filtrate was evaporated to a minimum volume and kept in a refrigerator. A pale yellow crystalline compound, [Pt^{IV}(DACH)trans(acetate)$_2$Cl$_2$], was separated out, filtered and dried under vacuum (yield: 70%).

The resulting [Pt^{IV}(DACH)*trans*(acetate)$_2$Cl$_2$] compound (200 mg) was dissolved in 250 mL of hot water, and the volume of the solution was reduced to a minimum and kept aside for slow evaporation at room temperature. Within 3–4 days yellow needles of [Pt^{IV}(DACH)*trans*(acetate)$_2$Cl$_2$] were separated from the solution, which were used for X-ray crystallography.

Synthesis of [Pt^{IV}(DACH)*trans*(propionate)$_2$Cl$_2$] (2). To a suspension of [Pt^{IV}(DACH)*trans*(OH)$_2$Cl$_2$] (2.08 g, 5 mmol) in 200 mL of acetonitrile, 8 mL of propionic anhydride (15-fold) was added. The reaction mixture was refluxed at 80 °C for 15 h. A clear yellow solution was obtained, which was then evaporated to dryness under reduced pressure. The resulting yellow residue was redissolved in acetone and filtered. The filtrate was evaporated to a minimum volume and then kept in refrigerator. The pale-yellow crystalline compound obtained was isolated by filtration and dried under vacuum (yield: 72%).

Complexes **3**–**6** were prepared in a manner similar to that described above for complex **2**, by reacting *trans*-hydroxy complex with the corresponding anhydrides.

Crystallographic measurements. The crystal was encapsulated in a thin shell of epoxy cement and mounted on the tip of a glass fiber. Data were collected with a Rigaku AFC5-S automated four-circle diffractometer using the TEXSAN 5.0 software package[50] and were collected for Lorentz/polarization effects and absorption (ψ-scans). Data collection and refinement parameters are summarized in Table 3. Scattering factors were taken from the literature.[51] The structure was solved using the direct methods routine of SHELXTL-PLUS software package (PC version).[52] Refinement of F^2 for all reflections, except those with very negative F^2 values, was performed with a personal computer loaded with SHELXL-93 software.[53] Weighted R factors (R_W) and all goodness of fit (S) values were based on F^2, while conventional R factors (R) were based on F with F set to 0 for negative F^2. The observed criterion of F^2 is used only for calculating R factors observed and was not relevant to the choice of reflections for refinement. R factors based on F^2 were statistically about twice as large as those based on F, and R factors based on all of the data were even larger. The weighing factor $w = [\sigma^2(Fo^2) + (xP)^2 + yP]^{-1}$, where $P = (Fo^2 + 2Fc^2)/3$, was refined for x and y.

There are two independent molecules both of which lie on crystallographic 2-fold axes. The molecules are essentially identical with the bond lengths and bond angles were the same within the experimental error. Only the Pt and Cl atoms were refined anisotropically. Since the space groups C2, Cm and C2/m cannot be distinguished by systematic absences, structure solutions were attempted in all three cases. Because there are two independent molecules in the asymmetric unit in C2 there was a possibility that a symmetry element was missing which related these two molecules, but no reasonable solution or refinement was obtained for either Cm or C2/m.

Cytotoxic evaluations

The human ovarian 2008 tumor cell line was obtained from Dr. Stephen B. Howell (University of California, San Diego). Platinum complexes were dissolved in water (carboxylate analogues) or saline (cisplatin and tetraplatin), passed through a 0.22 μM filters, and their

cytotoxicity determined in vitro against tumor cells, as described previously.[54] Briefly, cells were cultured in RPMI 1640 medium containing 5% fetal calf serum, and cytotoxicity determined by an MTT assay after continuous drug exposure for 5 days. The data were plotted as drug concentration against cell survival using a software program, and IC_{50} values (drug concentration giving 50% survival) determined directly from the plot.

Supporting information available

Tables S1–S4 list complete bond lengths and angles, atomic coordinates and equivalent isotropic displacement parameters, anisotropic displacement parameters, and hydrogen coordinates, and Table S5 lists observed and calculated structure factors can be obtained from the authors on request.

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