Structural Characterization on Two (Diamine)(1,1-cyclobutanedicarboxylato)platinum(II) Anticancer Drugs

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The success of *cis*-dichlorodiammineplatinum(II) (cisplatin) as an anticancer drug has prompted research on a broad spectrum of new platinum complexes which also show effective drug activity. Side effects of cisplatin chemotherapy include severe emesis and nephrotoxicity. Other properties which limit the efficacy of cisplatin as a drug include a narrow range of responsive tumors and the development of resistance in tumor cells. Research carried out over the past few years has been directed at new complexes which show decreased renal toxicity and emetic effects, greater overall clinical antitumor effectiveness, a broader spectrum of activity, and a lack of cross-resistance to cisplatin. Second-generation drug complexes containing malonate and 1,1-cyclobutanedicarboxylate ligands have been studied and found to exhibit no significant nephrotoxic effect; diammine(1,1-cyclobutanedicarboxylato)-platinum(II) (carboplatin) is one of the most clinically successful members of the series [1–3]. The decreased nephrotoxicity of these complexes over cisplatin has been related to their greater pharmacokinetic stability in solution [4, 5]. Hydrolysis of the bidentate dicarboxylate ligand to form the active diammineplatinum(II) product occurs far more slowly than hydrolysis of the dichloro complex. Drug excretion is carried out by glomerular filtration in the kidney. The nephrotoxic effect of cisplatin appears associated with the active hydrolysis product which forms over a period of minutes. The half-life of a diamminemalonatoplatinum(II) complex under comparable conditions is of the order of days and clearance occurs with most of the drug complex intact [4]. Consequently, the dicarboxylate complexes show no significant nephrotoxic effect, but must be administered at higher dosage levels to provide an effective amount of active hydrolysis product. To keep the volume of solution administered at a safe and convenient level, water solubility must be relatively high.

Third-generation drug complexes are currently under investigation which combine the malonate and cyclobutanedicarboxylate ligands with amine and diamine ligands to give a broad spectrum of activity [6]. It is also important that these complexes be well characterized and easily synthesized. In this context there has been little structural information presented on these new generation anticancer drugs. In this report we describe the features of the two complexes which have shown the greatest promise for further clinical investigation in our studies on third-generation platinum anticancer drugs, (4,4-bis(aminomethyl)tetrahydropyran)(1,1-cyclobutanedicarboxylato)platinum(II) (**1**), isolated from aqueous solution in the form of a dihydrate, and (1,3-dihydroxy-2,2-bis(aminomethyl)propane)(1,1-cyclobutanedicarboxylato)platinum(II) (**2**). Synthetic routes to these complexes and the results of toxicity and activity tests on the complexes will be published separately [7].

Experimental

Crystallographic Structure Determinations on $[C_5OH_8(CH_2NH_2)_2]Pt[C_4H_6(CO_2)_2]$ (1) and $[C(CH_2OH)_2(CH_2NH_2)_2]Pt[C_4H_6(CO_2)_2]$ (2)

Colorless crystals of both complexes were grown by slow evaporation of a methanol/water solution of the complex. Crystals were mounted on glass fibers and aligned on a Nicolet P3F automated diffractometer. Photographs indicated monoclinic symmetry for both crystals. Unit cell dimensions given in Table I for both crystals were calculated from the centered settings of 25 reflections with 2θ settings greater than 25°. Details of procedures used for both structure determinations are given in Table I.

For both structure determinations the position of the Pt atom was determined from a three-dimensional Patterson map. Phases derived from the Pt position were used to locate all other non-hydrogen atoms of the structures. Complex **1** was found to crystallize with two independent molecules per unit cell, both located upon crystallographic mirror planes, one at $x, 0, z$, the other at $x, \frac{1}{2}, z$. The coordination planes of both Pt atoms are bisected by the mirror planes, and the atoms of the cyclobutane rings lie on the planes. For both molecules, the oxygen atoms of the tetrahydropyran rings and the carbon atoms at the 2 and 6 positions of the rings were also found to lie on the crystallographic mirror planes. All four carbon atoms bonded to the quaternary carbons C14 and C24 were found to be disordered on either side of

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TABLE I. Crystal Data and Details of the Structure Determinations on $[C_5OH_8(CH_2NH_2)_2]Pt[C_4H_6(CO_2)_2]\cdot 2H_2O$ (1) and $[C(CH_2OH)_2(CH_2NH_2)_2]Pt[C_4H_6(CO_2)_2]$ (2)

	1	2
Crystal Data		
Formula	$PtO_7N_2C_{13}H_{26}$	$PtO_6N_2C_{11}H_{20}$
Molecular weight	517.42	471.38
Space group[a]	$P2/m$	$P2_1/n$
Crystal system	monoclinic	monoclinic
a (Å)[b]	15.102(2)	10.167(1)
b (Å)	8.432(2)	12.451(3)
c (Å)	13.124(2)	10.960(2)
β (°)	100.00(2)	102.71(2)
V (Å^3)	1645.8(5)	1353.3(8)
Z	4	4
D_{calc} (g cm^{-3})	2.096	2.313
D_{exp} (g cm^{-3})	2.10(2)	2.32(2)
$F(000)$	1008	904
μ (cm^{-1})	91.7	202.8
Crystal dimensions (mm)	0.43 × 0.37 × 0.11	0.40 × 0.24 × 0.18
Data collection and reduction		
Diffractometer	Syntex P3F	
Data collected	$+h, +k, \pm l$	
Radiation (Å)	Mo Kα (0.71069)	
Monochromator angle (°)	12.2	
Temperature (K)	294–296	
Scan technique	θ–2θ	
Scan range (2θ), min–max (%)	3.0–50.0	
Scan speed	4.0 to 30.0 deg/min	
Scan range	0.7° below $K\alpha_1$ and 0.7° above $K\alpha_2$	
Background	stationary crystal–stationary counter background time = 0.5 (scan time)	
Number of unique reflections measured	3196	2386
Number of observed reflections	2575	1994
Criterion	$F > 6\sigma(F)$	$F > 6\sigma(F)$
Absorption correction	empirical	empirical
Transmission coefficients (max–min)	0.93–0.33	0.98–0.63
Structure determination and refinement		
Scattering factors		neutral atoms[c]
R_1 and R_2[d]	0.036, 0.053	0.028, 0.041
Weight		$1/(\sigma(F)^2 + 0.0014F^2)$
Number of parameters	303	181
Ratio of observations to parameters	8.50	11.0
Maximum shift/error (non-hydrogen)	0.046	0.024

[a]Ref. 8a. [b]Cell dimensions were determined by least-squares fit of the setting angles of 25 reflections with 2θ in the range 20–30°. [c]Ref. 8b. [d]The quantity minimized in the least-squares procedures is: $\Sigma w(|F_o| - |F_c|)^2$; $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_2 = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(F_o)^2]^{1/2}$.

the mirror planes and were refined in disordered positions with half occupancies. At the conclusion of refinement with isotropic thermal parameters, peaks were noted on the difference Fourier map between adjacent complex molecules in locations which may well be occupied by water molecules hydrogen bonded to the carboxylate oxygen atoms of the cyclobutane dicarboxylate ligands. These water oxygen atoms were also located upon mirror planes and close to inversion centers so as to form a bridge between adjacent complex molecules consisting of four hydrogen-bonded water molecules. The presence of water molecules of hydration was confirmed by elemental analysis. Final cycles of refinement converged with $R = 0.036$ and $R_w = 0.053$. Maximum residual electron density was found to be 0.78 e$^-$/Å^3

in the vicinity of water molecule oxygen O23. Final positional and isotropic thermal parameters for the structure are given in Table II.

The atoms of complex **2** were found to occupy general positions in the unit cell. Refinement proceeded normally, converging with $R = 0.028$ and $R_w = 0.041$, and maximum residual electron density of 0.46 $e^-/Å^3$ near the Pt atom. Final positional and isotropic thermal parameters for the structure are given in Table III. Tables containing anisotropic thermal parameters and structure factors for both structure determinations are available as Supplementary Material.

TABLE II. Atomic Coordinates ($\times 10^4$) and Isotropic Thermal Parameters ($Å^2$, $\times 10^3$) for $[C_5OH_8(CH_2NH_2)_2]$-$Pt[C_4H_6(CO_2)_2]\cdot 2H_2O$

	x	*y*	*z*	U_{eq}[a]
Pt1	1572(1)	5000	47(1)	34(1)
O1	1730(4)	6695(8)	−975(4)	63(2)
N1	1400(4)	6754(10)	1043(6)	63(3)
O11	2373(5)	7507(11)	−2243(5)	101(4)
C11	2310(6)	6493(14)	−1600(6)	72(4)
C12	2864(8)	5000	−1491(8)	66(5)
C13	684(9)	3830(17)	1784(10)	36(3)[b,c]
C33	631(11)	6814(22)	1543(12)	46(4)[b,c]
C14	790(8)	5000	2298(9)	131(12)
C15	3670(10)	5000	−2090(9)	100(8)
C16	4283(11)	5000	−1189(12)	120(10)
C17	3590(7)	5000	−468(8)	51(4)
C18	1707(9)	4317(19)	3072(10)	48(5)[c]
C19	28(9)	5595(22)	2960(10)	54(7)[c]
O18	1036(9)	5000	4499(9)	67(5)
C10	1755(6)	5000	3955(6)	85(5)
C20	211(7)	5000	3870(7)	109(6)
O12	997(14)	0	−1883(14)	74(5)[b]
O13	595(27)	0	341(29)	187(15)[b]
Pt2	4545(1)	0	6655(1)	32(1)
O2	5462(4)	1717(7)	7027(4)	57(2)
N2	3649(5)	1726(8)	6210(5)	54(2)
O21	6768(5)	2523(11)	7823(6)	106(4)
C21	6180(6)	1504(14)	7713(6)	73(4)
C22	6268(8)	0	8366(9)	75(6)
C23	3073(9)	1209(16)	5050(9)	34(3)[b,c]
C43	3237(11)	−1885(19)	5166(11)	46(4)[b,c]
C24	2609(8)	0	4951(8)	116(10)
C25	7067(11)	0	9288(10)	142(12)
C26	6412(12)	0	10008(10)	84(7)
C27	5598(9)	0	9146(8)	65(5)
C28	2136(11)	−582(18)	3772(10)	52(6)[c]
C29	1828(10)	531(19)	5618(12)	51(6)[c]
O28	727(9)	0	4157(9)	70(6)
C30	1384(6)	0	3502(7)	85(4)
C20	1094(7)	0	5167(8)	142(8)
O22	5918(8)	5000	6476(8)	82(3)[b]
O23	4135(7)	5000	5656(7)	79(3)[b]

[a]U_{eq} defined as one-third of the trace of the orthogonalized U_{ij} tensor. [b]Atoms refined with isotropic thermal parameters. [c]Atoms refined with half-occupancy factors due to disorder.

TABLE III. Atomic Coordinates ($\times 10^4$) and Isotropic Thermal Parameters ($Å^2$, $\times 10^3$) for $[C(CH_2OH)_2(CH_2$-$NH_2)_2]Pt[C_4H_6(CO_2)_2]$

	x	*y*	*z*	U_{eq}[a]
Pt	2271(1)	669(1)	69(1)	15(1)
O1	3605(5)	612(3)	−1066(4)	28(2)
O2	778(5)	989(4)	−1435(4)	29(1)
O3	4256(5)	1303(4)	−2687(4)	37(2)
O4	242(5)	1648(4)	−3353(4)	35(2)
O5	2147(6)	−676(4)	3132(5)	39(2)
O6	4354(5)	2058(4)	4994(4)	42(2)
N1	3742(5)	262(5)	1571(5)	27(2)
N2	944(6)	879(4)	1184(5)	25(2)
C1	3500(7)	1318(5)	−1944(6)	25(2)
C2	2385(6)	2153(5)	−2066(6)	22(2)
C3	1045(6)	1557(5)	−2333(5)	23(2)
C4	2610(7)	2939(5)	−886(6)	30(2)
C5	2882(9)	3878(6)	−1745(7)	40(3)
C6	2510(7)	3137(5)	−2914(6)	30(2)
C7	3970(7)	1064(6)	2606(6)	28(2)
C8	2745(7)	1230(5)	3201(6)	26(2)
C9	1475(7)	1623(5)	2258(6)	29(2)
C10	2468(8)	243(6)	3940(6)	35(2)
C11	3074(8)	2190(6)	4136(7)	36(2)

[a]U_{eq} defined as one-third of the trace of the orthogonalized U_{ij} tensor.

Discussion

Structural features of both **1** and **2** show a very regular square-planar geometry for the metal, with Pt–O and Pt–N lengths in the 2.03 Å range. Figures 1 and 2 contain views of the complex molecules; selected bond distances and angles are given in Table IV. The dihedral angles between Pt, N1, N2 and Pt, O1, O2 planes are 6.2° and 8.3°, respectively, for **1** and **2**. The bite angles of both the diamine and dicarboxylate ligands are close to 90° in both structures, giving a very regular square-planar coordination geometry.

The absence of strain in the malonate–platinum chelate ring must contribute to the kinetic stability of the six-membered dicarboxylate chelate ring. The cyclic ether and hydroxyl functionalities of the diamine ligands were included to enhance water solubility. For example, the analog of **1** with a cyclohexyl ring in place of the diamine tetrahydropyran has a solubility of only 1.0 mg/ml in water, while the solubility of **1** exceeds 100 mg/ml. For comparison, the solubility of cisplatin is 1.0 mg/ml and that of carboplatin is 10 mg/ml. The solubility of **2** is lower, 7.0 mg/ml, but its drug potency is unusually high. The unusually high solubility of **1** appears partially related to water solvate molecules which cocrystallize with the complex. Dehydration of **1** by heating solid samples *in vacuo* leads to lower solubility of approxi-

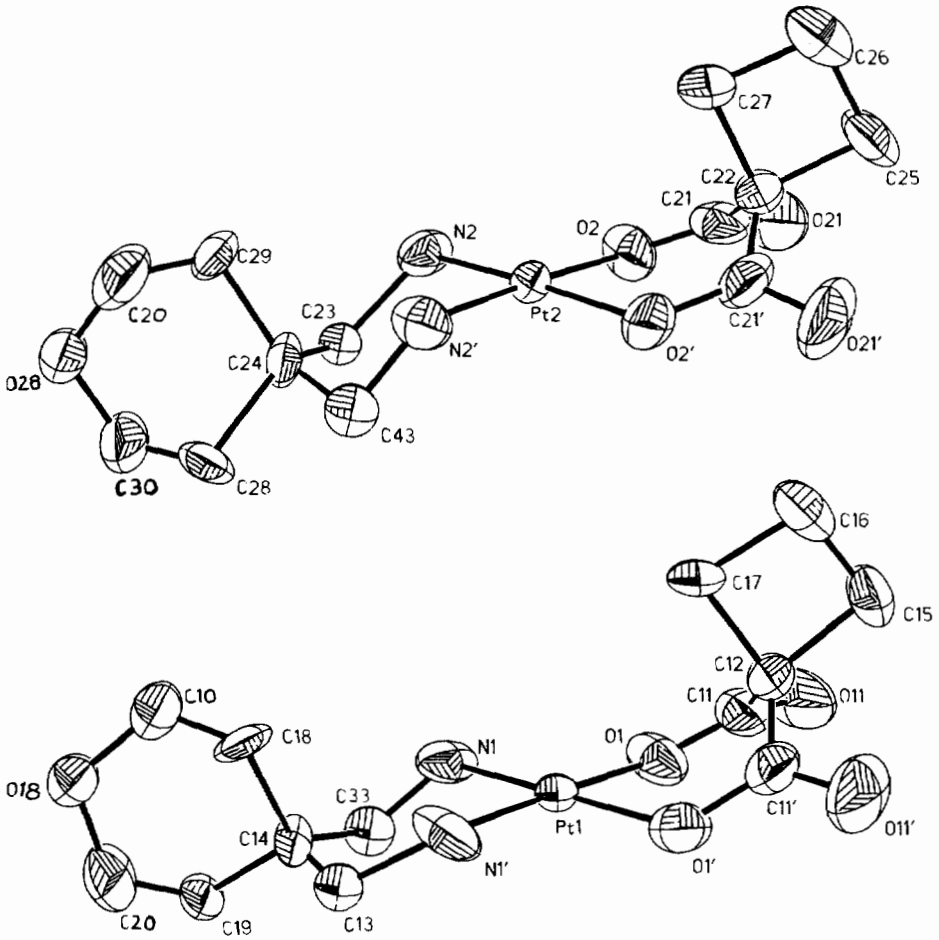

Fig. 1. ORTEP view showing the two independent molecules of $[C_5OH_8(CH_2NH_2)_2]Pt[C_4H_6(CO_2)_2]$ (1).

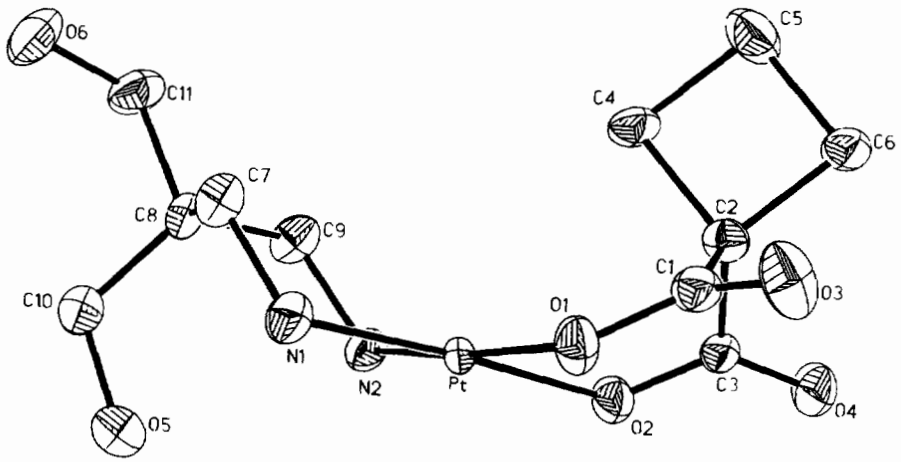

Fig. 2. ORTEP view showing the $[C(CH_2OH)_2(CH_2NH_2)_2]Pt[C_4H_6(CO_2)_2]$ (2) molecule.

mately 40 mg/ml. In the crystal structure of **1**, four water molecules located on a crystallographic mirror plane bridge adjacent complex molecules by hydrogen bonding with carboxylate oxygen atoms and with one another. Establishing the presence of solvate molecules contributes to defining the formulation of the complex. This has proven to be a complication with development of new, water-soluble platinum drugs.

TABLE IV. Selected Bond Distances and Angles for $[C_5OH_8(CH_2NH_2)_2]Pt[C_4H_6(CO_2)_2]\cdot 2H_2O$ (1) and $[C(CH_2OH)_2(CH_2NH_2)_2]Pt[C_4H_6(CO_2)_2]$ (2)

1		2	
$[C_5OH_8(CH_2NH_2)_2]Pt[C_4H_6(CO_2)_2]\cdot 2H_2O$			
Distances (Å)			
Pt1–O1	2.003(6)	Pt2–O2	2.005(6)
Pt1–N1	2.021(8)	Pt2–N2	2.005(7)
O1–C11	1.31(1)	O2–C21	1.30(1)
O11–C11	1.22(1)	O21–C21	1.23(1)
C11–C12	1.50(1)	C21–C22	1.52(1)
N1–C33	1.43(2)	N2–C23	1.41(2)
Angles (deg)			
O1–Pt1–O1	91.1(4)	O2–Pt2–O2′	92.4(3)
O1–Pt1–N1	87.4(3)	O2–Pt2–N2	87.1(3)
N1–Pt1–N1′	94.1(5)	N2–Pt2–N2′	93.1(4)
$[C(CH_2OH)_2(CH_2NH_2)_2]Pt[C_4H_6(CO_2)_2]$			
Distances (Å)			
Pt–O1	2.034(5)	O3–C1	1.236(9)
Pt–O2	2.020(4)	O4–C3	1.236(7)
Pt–N1	2.030(5)	C1–C2	1.522(9)
Pt–N2	2.026(6)	C2–C3	1.522(9)
O1–C1	1.291(8)	N1–C7	1.490(9)
O2–C3	1.288(8)	N2–C9	1.502(8)
Angles (deg)			
O1–Pt–O2	89.4(2)	Ni–Pt–N2	90.7(2)
O1–Pt–N2	174.6(2)	O1–Pt–N1	90.9(2)
O2–Pt–N1	176.9(2)	O2–Pt–N2	89.2(2)

Supplementary Material

Tables containing anisotropic thermal parameters for **1** and **2** (2 pages) and listings of observed and calculated structure factors for both structures (34 pages) are available from the authors on request.

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