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Unusual Dimeric Chemical Structure for a Carboplatin Analogue as a Potential Anticancer Complex

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An unexpected and unusual dimeric platinum(II) tetracarboxylate complex was obtained by the reaction of *cis*-$[Pt(NH_3)_2I_2]$ with disilver dicarboxylate. The complex exhibits greater in vitro anticancer activity and lower toxicity in mice than its parent compound, carboplatin, and is therefore worthy of further evaluation as a potential antitumor dinuclear platinum agent.

Platinum-based compounds are widely used in antitumor therapy of solid tumors and represent the cornerstone for the treatment of testicular and ovarian tumors and lung and colorectal carcinomas. In particular cisplatin, its analogue carboplatin (Figure 1), and the diaminocyclohexane-containing complex oxaliplatin are fundamental components of standard chemotherapy.[1,2] Despite the therapeutic benefit of platinum-based treatment regiments, the efficacy of platinum drugs is still limited by side effects and intrinsic and acquired resistances.[3] Therefore, the search for new potent platinum drugs is continuing, and some pioneering strategies have emerged. These strategies have been represented by the synthesis of nonclassical platinum compounds.[4,5] However, the direct modification of the clinically established platinum drugs is an effective way.[6−8] On the one hand, there is still the possibility of finding new complexes, exhibiting an improved pharmacological profile. On the other hand, the investigation of every new analogue will contribute to a deeper understanding of the mechanism of action of platinum tumor-inhibiting complexes, finally also leading to a more reliable structure−activity relationship.

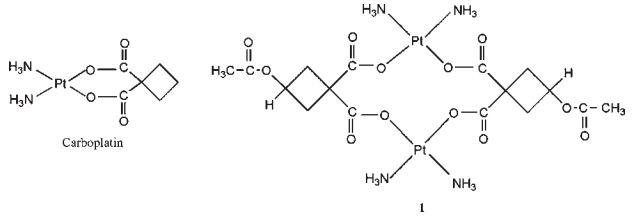

Figure 1. Structures of carboplatin and the dinuclear complex **1**.

As part of an ongoing program in our laboratory aimed at improving the pharmacological profile of carboplatin, the cyclobutane ring was substituted with $OCOCH_3$ at position 3 to increase the water solubility of carboplatin. A carboplatin derivative with OH at position 3 of the cyclobutane ring was reported to have a mononuclear structure similar to that of carboplatin and showed comparable antitumor activity.[9] Surprisingly, we obtained an unexpected and unusual dimeric complex, *cis*-tetrammine-μ-bis(3-acetoxyl-1,1-cyclobutanedicarboxylato)-O^1,O^2)diplatinum(II) (**1**; Figure 1), after the acetoxyl group was used to replace the H atom of carboplatin at position 3. In order to further test whether other platinum complexes of 3-acetoxyl-1,1-cyclobutanedicarboxylate have similar dimeric structures, a series of *cis*-$[PtA_2$(3-acetoxyl-1,1-cyclobutanedicarboxylato)] species, where A_2 = 1*R*,2*R*-diaminocyclohexane (the carrier group of oxaliplatin), (4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane (the carrier group of eptaplatin), and *trans*-1,2-cyclobutanebis(methylamine) (the carrier group of labaplatin), were prepared and characterized. They all had regular mononuclear structures. To the best of our knowledge, **1** is the first structurally characterized dimeric platinum(II) tetracarboxylate complex. No other platinum complexes with the general formula *cis*-$[PtA_2X_2]$ (A_2 = $2NH_3$/diamine, X_2 = dicarboxylates) reported to date display such a dimeric structural feature. More interestingly, **1** exhibits greater in vitro antitumor activity and less toxicity in mice than its parent compound carboplatin and is

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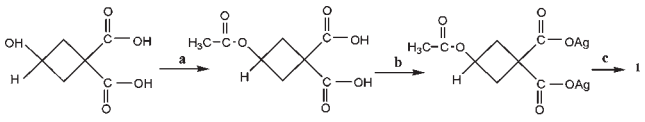
Scheme 1. Synthesis of **1**[a]



[a] (a) CH_3COCl, 40−50 °C, 4 h; (b) $NaHCO_3$, $AgNO_3$, 20−25 °C; (c) *cis*-$[Pt(NH_3)_2I_2]$, 50 °C, 16 h .

therefore worthy of further evaluation as a potential dinuclear platinum antitumor agent because multinuclear platinum complexes are characterized by a peculiar DNA binding mode and higher antitumor potency than the mononuclear complexes.[10]

Complex **1** was obtained by following Scheme 1. **4** was prepared according to the reported method.[9] Acetylation of **4** with CH_3COCl gave rise to **3**. The reaction of *cis*-$[Pt(NH_3)_2I_2]$ with **3** (an insoluble disilver salt of **2**) yielded **1** (yield 50%), followed by recrystallization from water to obtain a sample for structural characterization and biological tests. The purity was determined by revered-phase high-performance liquid chromatography to be >98.0% (see the Supporting Information). The structural characterization was performed by elemental analysis, Fourier transform infrared (FT-IR), ^1H and ^{13}C NMR, and positive-ion fast atom bombardment mass spectrometry (FAB^+-MS) spectroscopic data along with X-ray crystallography.[11,12] The data are in good agreement with the structure of **1**. The $\nu_a-\nu_s$ value in the IR spectra is larger than 200 cm^{-1}, suggesting that COO^- acts as a monodentate ligand, and its coordination is also confirmed by the downfield shift of signals in ^{13}C NMR upon platinum binding (shift from 172.1 and 172.6 ppm to 176.4 and 176.8 ppm) (see the Supporting Information). **1** is more water-soluble (40 mg/mL at 25 °C) than carboplatin (17 mg/mL at 25 °C).

A molecular plot of the chemical structure of **1** is depicted in Figure 2. Selected bond lengths and angles are given in Table 1. Each platinum(II) has a square-planar geometry and

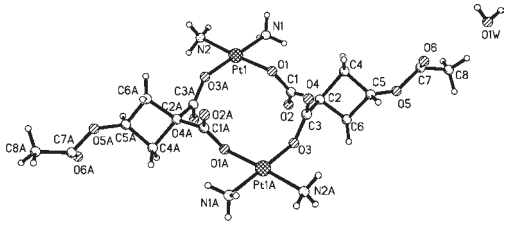


Figure 2. X-ray structure of complex **1**.

Table 1. Selected Bond Lengths [Å] and Angles [deg] of Complex **1**[a]

Pt1−N1	2.011(5)	Pt1−N2	2.027(5)
Pt1−O1	2.032(4)	Pt1−O3	2.034(4)
N1−Pt1−N2	90.2(2)	N1−Pt1−O1	90.64(18)
N2−Pt1−O1	174.92(18)	N1−Pt1−O3	177.04(17)
N2−Pt1−O3	91.99(19)	O1−Pt1−O3	87.00(17)
C1−O1−Pt1	121.2(4)	C3−O3−Pt1	124.4(3)

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

is coordinated to two N atoms of ammines and two O atoms of carboxylate ligands. The two atoms Pt1 and Pt1A and the atoms O1, C1, C2, C3,O3, O1A, C1A, C2A, C3A, and O3A constitute an unusual 12-membered chelate ring in this dimeric platinum(II) tetracarboxylate complex. The 12-membered ring adopts a distorted boat conformation, which is entirely different from what was observed in a 6-membered chelate ring in the other regular platinum(II) dicarboxylate complexes.[13−16] The cyclobutane ring is nearly perpendicular to the platinum(II) coordination plane. The Pt−N bond length (2.011−2.027 Å) and the Pt−O bond length (2.032−2.034 Å) are in the normal range, consistent with other similar *cis*-diam(m)inedicarboxylate complexes such as carboplatin and oxaliplatin.[17−21] The distance between the two Pt atoms is 6.195 Å. Every platinum bonding with two ammines is considerably strained, resulting in an expansion of the N1−Pt−N2 bond angle to 90.2(2)°. The structures of the cyclobutane rings are disordered. Atoms C5 (C5A) and O5 (O5A) were found in two sites, giving rise to two conformers. This is very similar to what was observed in the cyclobutane ring of carboplatin.[13] The platinum complex is involved in extensive intermolecular hydrogen bonding with ammine groups as hydrogen-bond donors and the O atoms of the carboxylate as acceptors.

The in vitro anticancer activity of **1** and its parent carboplatin as the control was assessed by the standard MTT assay[22]

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(11) Compound **1**. Mp152 °C (dec). Anal. Found (% calcd for $C_{16}H_{28}N_4O_{12}Pt_2\cdot H_2O$): C, 22.1 (21.9); H, 3.45 (3.42); N, 6.35 (6.39), Pt, 44.1 (44.5). FAB^+-MS: $[M-H_2O]^+$ *m/z* 859 (10%), $[(M-H_2O)/2 +$ glycerine$]^+$ *m/z* 522 (15%), $[(M-H_2O)/2]^+$ *m/z* 430 (100%), $[(M-H_2O)/2-CH_3COO]^+$ *m/z* 370 (15%). ^1H NMR (DMSO, 500.1 MHz, ppm): 1.97 (s, 6H, $2CH_3$), 2.53 (m, 4H, $2CH_2$), 3.21 (m, 4H, $2CH_2$), 4.14 (s, 12H, $4NH_3$), 4.64 (s, 2H, 2C*H*). ^{13}C NMR (DMSO, 100.6 MHz, ppm): 21 (CH_3), 38 (CH_2), 49 (*C*), 64 (CH), 170.0 (CH_3COO), 176.4, 176.8 (2*C*OO). FT-IR (KBr, cm^{-1}): 3298 [vs, $\nu(NH_3)$], 1722 [m, ν(C=O)], 1639 (vs, $\nu_{a(COO)}$), 1374 (s, $\nu_{s(COO)}$).

(12) Crystallograpic data of compound **1**: $C_{16}H_{28}N_4O_{12}Pt_2\cdot H_2O$, MW = 876.62, monoclinic, space group *P*2(1)/*c*, *a* = 14.1675(13) Å, *b* = 8.7965(8) Å, *c* = 11.0801(10) Å, β = 105.3140(10)°, *V* = 1331.8(2) $Å^3$, *Z* = 2. Crystal dimensions 0.18 × 0.11 × 0.08 mm^3 were used for measurements on a Bruker SMART APEX II CCD detector with a graphite monochromator (ω scan, $2\theta_{max}$ = 56.46°) with Mo Kα radiation. A total of 8343 reflections were collected and 3106 unique reflections, $I > 2\sigma(I)$. Final *R* indices: R_f = 0.0284, wR2 = 0.0680, *S* = 0.923 . The crystal structure of **1** was solved by direct methods with *SHLXS-97* (Sheldrick, 1990) and expanded using a difference Fourier technique, refined by the program *SHLXL-97* (Sheldrick, 1997) and full-matrix least-squares calculations. Crystallographic data for the structure of **1** have been deposited in the Cambridge Crystallographic Data Centre (deposition number CCDC 755177). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, U.K.; fax (+44) 1223-336-033 or e-mail desposit@ccdc.cam.ac.uk).

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Table 2. Antitumor Activities of **1** and Carboplatin against Tumor Cells

	IC_{50} [μM]	
cell lines[a]	carboplatin	**1**
A549/ATCC	41.9 ± 4.3	10.9 ± 1.7
NCI-H460	11.9 ± 1.5	6.4 ± 1.0
SGC-7901	26.8 ± 3.0	6.5 ± 1.3
SK-OV-3	25.6 ± 3.3	5.6 ± 0.9
HT-29	68.1 ± 7.8	23.6 ± 2.5
HCT-116	49.1 ± 3.0	18.9 ± 2.2
Ramos	25.4 ± 2.9	4.1 ± 0.3
HL60	40.2 ± 4.3	5.2 ± 1.2

[a] A549/ATCC, NCI-H460 = human lung cancer cell lines, SGC-7901 = human gastric carcinoma cell lines, SK-OV-3 = human ovarian cancer cell lines, HT-29,HCT-116 = human colon cancer cell lines, Ramos = human lymphocytic cancer cell lines, and HL60 = human leukemia cell lines.

using human tumor cell lines, and the results are summarized in Table 2. **1** strongly suppressed the growth of NCI-H460, SGC-7901, SK-OV-3, Ramos, and HL60. The concentrations required for 50% inhibition (IC_{50}) of these tumor cells are less than 10 μM. It also shows moderate activity against A549/ATCC, HT-29, and HCT-116, which are insensitive to carboplatin. More importantly, **1** is more active than carboplatin in all types of malignant tumor cells tested.

The preliminary toxicity was evaluated by a lethal dose of the compounds in animals.[23] As seen from Table 3, LD_{10} (dose causes 10% death of animals) and LD_{50} (dose causes 50% death) of **1** were found to be 193.4 and 224.3 mg/kg, respectively, which are much larger than the values of carboplatin (LD_{10} = 118.3 mg/kg; LD_{50} = 139.0 mg/kg), indicating that **1** is less toxic than carboplatin in mice following intravenous adminstration.

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Table 3. Acute Toxicity of **1** and Carboplatin in Mice

	lethal dose [mg/kg]	
	LD_{10}	LD_{50}
1	193.4	224.3
carboplatin	118.3	139.0

In summary, we have reported a novel carboplatin-analogue platinum complex with an unprecedented chemical structure *cis*-tetrammine-μ-bis(3-acetoxy-1,1-cyclobutanedicarboxylato-O^1,O^2)diplatinum(II). It is interesting that no other platinum complexes with the general formula *cis*-[PtA_2X_2] (A_2 = $2NH_3$/diamine, X_2 = dicarboxylates) reported to date display such a dimeric structural feature. The reason for forming such a unique structure needs further investigation. More importantly, the complex exhibits greater in vitro anticancer activity and lower toxicity than its parent compound carboplatin.

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Supporting Information Available: X-ray crystallographic dat in CIF format, synthesis and characterization of **1** and **3**, and Figures S1−S4. This material is available free of charge via the Internet at http://pubs.acs.org.