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# Structural Features of a New Dinuclear Platinum(II) Complex with Significant Antiproliferative Activity

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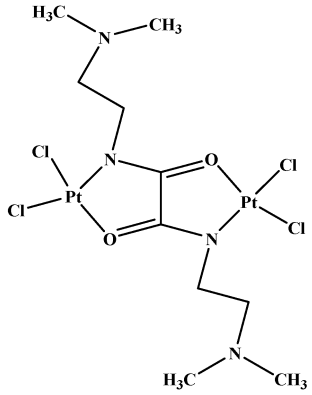
A novel dinuclear platinum(II) complex, [$Pt_2$-*N*,*N*′-bis(2-dimethylaminoethyl oxamide)$Cl_4$], showing peculiar structural features, has been prepared and characterized. X-ray diffraction data reveal that the two platinum ions are simultaneously bound to the *N*,*N*′-bis-(2-dimethylaminoethyl) oxamide ligand, on opposite sides. The coordination environment of both platinum centers is square planar, with identical $NOCl_2$ donor sets. The complex is poorly soluble within a physiological buffer but moderately soluble in DMSO. Preliminary in vitro studies point out that this dinuclear platinum complex exhibits significant growth-inhibiting properties on a panel of cultured human tumor cell lines, although less pronounced than those of cisplatin.

Since the discovery of the antitumor activity of cisplatin by Rosenberg et al.[1] a very large number of mononuclear platinum(II) complexes have been synthesized, and their cytotoxic and antitumor properties carefully evaluated on appropriate biological models.[2] Unfortunately, in contrast to general expectations, most investigated platinum(II) complexes turned out to exhibit biological activities very similar to those of cisplatin with an almost superimposable spectrum of antitumor properties and, thus, no significant therapeutic advantage.

In recent years, several research efforts in the field of platinum metallodrugs have been directed toward platinum complexes with innovative structural motifs that might exhibit a molecular mechanism substantially different from that of cisplatin and manifest a different pattern of cytotoxic and pharmacological effects. In this frame, various polynuclear platinum complexes have been designed and synthesized that act as multidentate ligands toward DNA and produce adducts substantially different from those of cisplatin.[3] The group of Nick Farrell has been very active in this field; remarkably one of their compounds, the trinuclear platinum complex BBR3464, is presently undergoing advanced clinical trials.[4]

**Chart 1.** Schematic Drawing of the [$Pt_2$-*N*,*N*′-bis(2-dimethylaminoethyl oxamide)$Cl_4$] Complex




We report here on the synthesis and the complete structural characterization of a new—and relatively simple—dinuclear platinum compound, namely, [$Pt_2$-*N*,*N*′-bis(2-dimethylaminoethyl oxamide)$Cl_4$] (Chart 1); preliminary biological data for this compound are presented as well. This compound is described in the US Patent 6,130,245 (2000) by Unitech Pharmaceuticals.

[$Pt_2$-*N*,*N*′-bis(2-dimethylaminoethyl oxamide)$Cl_4$] was prepared by direct reaction of $K_2PtCl_4$ with the ligand *N*,*N*′-bis(2-dimethylaminoethyl) oxamide, in aqueous solution according to the reported procedure.[5] Crystals of the complex suitable for X-ray diffraction studies were directly obtained from the preparative procedure, after 1 week The quality of the crystals was not very high but good enough to obtain interpretable reflections. In the hope to improve the overall

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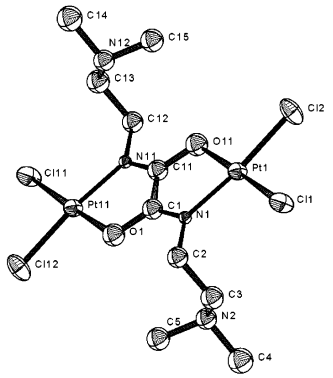


**Figure 1.** Geometry of [$Pt_2$-*N*,*N*′-bis(2-dimethylaminoethyl oxamide)$Cl_4$]. Thermal ellipsoids for the Pt and Cl atoms are drawn at the 50% probability level. Selected bond lengths (Å) and angles (deg): Pt(1)−Cl(1), 2.29(1); Pt(1)−Cl(2), 2.30(1); Pt(1)−O(1)a, 2.04(4); Pt(1)−N(1), 2.01(2); ∠Cl(1)−Pt(1)−Cl(2), 89.9(4); ∠Cl(1)−Pt(1)−O(1)a, 178.1(8); ∠Cl(2)−Pt(1)−O(1)a, 91.9(9); ∠Cl(1)−Pt(1)−N(1), 96.0(7); ∠Cl(2)−Pt(1)−N(1), 173.2(8); ∠N(1)−Pt(1)−O(1)a, 82(1). Symmetry operations like CIF format: 3_656 ($-x + 1$; $-y$; $-z + 1$).

quality of the diffraction data we decided to collect four sets of data (octants collected $\pm h$, $\pm k$, $\pm l$). The resulting structure is shown in Figure 1. A half-molecule is contained in the asymmetric unit. Notably the bis(2-dimethylaminoethyl oxamide) molecule is simultaneously coordinated to two platinum centers, acting as a bidentate ligand, on either side, through the amide nitrogen and the carbonyl oxygen; the two remaining positions of the coordination polyhedron are occupied by two chlorides. As a result, two five-membered rings form that are coplanar; the platinum chromophore is square planar with only modest distortions.[6] Thus, the obtained structure differs from that proposed in the US Patent 6,130,245 consisting of two $PtN_2Cl_2$ chromophores. Remarkably, this innovative dinuclear platinum complex shows two adjacent $PtCl_2$ functions (with a fixed Pt−Pt distance of 3.76 Å) connected by a rigid spacer, a peculiar structural motif for polynuclear platinum complexes. In addition, this complex bears two terminal tertiary amino groups that are not coordinated to the platinum centers and are, in principle, prone to protonation.

The bond distances, considering the standard deviations, are in agreement with the mean values reported in the literature.[10] The quality of the data does not permit anisotropic refinement of the ligand atoms; thus, the mentioned atoms were refined only isotropically, as shown in Figure 1.

**Table 1.** Cellular Growth (% with Respect to Control) of Selected Tumor Lines Exposed to $1 \times 10^{-5}$ M Concentrations of Either Platinum Complex

| cell line | $Pt_2$ complex | cisplatin |
|---|---|---|
| A549 | 81.50 | 20.61 |
| HT29 | 78.50 | 26.66 |
| A2780/S | 53.13 | 2.61 |
| MCF7 | 46.87 | 23.51 |

This dinuclear platinum complex is poorly soluble in aqueous solutions but moderately soluble in DMSO. This allowed us to record its absorption spectra that are dominated by a main transition at 280 nm with a broad feature around 340 nm. The latter one is attributed to a chloride to platinum LMCT, similarly to the case of cisplatin.[11]

The $^1$H NMR spectrum, recorded at 300 MHz, on a [$Pt_2$-*N*,*N*′-bis(2-dimethylaminoethyl oxamide)$Cl_4$] sample, freshly dissolved in deuterated DMSO, shows an intense signal at 2.78 ppm, assigned to the methyl groups of the uncoordinated tertiary amino groups. Notably, the chemical shift of this signal is not significantly modified with respect to the free ligand (2.76 ppm). After several hours, new signals, of fractionary intensity, are detected in the $^1$H NMR spectrum of the dinuclear platinum complex, that are suggestive of the formation of multiple species in solution, possibly as a consequence of hydrolysis and/or oligomerization processes.

The biological properties of the dinuclear platinum complex were assayed in vitro on the following human tumor cell lines: A549 (lung carcinoma), HT29 (colon carcinoma), A2780/S (ovaric carcinoma), and MCF7 (breast carcinoma) (Table 1). Specifically, the toxicity of a single concentration of the complex on cell proliferation was evaluated in comparison to cisplatin.[12] Although the measured cytotoxic activity is, on the average, less pronounced than that of

(5) Patent Number: 6,130,245. Date of patent: Oct. 10, 2000. Inventor: Jiajiu Shaw. [$Pt_2$-*N*,*N*′-bis(2-dimethylaminoethyl oxamide)$Cl_4$] was prepared by direct reaction of $K_2PtCl_4$ with the ligand *N*,*N*′′-bis(2-dimethylaminoethyl) oxamide at a molar ratio of 2:1. A 0.01 M aqueous solution of *N*,*N*′-bis(2-dimethylaminoethyl) oxamide (0.1424 g in 50 mL) was slowly added to a 0.02 M aqueous solution of potassium tetrachloroplatinate(II) while mixing. The resulting solution, light brown in color, was kept at room temperature for about 1 week. The orange-colored crystalline particles were precipitated out, filtered off, and washed with ice water. C,H,N analysis was the following: calcd C 15.76, H 2.91, N 7.36; found C 15.72, H 3.06, N 7.06.

(6) Crystal data: $C_{10}H_{20}Cl_4N_4O_2Pt_2$, monoclinic, space group $P21/n$, $a = 5.896(4)$ Å, $b = 13.527(4)$ Å, $c = 11.731(3)$ Å, $\beta = 100.30(3)°$, $V = 920.4(7)$ Å$^3$, $Z = 2$, $D_c = 2.744$, $\mu = 34.076$ mm$^{-1}$ for Cu Kα radiation; 5658 reflections (2Θ range (deg) = 5−124) were measured on a Rigaku AFC5 diffractometer (room temperature). Data were corrected for Lorentz and polarization effects. An empirical absorption correction, based on azimuthal scans of several reflections, was applied to the intensities.[7] The structure was solved using the SIR97 program[8] and refined as full matrix in the least-squares calculation using CAOS programs.[9] Use of 812 observed reflections ($I_o > 3\sigma(I_o)$) after introduction of fixed contribution of 10 H atoms of the ligand gave $R = 0.101$ and $R_w = 0.129$.

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cisplatin, inhibition of cell proliferation produced by this complex on the various lines is still significant, with $IC_{50}$ values falling in the 10−30 $\mu$M range.

In conclusion, we have reported here the structural characterization and some preliminary biological results of a rather simple but innovative dinuclear platinum complex. This complex exhibits a peculiar structure with the *N*,*N*′-bis(2-dimethylaminoethyl) oxamide moiety bridging two platinum centers and acting as a bidentate ligand toward both of them. In vitro biological assays suggest that this dinuclear platinum compound is still rather active against selected human tumor cell lines. Studies are in progress to improve the solubility of [$Pt_2$-*N*,*N*′-bis(2-dimethylaminoethyl oxamide)$Cl_4$] in aqueous solution, to describe its interactions with DNA, and to elucidate its cellular pharmacology.

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**Supporting Information Available:** Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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