PREPARATION AND CRYSTAL STRUCTURE OF A PLATINUM(II) COMPLEX OF $[\text{CH}_2\text{N}(\text{CH}_2\text{COOH})\text{CH}_2\text{CONH}_2]_2$, THE HYDROLYSIS PRODUCT OF AN ANTI-TUMOUR BIS(3,5-DIOXOPIPERAZIN-1-YL)ALKANE

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Abstract

The synthesis and crystal and molecular structures of the platinum(II) complex $\text{Pt}(\text{HL})\text{Cl}$ where H_2L is the diacid diamide $[\text{CH}_2\text{N}(\text{CH}_2\text{COOH})\text{CH}_2\text{CONH}_2]_2$, a hydrolytic metabolite of an antitumour active bis(3,5-dioxopiperazin-1-yl)alkane are reported. The complex is square planar and contains HL^- as a tridentate 2N (amino), O (carboxylate) donor. The metal to ligand bond distances are Pt-Cl 2.287(1) Å, Pt-O 2.002 (1) Å, Pt-N_{trans} Cl 2.014(1) Å and Pt-N_{trans} O 2.073 Å. There is extensive hydrogen bonding, each molecule of $\text{Pt}(\text{HL})\text{Cl}$ being intermolecularly hydrogen bonded to ten others giving a 3-dimensional network. There is also one intramolecular H-bond.

Introduction

The bis(3,5-dioxopiperazin-1-yl)alkanes (I) are a family of antitumour drugs of which the propane derivative is the most effective and is marketed under the name Razoxane, R = Me.¹⁻³ These drugs were synthesised in the expectation that they would enter cells and then undergo intracellular hydrolytic metabolism to chelating agents which would interfere with metalloenzymes essential for tumour cell growth. There are a number of possible hydrolytic metabolites one of which is the bis-acid, bis-amide, $\text{H}_2\text{NOCCH}_2(\text{HOOCCH}_2)\text{NCH}_2\text{CH}(\text{R})\text{N}(\text{CH}_2\text{COOH})\text{CH}_2\text{CONH}_2$, H_2L .

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We decided to synthesise platinum(II) complexes of ligands of this type for testing as antitumour agents and in this paper report on the preparation, properties and crystal structure of $Pt(HL)Cl$, where $R = H$.

Experimental

The ligand H_2L , N,N' -dicarboxamidomethyl- N,N' -dicarboxymethyl-1,2-diaminoethane, was prepared by a literature reported method for similar compounds,⁴ as follows.

1.2-Bis(3,5-dioxopiperazin-1-yl)ethane (20.0 g, 79 mmol),⁵ and copper(II) acetate monohydrate (15.0 g, 75 mmol) in water (20 cm³) were stirred together at room temperature for 2 days to give a blue solution which was then heated under reflux for 4 hours. The solution was evaporated under reduced pressure until 10 cm³ remained and this on standing at room temperature gave a blue crystalline complex. This was collected by suction filtration and dried at room temperature. The product (17.5 g, 50 mmol) which is the copper(II) complex of the title ligand, was dissolved in hot water (250 cm³) and acetic acid (5.00 cm³) was added to the solution which was then saturated with hydrogen sulphide. The precipitated cupric sulphide was removed by gravity filtration. The filtrate was passed through a column containing Kieselguhr and evaporated under reduced pressure to give a yellow oil. The oil was triturated and twice recrystallised from aqueous methanol-isopropanol to give H_2L as a colourless solid. Yield 9.9 g (34.1 mmol), 69% from the copper(II) complex. m.p. 168° C (dec). Microanalysis: Found: C 41.15, H 6.35, N 19.24%. $C_{10}H_{18}N_4O_6$ requires C 41.38, H 6.25, N 19.30.

The complex $Pt(HL)Cl$ was prepared as follows. H_2L (0.31 g, 1.1 mmol) was dissolved in deionized water (15 cm³) by heating to 60°C for 5 minutes, then allowed to cool to 30°C and treated dropwise, whilst stirring, with a solution of $K_2[PtCl_4]$ (0.43 g, 1 mmol) in water (5 cm³). After 12 days at room temperature yellow crystals

of Pt(HL)Cl were obtained, these were filtered under suction and dried at room temperature. Yield 0.33 g, 64%. Microanalysis: Found: C 22.58, H 3.35, N 10.41 Cl 6.81%. $C_{10}H_{17}N_4O_6PtCl$ requires C 23.09, H 3.30, N 10.77, Cl 6.83.

Spectroscopy

IR spectra were recorded as Nujol mulls between NaCl plates on a Philips PU 9714 spectrophotometer and UV-VIS spectra were recorded on a Philips 89730 UV/VIS scanning spectrophotometer.

X-ray Crystallography

A rectangular shaped crystal measuring 0.32 x 0.25 x 0.33 mm was selected and used for data collection, the results of which are summarised in Table 1. X-ray data were obtained on an Enraf-Nonius CAD4F diffractometer using monochromated MoK_{α} radiation $\lambda = 0.7093 \text{ \AA}$. The structure was solved by direct methods, SHELX 86,⁶ and refined by full matrix least squares using SHELX 76.⁷ Data were corrected for Lorentz and polarization effects and for absorption.⁸ Hydrogen atoms were included in calculated positions with fixed thermal parameters on the methylene carbon atoms only. The non-hydrogen atoms were refined anisotropically. The atomic scattering factors for non-hydrogen and hydrogen atoms and the anomalous dispersion correction factors for non-hydrogen atoms were taken from the literature.⁹⁻¹¹ All calculations were performed on a VAX 6610 computer. The ORTEP program was used to obtain the drawings.¹²

Results and Discussion

The addition of a solution $K_2[PtCl_4]$ to a solution of H_2L produced crystals of the complex Pt(HL)Cl, the crystal and molecular structure of which shows that the geometry around the metal is approximately square planar and that HL is present as a tridentate 2N (amine), O (carboxylate) ligand. The IR spectrum of the complex in the C=O stretching region shows bands at 1730 cm^{-1} (unionized COOH group), 1670 cm^{-1} (amide I band) and 1630 cm^{-1} (coordinated COO^-).¹³ The UV spectrum of an aqueous solution of the complex shows bands at 350 (15.3), 24.6 (93) and 230 (344) nm with ϵ values in $\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ given in parenthesis.

Table 1. Summary of X-ray diffraction data.

Formula	C ₁₀ H ₁₇ ClN ₄ O ₆ Pt
Crystal size (mm)	0.32 x 0.25 x 0.33
M (a.m.u.)	519.811
Crystal system	Monoclinic
Space group	P2 ₁ /c
a (Å)	6.631 (1)
b (Å)	12.407 (2)
c (Å)	17.470 (2)
β (°)	96.43
U (Å ³)	1428 (1)
Z	4
D _c g cm ⁻³	2.417
μ cm ⁻¹	96.32
F ₀₀₀	992
Radiation	Mo K _α
Graphite Monochromator	λ = 0.7093 Å
Diffractometer	Enraf-Nonius CAD4F
Orienting Reflections, Range	25, 13 < Θ < 20°
Temperature (°C)	22
Scan method	ω-2Θ
Data Collection Range	2 < 2Θ < 64°
No. unique data	3506
Total 1 > 3 σ 1	3099
No. of parameters fitted	200
Transmission factors, max/min	1.28/0.86
R ^a , R _w ^b	3.72%, 4.26%
Quality-of-fit indicator ^c	2.49
Largest Shift/esd, final cycle	< 0.001
Largest positive peak (e/Å ³)	2.06
Largest negative peak (e/Å ³)	-1.10

$$^aR = [\sum |F_o| - |F_c|] / \sum |F_o|$$

$$^bR_w = [[\sum w(|F_o - F_c|)^2] / [\sum w(|F_o|)^2]]^{1/2}; w = 1/[(\sigma F_o)^2 - 0.001019 * F_o^2]$$

$$^c\text{Quality-of-fit} = [\sum w(|F_o| - |F_c|)^2 / (N_{\text{obs}} - N_{\text{parameters}})]^{1/2}$$

In Fig. 1 is shown an ORTEP diagram of the complex with selected bond and interatomic distances and angles listed in Table 2. The Pt-Cl bond distance (2.287 Å) is similar to that found in other complexes such as *cis* and *trans*-[Pt(NH₃)₂Cl₂] for which Pt-Cl = 2.33 Å and 2.32 Å respectively,¹⁴ K[Pt(NH₃)Cl₃]·H₂O where Pt-Cl = 2.31 Å (the 3 Pt-Cl bond lengths are identical within experimental error),¹⁵ and [PtCl₄]²⁻ where Pt-Cl = 2.317 Å.¹⁶ The Pt-O bond distance is 2.002 Å which is the same as that reported for the Pt-O bond in *trans*-bis(glycinato)platinum(II).¹⁷ Since metal to ligand bond distances in platinum(II) complexes depend on the nature of the donor atom and also on the ligand *trans* to the leaving group as defined by the *trans* influence,¹⁶ the identical values of the Pt-O bond distances quoted is not surprising since both are carboxylate oxygen atoms and both are *trans* to nitrogen atoms, albeit primary in one case and tertiary in the other. The C=O and C-O bond distances in the coordinated carboxylate groups are 1.237 Å and 1.287 Å respectively for Pt(HL)Cl which compares with 1.231 Å and 1.290 Å for Pt(Gly)₂. The Pt-N bond distances in Pt(HL)Cl are 2.014 Å for the bond *trans* to Cl⁻ and 2.073 Å for the bond *trans* to COO⁻. Since the nitrogen atoms are very similar, both being tertiary and both attached to three CH₂ groups the difference in bond distances may be partly due to the higher *trans* influence of COO⁻ relative to Cl⁻ and also to the fact that the N *trans* to Cl⁻ is part of two chelate rings while the other N is involved in only one such ring.

Fig. 1 An ORTEP diagram of Pt(HL)Cl showing the numbering scheme used.

The molecular structure of $\text{Pt}(\text{HL})\text{Cl}$ shows that there is extensive hydrogen bonding, each molecule being involved in intermolecular hydrogen bonds to ten other molecules, giving rise to a 3-dimensional network. In Fig 2 is shown a typical molecule viewed down the x-axis and for clarity shows its contacts with only 8 other molecules. The remaining two contacted molecules lie above and below the plane. There is one intramolecular hydrogen bond formed between N(2) and O(6) which has a distance of 3.086 Å. The hydrogen bonds distances are shown in the Table 3.

Table 2. Selected Bond and Interatomic Distances (Å) and Angles (°) in $\text{Pt}(\text{HL})\text{Cl}$.

Pt(1) - Cl(1)	2.287 (1)	Pt(1) - O(2)	2.002 (4)
Pt(1) - N(1)	2.014 (4)	Pt(1) - N(3)	2.073 (4)
Pt(1) - C(1)	2.784 (6)	Pt(1) - C(2)	2.761 (6)
Pt(1) - C(5)	2.778 (5)	Pt(1) - C(6)	2.866 (5)
Pt(1) - C(7)	2.891 (5)	O(1) - C(2)	1.237 (8)
O(2) - C(2)	1.287 (8)	O(3) - C(4)	1.229 (8)
O(2) - C(8)	1.184 (8)	O(5) - C(8)	1.308 (8)
O(6) - C(10)	1.217 (8)	N(1) - C(1)	1.496 (7)
N(1) - C(3)	1.490 (7)	N(1) - C(5)	1.501 (7)
N(2) - C(4)	1.332 (8)	N(3) - C(6)	1.544 (6)
N(3) - C(7)	1.522 (7)	N(3) - C(9)	1.498 (7)
N(4) - C(10)	1.347 (7)	C(1) - C(2)	1.55 (1)
C(3) - C(4)	1.510 (8)	C(5) - C(6)	1.507 (8)
C(7) - C(8)	1.536 (8)	C(9) - C(10)	1.492 (8)
O(2) - Pt(1) - Cl(1)	93.8 (1)		
N(1) - Pt(1) - O(2)	83.6 (2)		
N(3) - Pt(1) - N(1)	88.1 (2)		
N(3) - Pt(1) - Cl(1)	94.3 (1)		
N(3) - Pt(1) - O(2)	170.5(2)		
N(1) - Pt(1) - Cl(1)	176.5 (1)		

The fractional atomic coordinates for the non-hydrogen atoms are listed in Table 4. Additional material available from the Cambridge Crystallographic data centre includes a full listing of the remaining bond angles, H-atom coordinates and thermal parameters.

Table 3. Hydrogen bond distances in Pt(HL)Cl.

Hydrogen bonds	Distance, Å
N(2)-O(3)	2.891
N(2)-O(5)	3.080
N(2)-O(6), (intra)	3.086
N(4)-O(2)	3.032
N(4)-O(4)'	3.080
O(1)-O(5)	2.752

Fig. 2. A view along the x-axis showing intermolecular contacts.**Table 4.** Fractional atomic coordinates $\times 10^4$ (Å) for Pt(HL)Cl.

Atom	x	y	z	Atom	x	y	z
Pt(1)	1622.7(3)	6723.0(2)	2654.4(1)	C(1)	-294(11)	6941(5)	3984(4)
Cl(1)	3684(2)	7543(1)	1864(1)	C(2)	1799(11)	7495(5)	4143(3)
O(1)	2285(10)	7983(5)	4753(3)	C(3)	384(9)	5029(4)	3744(3)
O(2)	2981(7)	7423(3)	3609(2)	C(4)	2404(10)	5054(5)	4238(4)
O(3)	2548(7)	5442(5)	4889(3)	C(5)	-2198(8)	5963(5)	2894(3)
O(4)	-3249(8)	5658(4)	469(3)	C(6)	-1810(8)	5390(5)	2164(3)
O(5)	-3763(7)	7400(4)	311(3)	C(7)	-1196(9)	6933(4)	1276(3)
O(6)	2083(8)	4106(4)	2295(3)	C(8)	-2838(10)	6562(5)	641(3)
N(1)	-204(6)	6088(3)	3384(2)	C(9)	903(9)	5293(5)	1261(3)
N(2)	3980(8)	4626(4)	3937(3)	C(10)	2308(9)	4485(5)	1667(3)
N(3)	-217(7)	6011(4)	1757(2)				
N(4)	3846(8)	4191(4)	1270(3)				

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