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Structure and Activity Relationships of Platinum Complexes Related to Antitumour Activity: The Crystal and Molecular Structure of *trans*-Dichlorobis(cyclohexylamine)platinum(II)

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Crystals of *trans*-dichlorobis(cyclohexylamine)platinum(II), $PtCl_2(C_6H_{11}NH_2)_2$, are orthorhombic, space group *Pbcn*, with four molecules in a cell of dimensions $a = 26\cdot170$ (9), $b = 6\cdot673$ (2) and $c = 9\cdot002$ (4) Å. Intensity data were collected on a four-circle diffractometer with Mo $K\bar{\alpha}$ radiation. The structure was solved by the heavy-atom method and refined by full-matrix least squares to a final conventional R value of 0·041 for 1131 observed reflections. The Pt atom configuration is square-planar with the N and Cl atoms in *trans* positions. The cyclohexyl ring assumes a chair-like conformation.

Introduction

Since the discoveries by Rosenberg, Van Camp, Trosko & Mansour (1969, and references therein), it has been shown that certain complexes of the platinum-group metals exhibit interesting biological effects. At low concentrations some are effective bactericides while others stop cell division and force bacteria to grow into long filaments. Some of these complexes are also very potent broad-spectrum antitumour agents. Indeed, it is considered that Pt^{II} complexes inhibit DNA synthesis by direct interaction with the nucleic acid (Harder & Rosenberg, 1970). In addition, it has been found that this interaction depends on hetero-cyclic base composition (Macquet & Theophanides, 1975; Millard, Macquet & Theophanides, 1975), guanine being the preferred site of attack, at least at low complex/DNA ratios, and induces localized conformational changes in DNA (Munchausen & Rahn, 1975; Tamburro, Celotti, Furlan & Guantieri, 1977).

From a general survey seeking relationships between activity, toxicity and structure a general conclusion arose which is in agreement with that of Rosenberg, Van Camp, Trosko & Mansour (1969), namely that the complexes should be uncharged, two amines should be present, these ligands should be *cis* to one other and the complexes are most effective when the other two sites are occupied by Cl (Braddock, Connors, Jones,

Khokhar, Melzack & Tobe, 1975, and references therein).

It is our purpose to study by means of X-ray analysis a number of antitumour agents, in order to contribute to the better understanding of the correlation between molecular structure and pharmacological activity. We present here the crystal and molecular structure of *trans*-dichlorobis(cyclohexylamine)-platinum(II). All previous attempts to obtain crystals of the *cis* isomer have failed.

Experimental

Yellow needle-shaped crystals of *trans*-dichlorobis(cyclohexylamine)platinum(II), $PtCl_2(C_6H_{11}NH_2)_2$, elongated along **c**, were obtained by slow evaporation of the solvent from a solution of chloroform. Preliminary photographic data showed that the crystals are orthorhombic, space group *Pbcn*.

Lattice constants were obtained from a least-squares analysis of the setting angles of reflections measured on a four-circle diffractometer with Mo $K\bar{\alpha}$ radiation monochromatized by a graphite crystal.

The intensities were collected from a crystal of approximate dimensions $0.09 \times 0.14 \times 0.43$ mm on a Philips PW 1100 four-circle diffractometer operating in the ω-scan mode (scan width $= 1.2°$, scan speed $= 0.03°$ s^{-1}). 1877 independent reflections up to $\theta = 28°$ were measured, of which 1131 had intensities greater than twice their standard deviation (σ), σ being calculated from the counting statistics of the measurements.

During the data collection two standard reflections were measured every 90 min to check the stability of the crystal and electronics. Intensities were corrected for Lorentz and polarization effects and were then converted to the absolute scale by Wilson's method. An experimental absorption correction was applied following the method proposed by North, Phillips & Mathews (1968). Crystal data are given in Table 1.

Table 1. *Crystal data for* $PtCl_2(C_6H_{11}NH_2)_2$

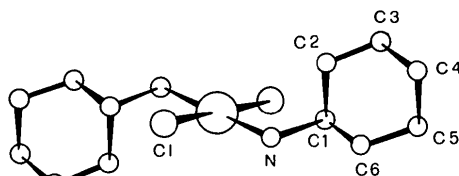| Space group *Pbcn*		Z	4
λ(Mo $K\bar{\alpha}$)	0.7107 Å	V	1571.79 Å³
a	26.170 (9)	D_o	1.96 g cm⁻³
b	6.673 (2)	D_c	1.96
c	9.002 (4)	F(000)	896
M_r	464.33	μ(Mo $K\bar{\alpha}$)	96.95 cm⁻¹

Fig. 1. Perspective view of the molecule.

Structure determination and refinement

The structure was determined by the heavy-atom technique. A Patterson synthesis revealed a Pt atom at the origin and two other peaks which were clearly Pt—Cl vectors. The positions of the remaining non-hydrogen atoms were derived from subsequent difference Fourier maps. The conventional R value was 0.18. The structure was refined by full-matrix least-squares methods and the R value was reduced to 0.048. At this stage a difference Fourier map yielded the H atom coordinates, which were included in the refinement, but not varied.

The correction for the real and imaginary parts of the anomalous dispersion was applied for Pt and Cl only (*International Tables for X-ray Crystallography*,

Table 2. *Final positional parameters (with e.s.d.'s in parentheses) for non-hydrogen atoms*

	x	y	z
Pt	0	0	0
Cl	0.0549 (1)	−0.2669 (3)	0.0278 (3)
N	0.0557 (2)	0.1938 (9)	−0.0802 (7)
C(1)	0.1098 (3)	0.1711 (12)	−0.0327 (9)
C(2)	0.1145 (3)	0.2182 (12)	0.1330 (9)
C(3)	0.1705 (3)	0.2044 (15)	0.1840 (10)
C(4)	0.2056 (4)	0.3396 (15)	0.0917 (11)
C(5)	0.1993 (3)	0.2919 (14)	−0.0748 (10)
C(6)	0.1445 (3)	0.3112 (14)	−0.1239 (10)

Table 3. *Fractional coordinates for the hydrogen atoms*

	x	y	z
H(C1)	0.120	0.030	−0.047
H'(C2)	0.094	0.131	0.197
H''(C2)	0.105	0.355	0.162
H'(C3)	0.180	0.045	0.178
H''(C3)	0.168	0.249	0.308
H'(C4)	0.192	0.493	0.114
H''(C4)	0.244	0.321	0.128
H'(C5)	0.216	0.143	−0.094
H''(C5)	0.223	0.389	−0.135
H'(C6)	0.130	0.455	−0.118
H''(C6)	0.141	0.275	−0.241
H'(N)	0.042	0.329	−0.049
H''(N)	0.058	0.161	−0.201

Table 4. *Intramolecular bond distances (Å) and angles (°) with e.s.d.'s in parentheses*

Pt—Cl	2.302 (2)	Cl—Pt—N	85.4 (1)
Pt—N	2.078 (5)	Pt—N—C(1)	120.3 (4)
N—C(1)	1.485 (7)	N—C(1)—C(2)	109.7 (5)
C(1)—C(2)	1.530 (8)	N—C(1)—C(6)	110.3 (5)
C(2)—C(3)	1.536 (8)	C(1)—C(2)—C(3)	110.9 (5)
C(3)—C(4)	1.532 (9)	C(2)—C(3)—C(4)	111.9 (5)
C(4)—C(5)	1.541 (10)	C(3)—C(4)—C(5)	110.0 (5)
C(5)—C(6)	1.507 (9)	C(4)—C(5)—C(6)	111.6 (6)
C(6)—C(1)	1.540 (8)	C(5)—C(6)—C(1)	110.7 (5)
		C(6)—C(1)—C(2)	110.3 (5)

Table 5. *Torsion and dihedral angles* (°)

The torsion angle of the bonded group $A-X-Y-B$ is the angle between the planes $A-X-Y$ and $X-Y-B$. It is positive if clockwise and negative counterclockwise (Klyne & Prelog, 1960).

Cl–Pt–N–C(1)	10·0	C(2)–C(3)–C(4)–C(5)	54·4
Pt–N–C(1)–C(2)	66·5	C(3)–C(4)–C(5)–C(6)	−56·1
N–C(1)–C(2)–C(3)	177·7	C(4)–C(5)–C(6)–C(1)	58·0
N–C(1)–C(6)–C(5)	−170·0	C(5)–C(6)–C(1)–C(2)	−57·8
C(1)–C(2)–C(3)–C(4)	−55·4	C(6)–C(1)–C(2)–C(3)	56·0

Dihedral angles between planes

C(1)C(2)C(3)–C(4)C(5)C(6)	1·2
C(2)C(3)C(4)–C(5)C(6)C(1)	2·2
C(2)C(1)C(6)–C(3)C(4)C(5)	1·9
PtNC(1)–C(2)C(1)C(6)	61·9

Fig. 2. Outline of the Cl atom environment with the most relevant intramolecular contact distances.

1974). The refinement was carried out minimizing the quantity $\sum w(|F_o| - |F_c|)^2$, $w = 3.36/[\sigma^2(F) + 0.0011F^2]$, to give constant values of $w\Delta^2$, independent of the value of $|F_o|$. The final R value for the 1131 reflections with $I > 2\sigma(I)$ was 0·041 $(R_w = 0.047)$.*

The calculations were carried out on the Cyber 76 computer of the Centro di Calcolo Interuniversitario dell'Italia Nord Orientale with the *SHELX* 76 system of crystallographic programs (Sheldrick, 1976). The scattering factors were those of *International Tables for X-ray Crystallography* (1974).

Results and discussion

A perspective view of the molecule showing its conformation and the numbering system is presented in Fig. 1. The final structural parameters, with their e.s.d.'s, of the non-hydrogen and H atoms are reported in Tables 2 and 3 respectively; in Table 4 the bond lengths and valence angles for all non-hydrogen atoms, not corrected for changes due to thermal vibrations, are given. Some torsion and dihedral angles are shown in Table 5.

Bond lengths and angles have their expected values. In particular, Pt–Cl [2·302 (2) Å] and Pt–N [2·078 (5) Å] are in good agreement with values reported for analogous compounds (Barnes, Iball & Weakley, 1975; Colamarino & Orioli, 1975; Iball, MacDougall & Scrimgeour, 1975; Lauher & Ibers, 1975). All C–H lengths are in the range 0·9–1·1 Å. The Pt atom assumes a square-planar configuration with N and Cl atoms in *trans* positions. All these atoms lie strictly on the same plane owing to crystallographic symmetry requirements. Therefore, the only departure from the exact square-planar configuration is represen-
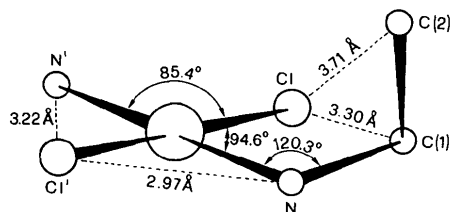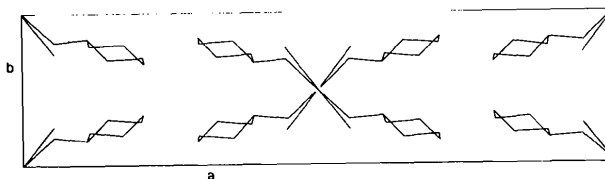
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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33456 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Fig. 3. The crystal structure projected down c.

ted by the different values of the two Cl–Pt–N angles (85·4 and 94·6° respectively). This could be explained by examining Fig. 2 where the most relevant intra-molecular contact distances are marked. The value of the N–Pt–Cl angle, 94·6°, could be justified by the steric hindrance between Cl and the cyclohexyl ring through C(1), the distance C(1)···Cl being still shorter than the sum of the van der Waals radii. This conclusion is also supported by the unusual value of the C(1)–N–Pt angle (120·3°).

The C(sp^3)–N bond value, 1·485 (7) Å, is very close to that of the standard single bond. In addition, the N atom, which seems to exhibit a distorted tetrahedral configuration, is equatorial with respect to the cyclohexyl ring, which assumes a chair-like conformation with torsion angles in the range 54·4–58·0 (mean 56·3°). Bond lengths and valence angles within the ring [average: 1·531 (9) Å and 110·9 (5)° respectively] have values very similar to those found for this kind of aliphatic ring.

Finally, the crystal packing (Fig. 3) is determined solely by van der Waals forces and none of the inter-molecular contact distances are shorter than the sum of the van der Waals radii. In particular, the shortest Pt···Pt contacts (4·50 and 6·67 Å) compare well with the distances found in the crystal structures of several Pt[II] complexes (Barnes, Iball & Weakley, 1975; Colamarino & Orioli, 1975; Lauher & Ibers, 1975). These values, however, are far longer than that of 3·40 Å, which has been reported for compounds where stacking occurs and which was assumed to be an indication of metal–metal interaction (Iball, Mac-Dougall & Scrimgeour, 1975).

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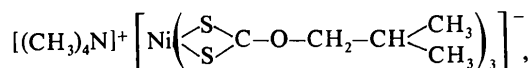

The Crystal Structure of Tetramethylammonium Tris(*O*-isobutyl dithiocarbonato)nickelate(II)

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The crystal structure of the title compound,

$$[(CH_3)_4N]^+ \left[Ni\left(\underset{S}{\overset{S}{\diagup}} \hspace{-0.3em} C{-}O{-}CH_2{-}CH{\overset{CH_3}{\underset{CH_3}{\diagdown}}} \right)_3 \right]^-,$$

has been determined from three-dimensional intensities, measured on a computer-controlled Philips PW 1100 single-crystal diffractometer (1898 observed reflexions). The crystals are monoclinic, space group $P2_1/c$, with $a = 11 \cdot 0536$ (6), $b = 19 \cdot 3833$ (9), $c = 15 \cdot 5217$ (9) Å, $\beta = 117 \cdot 89$ (1)°, and $Z = 4$. The structure was solved by direct phase determination with *MULTAN*. The positional and thermal parameters of the atoms were refined by full-matrix least-squares calculations to a final $R = 0 \cdot 050$ ($R_w = 0 \cdot 041$). The anion shows approximate trigonal symmetry, with the Ni atom surrounded by six S atoms at the apices of a distorted octahedron. The Ni–S distances are in the range 2·385–2·478 Å, whereas in the dithiocarbonate ligands the C–S distances range between 1·657 and 1·683 Å and C–O distances between 1·342 and 1·356 Å. The roughly planar anions form layers approximately parallel to (104), and are interconnected by the tetramethylammonium cations, which are distributed both in and between the layers.

Introduction

Ionic tris(dithiocarbonato) complexes of bivalent metals have been of considerable interest in the past decade. So far as we know, of the Ni^{II} complexes only trimethylphenylammonium tris(*O*-ethyl dithiocarbonato)nickelate(II) (D'Addario, 1970) has been structurally analysed.

Since a number of new compounds, progressively more heavily substituted, have recently been prepared at the Inorganic Chemistry Laboratory of the University of Thessaloniki (Hatzikostas & Manoussakis, 1977), it was considered advisable to carry out a systematic structure investigation of certain selected members of the group. The structure of tetramethylammonium tris(*O*-isobutyl dithiocarbonato)nickelate(II) (TMAIXN hereafter) is the first to be determined.