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The Crystal Structures and Absolute Configurations of the Anti-Tumor Complexes Pt(oxalato)(1R,2R-cyclohexanediamine) and Pt(malonato)(1R,2R-cyclohexanediamine)

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*The absolute configurations of the anti-tumor complexes [Pt(oxalato)(*trans*-l-dach)] and [Pt(malonato)(*trans*-l-dach)] (*trans*-l-dach = 1R,2R-cyclohexanediamine) have been determined by X-ray anomalous scattering techniques. These complexes are particularly interesting because they show higher anti-tumor activity than the corresponding Pt complexes with other 1,2-cyclohexanediamine(dach) ligands, namely those with *trans*-d-dach (1S,2S-dach) or *cis*-dach (1R,2S-dach). The oxalato and malonato ligands are found to bind to the Pt atom in a chelating fashion, through one oxygen atom from each of the two carboxylate groups. Crystallographic details: Pt(oxalato)(*trans*-l-dach): space group $P2_1$ (monoclinic); $a = 11.230(11)$ Å, $b = 9.914(5)$ Å, $c = 4.716(3)$ Å, $\beta = 90.86(6)°$; $R = 4.0\%$ for 1526 reflections. Pt(malonato)(trans-l-dach): space group $P2_1$ (monoclinic); $a = 11.568(5)$ Å, $b = 10.007(5)$ Å, $c = 5.187(3)$ Å, $\beta = 99.16(4)°$; $R = 4.8\%$ for 1675 reflections.*

Introduction

Since the initial discovery of the anti-cancer properties of *cis*-[$PtCl_2(NH_3)_2$] [1] many metal complexes have been tested for anticancer activity, especially platinum(II) compounds [2]. *Cis*-[$PtCl_2(NH_3)_2$] analogs are usually made by varying the amine ligand, substituting the chloride ligands by different 'leaving groups' or, in a few cases, by varying the oxidation state to Pt(IV). The *cis* coordination by two amines and two leaving groups seems to be a necessary prerequisite for an active Pt-drug. The analog screening has resulted in several drugs which are now undergoing clinical testing. Among these second-generation Pt-drugs are a series of compounds which have as the amine ligand 1,2-cyclohexanediamine [3], which will be abbreviated as dach.

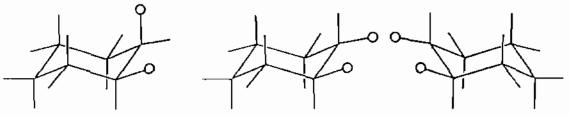

Fig. 1. Isomeric forms of 1,2-cyclohexanediamine.

The ligand dach has three isomeric forms (shown in Fig. 1), two of which are optical isomers of each other. Initial studies were conducted with complexes made from unresolved mixtures [4–6]. Subsequent tests, with complexes made from the separated isomers, have shown that they have different activities. It was found, for example, that complexes of [Pt(*trans*-l-dach)]$^{2+}$ have a slightly higher activity than corresponding complexes of *trans*-d-dach or *cis*-dach [7, 8].

From the differences in anti-cancer effects, it seems to follow that the various [PtX_2(dach)] complexes interact differently with DNA. This point has been addressed [7] and it was concluded on steric grounds that the [Pt(*trans*-dach)]$^{2+}$ complexes could more easily enter the large groove of the DNA double-helix to interact with the DNA bases than those of [Pt(*cis*-dach)]$^{2+}$. This may account for the higher activity of *trans vs. cis*, but it does not explain the difference between the *trans*-l and *trans*-d activities. However, the fact that this difference in activity is not fully understood is not surprising, because the details regarding the active site and the absolute stereochemistry of the binding of Pt-drugs to DNA are still unresolved.

The crystal structures of three complexes of platinum with dach have been reported in the literature: $PtCl_2$(*cis*-dach) and $PtBr_2$(*cis*-dach) [9] and *trans*-[$PtCl_2$(*trans*-l-dach)$_2$] [Pt(*trans*-l-dach)$_2$]-Cl_4 [10]. In this paper, the structures of Pt(oxalato)-(*trans*-l-dach) and Pt(malonato)(*trans*-l-dach) are described, and the absolute configuration of the

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TABLE I. Coordinates and Thermal Parameters for Pt(oxalato)(*trans*-l-dach).

Atom	x	y	z	B
Pt	0.0407(3)	0.0(0)	0.3394(7)	[a]
O1	−0.076(1)	0.133(2)	0.171(3)	2.3(3)
O2	−0.064(1)	−0.135(2)	0.128(3)	2.5(3)
C7	−0.149(2)	0.078(3)	0.019(5)	3.4(6)
C8	−0.149(2)	−0.078(2)	−0.029(3)	1.0(3)
O3	−0.227(2)	0.143(2)	−0.132(3)	3.3(4)
O4	−0.216(1)	−0.138(2)	−0.179(3)	3.0(4)
N1	0.161(2)	0.142(2)	0.484(4)	2.7(5)
N2	0.152(1)	−0.133(2)	0.539(3)	1.4(3)
C1	0.252(1)	0.068(2)	0.678(3)	2.4(3)
C2	0.276(1)	−0.065(2)	0.543(3)	2.4(2)
C6	0.366(2)	0.160(2)	0.677(5)	3.5(5)
C3	0.369(2)	−0.142(2)	0.707(4)	2.5(5)
C5	0.467(2)	0.075(2)	0.846(4)	3.5(3)
C4	0.485(2)	−0.065(2)	0.716(4)	3.4(3)

	[a]U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	0.0194(3)	0.0170(3)	0.0370(3)	−0.0028(8)	−0.0021(2)	−0.0022(6)

[a] The form of the anisotropic thermal ellipsoid is $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$.

TABLE II. Distances and Angles for Pt(oxalato)(*trans*-l-dach).

Atom	Atom	Distance (A)
Pt	O1	2.01(2)
Pt	O2	2.04(2)
Pt	N1	2.06(2)
Pt	N2	2.04(2)
O1	C7	1.21(3)
O2	C8	1.32(2)
C7	C8	1.56(3)
C7	O3	1.29(3)
C8	O4	1.19(2)
N1	C1	1.54(3)
N2	C2	1.54(2)
C1	C2	1.49(2)
C1	C6	1.57(3)
C2	C3	1.51(3)
C6	C5	1.61(3)
C3	C4	1.50(3)
C5	C4	1.53(3)

Atom	Atom	Atom	Angle (°)
O2	Pt	O1	82.5(6)
N1	Pt	O1	96.0(7)
N2	Pt	O1	175.6(6)
N1	Pt	O2	169.7(7)
N2	Pt	O2	98.6(6)
N2	Pt	N1	83.8(7)
C7	O1	Pt	112(2)
C8	O2	Pt	141(1)
C8	C7	O1	122(2)

TABLE II. *(continued)*

Atom	Atom	Atom	Angle (°)
O3	C7	O1	124(2)
O3	C7	C8	114(2)
C7	C8	O2	110(2)
O4	C8	O2	124(2)
O4	C8	C7	125(2)
C1	N1	Pt	107(1)
C2	N2	Pt	106(1)
C2	C1	N1	107(1)
C6	C1	N1	105(1)
C6	C1	C2	111(1)
C1	C2	N2	103(1)
C3	C2	N2	114(1)
C3	C2	C1	111(1)
C5	C6	C1	106(2)
C4	C3	C2	111(2)
C4	C5	C6	112(2)
C5	C4	C3	111(2)

trans-l-dach ligand determined in each case. In both compounds, the platinum atom is chelated by one oxygen atom from each of the two carboxylic acid groups.

Experimental

Colorless crystals of the title compounds were prepared using published procedures [7a, 11]. The

TABLE III. Coordinates and Thermal Parameters for Pt(malonato)(*trans*-l-dach).

Atom	*x*	*y*	*z*	*B*
Pt	0.0555(4)	0.0(0)	0.1289(8)	[a]
O1	0.073(1)	0.137(1)	0.219(2)	2.7(3)
O2	0.053(1)	−0.145(2)	0.294(3)	3.7(3)
C7	0.138(2)	0.134(2)	0.433(4)	2.8(4)
C8	0.130(1)	0.025(2)	0.626(3)	3.6(4)
C9	0.132(2)	−0.113(2)	0.505(3)	2.4(4)
O3	0.211(1)	0.225(1)	0.501(2)	3.4(3)
O4	0.202(1)	−0.203(2)	0.597(2)	3.8(3)
N1	−0.173(1)	0.138(2)	−0.037(3)	2.8(3)
N2	−0.191(2)	−0.131(2)	0.031(3)	3.6(4)
C1	−0.276(2)	0.071(2)	−0.175(3)	3.1(3)
C2	−0.299(2)	−0.048(2)	−0.020(3)	2.8(3)
C6	−0.386(2)	0.159(2)	−0.229(4)	3.9(4)
C3	−0.403(2)	−0.136(2)	−0.142(4)	3.9(4)
C5	−0.493(2)	0.082(2)	−0.353(4)	4.6(4)
C4	−0.515(2)	−0.041(2)	−0.191(4)	4.5(4)

	[a]U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pt	0.0286(4)	0.0224(4)	0.0354(4)	0.0003(7)	0.0018(2)	−0.0013(5)

[a]The form of the anisotropic temperature factor is as given in Table I.

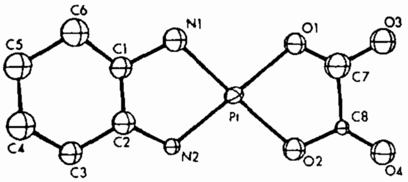

Fig. 2. Pt(oxalato)(*trans*-l-dach) with atomic labelling.

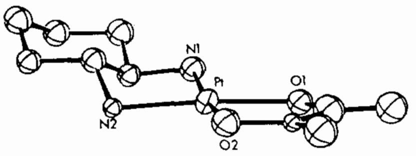

Fig. 3. Absolute configuration of Pt(oxalato)(*trans*-l-dach).

circular dichroism spectra of the compounds have been reported earlier [7b]. The crystals are thin, triangular plates with truncated vertices (*i.e.* six-sided polygons with alternating long/short edges).

Pt(oxalato)(1R,2R-cyclohexanediamine)

For the Pt(oxalato)(1R,2R-cyclohexanediamine) structure determination, a crystal was cut to form a trapezoidal plate, 0.65 mm at the base, 0.4 mm along the top, with a height of 0.25 mm and a thickness of 0.1 mm. This crystal was mounted in air on a glass fiber and oriented along what subsequently turned out to be the *c*-axis. A Syntex $P2_1$ automated four-circle diffractometer, with Mo Kα radiation and a graphite crystal monochromator, was used for intensity data collection. The unit cell parameters were determined by least-squares refinement of 15 centered reflections. The final unit cell was monoclinic, space group $P2_1$, with $a = 11.230(10)$ Å, $b = 9.914(5)$ Å, $c = 4.716(3)$ Å, $\beta = 90.86(6)^\circ$, and $Z = 2$.

Data were collected using the $2\theta/\theta$ scan technique for all reflections such that $3.5^\circ < 2\theta < 45.0^\circ$. Two Friedel-related quadrants, (+h, +k, ±l) and (−h, −k, ±l) were collected for the determination of the absolute configuration of the molecule. Throughout data collection three reflections were monitored periodically and no decay was observed. The data were processed with a Lorentz-polarization correction and an empirical absorption correction [12]. Of 1782 reflections collected, 1526 reflections with $I > 3\sigma(I)$ were retained for the ensuing structure analysis.

A Patterson analysis of the data gave the position of the platinum atom. A subsequent difference-Fourier map revealed all light atom positions. Least-squares refinement of the atomic coordinates and thermal parameters resulted in final agreement values of R = 4.0% and R_w = 5.3% [13]. Final coordinates and thermal parameters are listed in Table I. Interatomic distances and angles are given in Table II.

Refinement of the mirror-image of the molecule resulted in a significantly higher R-value (R = 4.3%, R_w = 5.7%). This indicated that the first set of atomic coordinates had the proper absolute configuration. The absolute configuration of the *trans*-l-dach ligand found here is consistent with those in previously-determined structures (*vide infra*).

TABLE IV. Distances and Angles for Pt(malonato)(*trans*-l-dach).

Atom	Atom	Distance (A)
Pt	O1	2.02(1)
Pt	O2	2.02(2)
Pt	N1	2.03(2)
Pt	N2	2.04(2)
O1	C7	1.24(2)
O2	C9	1.35(2)
C7	C8	1.50(3)
C7	O3	1.25(2)
C8	C9	1.51(3)
C9	O4	1.26(2)
N1	C1	1.45(2)
N2	C2	1.49(2)
C1	C2	1.48(2)
C1	C6	1.54(3)
C2	C3	1.54(3)
C6	C5	1.51(3)
C3	C4	1.60(3)
C5	C4	1.54(3)

Atom	Atom	Atom	Angle (°)
O2	Pt	O1	90.3(6)
N1	Pt	O1	93.2(6)
N2	Pt	O1	177.0(6)
N1	Pt	O2	176.4(6)
N2	Pt	O2	92.7(7)
N2	Pt	N1	83.8(7)
C7	O1	Pt	121(1)
C9	O2	Pt	118(1)
C8	C7	O1	121(2)
O3	C7	O1	122(2)
O3	C7	C8	117(2)
C9	C8	C7	113(2)
C8	C9	O2	120(2)
O4	C9	O2	116(2)
O4	C9	C8	123(2)
C1	N1	Pt	110(1)
C2	N2	Pt	106(1)
C2	C1	N1	108(1)
C6	C1	N1	115(2)
C6	C1	C2	110(1)
C1	C2	N2	109(1)
C3	C2	N2	109(1)
C3	C2	C1	116(1)
C5	C6	C1	113(2)
C4	C3	C2	107(2)
C4	C5	C6	112(2)
C5	C4	C3	111(2)

Figure 2 shows the atomic labelling and Fig. 3 depicts the Pt(oxalato)(*trans*-l-dach) molecule so that the chair configuration of the cyclohexane ring and the absolute configuration around the two chiral carbon atoms can be clearly seen.

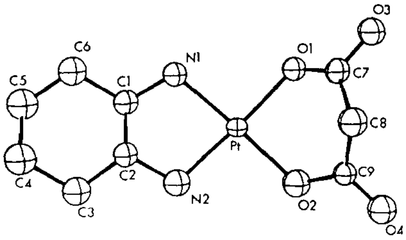

Fig. 4. Pt(malonato)(*trans*-l-dach) with atomic labelling.

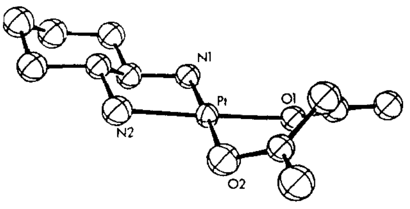

Fig. 5. Absolute configuration of Pt(malonato)(*trans*-l-dach).

Pt(malonato)(1R,2R-cyclohexanediamine)

For the Pt(malonato)(1R,2R-cyclohexanediamine) complex, one of the truncated-triangular plates was mounted on a glass fiber in air. The plate was 0.06 mm thick and had alternate sides of 0.12 mm and 0.20 mm. Preliminary precession photographs indicated the monoclinic space group $P2_1$, isomorphous with the oxalato complex. The unit cell parameters are: a = 11.568(5) Å, b = 10.007(5) Å, c = 5.187(3) Å, β = 99.16(4)°, and Z = 2. The (+h, +k, ±l) and (−h, −k, ±l) quadrants of data were collected and processed as described for the oxalato complex. There were 1731 unique reflections, 56 of which were rejected as too weak ($I < 3\sigma$). A Patterson analysis gave a platinum atom position similar to that for the oxalato complex and structure analysis proceeded, as before, to R = 4.8%, R_w = 6.3% (the least-squares refinement was carried out, incidentally, with anisotropic temperature factors for the Pt atom and isotropic temperature factors for all of the light atoms). Final coordinates and thermal parameters are listed in Table III. The distances and angles are given in Table IV.

The absolute configurations of the chiral carbon atoms were found to be the same as in the oxalato complex. The mirror-image of this molecule also refined to a higher R-value (R = 5.3%, R_w = 6.8%). The molecule and the atomic labelling are shown in Figs. 4 and 5.

Discussion

The molecular structures of Pt(oxalato)(*trans*-l-dach) and Pt(malonato)(*trans*-l-dach) have been determined. The absolute configurations have been established using the anomalous scattering properties of the platinum atom. The ratio of the R-values for the Pt(oxalato)(*trans*-l-dach) and Pt(malonato)(*trans*-

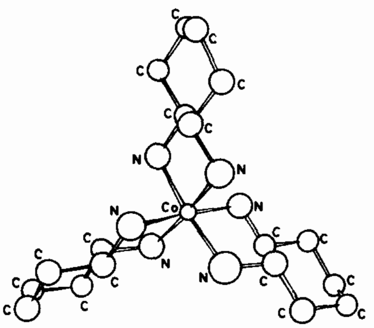

Fig. 6. The absolute configuration of the [Co(*trans*-d-dach)$_3$]$^{3+}$ cation in Tris(d-dach)ClCl$_3$·5H$_2$O (ref. 18).

l-dach) are 1.08 and 1.15, respectively. These results independently determine that the absolute configurations shown in Figs. 3 and 5 are correct to a probability level better than 99.5% [15].

The configuration of the *trans*-l-dach molecule described here agrees with previously-determined configurations of the d- and l-isomers of cyclohexanediamine [16–18]. For example, Fig. 6 shows the configuration of the other isomer, *trans*-d-dach, derived from the structure of tris(*trans*-d-dach)-cobalt(III) chloride pentahydrate [18]. Comparison of the configurations of the chiral carbons of Fig. 6 to those of Figs. 3 and 5 confirms that they are mirror images of each other, as they should be if our determinations are correct.

The molecular structures of Pt(oxalato)(*trans*-l-dach) and Pt(malonato)(*trans*-l-dach) reported here do not display any unusual or unexpected structural features. By themselves they do not explain why complexes with the *trans*-l-dach isomer are more active than those of the *trans*-d-dach or *cis*-dach isomers. They do, however, confirm the monomeric nature of the platinum complexes and show that the oxalato and malonato ligands coordinate in a chelating fashion, through an oxygen atom from each of the carboxylic acid groups (as opposed to bridged structures [19]).

The cyclohexane rings have the expected chair configuration, with the two amino groups in equatorial positions. The malonato ligand, in contrast, shows a boat conformation for the six membered $\overline{\text{Pt–O–C–C–C–O}}$ ring (Fig. 5). It is intriguing to note that this same boat conformation is found in another anti-tumor platinum–malonato complex, Pt(malonato)(2,2-dimethyl-1,3-diaminopropane) [23].

In general, complexes of Pt(*trans*-l-dach) have slightly higher antitumor activities than corresponding complexes of *trans*-d-dach or *cis*-dach. Pt(*trans*-d-dach) showed the most severe toxicity, while Pt(*cis*-dach) showed the least toxicity. Biological differences were observed between the three isomers.

The only difference between the two optical isomers is a conformational difference. 1R,2R-dach (*trans*-l-dach) takes the λ-gauche form, while 1S,2S-dach (*trans*-d-dach) takes the δ-gauche form. We speculate that the λ-gauche conformation may more easily approach the large groove of the right-handed helical DNA molecule than the δ-gauche conformation.

Acknowledgements

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$R = (\Sigma \| k\cdot F_{\mathbf{obs}}| - |F_{\mathbf{calc}}\|)/\Sigma(k\cdot F_{\mathbf{obs}})$
$R_{\mathbf{w}} =_{4} \{[\Sigma(w^2\cdot(|k\cdot F_{\mathbf{obs}}|^2 - |F_{\mathbf{calc}}|^2)^2]/[4\cdot\Sigma(w^2\cdot|k\cdot F_{\mathbf{obs}}|^4)]\}^{1/2}$
where k is an appropriate scaling factor and w is a weighting factor. The weighting factor used for all reflections in these determinations was $w = 1/\sigma(I)$.
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19 Though not expected to be present in the title compounds, carboxylic acid bridged dimeric structures are theoretically possible. Platinum dimers and trimers exist for simple Pt-complexes such as $[(NH_3)_2Pt(OH)_2Pt(NH_3)_2]^{2+}$ [20] and $[(NH_3)_2Pt(OH)]_3^{3+}$ [21] which have hydroxy bridges. Another example is the methylcystinate bridged complex $[(NH_3)_2Pt(C_5H_6N_3O)_2Pt(NH_3)_2]^{2+}$ [22].

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