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cis-[(4*R*,5*R*)-4,5-Bis(aminomethyl)-2,2-dimethyl-1,3-dioxolane-*N*,*N*′]-(malonato-*O*,*O*′)platinum(II), an anticancer agent

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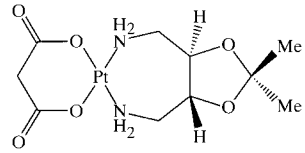
In the title compound, $[Pt(C_3H_2O_4)(C_7H_{16}N_2O_2)]$, the Pt atom is coordinated to two O and two N atoms in a square-planar arrangement. The two independent molecules, which have very similar structures, are approximately related by pseudo-twofold screw-axis symmetry. The six-membered chelate ring in the leaving ligand assumes a conformation intermediate between the half-chair and boat forms. The seven-membered ring in the carrier ligand assumes a twist-chair conformation and the oxolane ring assumes an envelope conformation. The crystal packing consists of extensive hydrogen-bonding networks which form two-dimensional molecular layers, and there are weak van der Waals interactions between these layers.

Comment

Cisplatin [*cis*-diamminedichloroplatinum(II)] is one of the effective anticancer agents currently available, although its clinical usefulness is limited by serious toxicity, development of acquired resistance and poor solubility in water (Rosenberg *et al.*, 1969). Numerous analogues have been synthesized in a search for alternative active agents, carboplatin and tetraplatin being the representative examples (Haines *et al.*, 1989; Hambley, 1997). The title compound, (I), is one of a series of compounds synthesized in an effort to find new potent platinum complexes with a broader spectrum of anticancer activity, lower toxicity and higher solubility in water (Kim *et al.*, 1994). These compounds contain the bidentate malonate ligand as a leaving group and the bidentate 4,5-bis(aminomethyl)-1,3-dioxalane ligand as a carrier group, that form the six- and seven-membered ring structures, respectively, with a Pt atom. The 1,3-dioxalane ring moiety was introduced to render the organoplatinum species more water solubility, thereby facilitating intravenous administration and being possibly less toxic due to a more facile excretion *via* the kidney. Various analogues with substituents at the terminal positions of the two ring systems have been found to be active with desirable properties and the analogue with an isopropyl group instead of the two methyl substituents has successfully passed the clinical test and is currently being marketed. We present here the crystal structure of the title compound, (I), as the first example in this new class of compounds.



(I)

The two molecules in the asymmetric unit have very similar structures although there are small differences in detail. They are approximately related by pseudo-twofold screw-axis symmetry parallel to the $a - c$ direction at $y = 0.185$ and to the $a + c$ direction at $y = 0.445$. Owing to this pseudosymmetry, the monoclinic cell may look like the orthorhombic cell, transformed by $a' = a + c$ (7.43 Å), $b' = a - c$ (12.12 Å) and $c' = b$, with one molecule in the asymmetric unit and space group $C222_1$.

The Pt atom is coordinated to two O and two N atoms in a square-planar arrangement (Fig. 1). The Pt—O distances are close to 2.0 Å as observed in several cisplatin analogues containing the same malonate ligand and the various carrier ligands. These analogues include the complexes containing two free ammine ligands (Rochon *et al.*, 1985) or the ligand with the five- (Cutbush *et al.*, 1983; Bruck *et al.*, 1984), six- (van Kralingen *et al.*, 1980) or seven-membered (Hoeschele *et al.*, 1994) ring structure as a carrier group. The Pt—N distances in the title compound and other analogues are also close to 2.0 Å, indicating that the size of ring does not exert any significant effect on Pt—N bonding. The O—Pt—O bite angle varies from 88 to 93° and the O···O bite distance varies from 2.78 to 2.93 Å in the complexes containing the malonate group. The N—Pt—N bite angles are 95.6 (7) and 94.6 (6)°, and the N—N bite distances are 2.99 (2) and 3.01 (2) Å for molecules *A* and *B*, respectively.

The six-membered chelate ring assumes a conformation intermediate between the half-chair and boat forms. This characteristic conformation is maintained in all analogues with the malonate ligand although the ring shows, albeit small, conformational flexibility. The seven-membered chelate ring

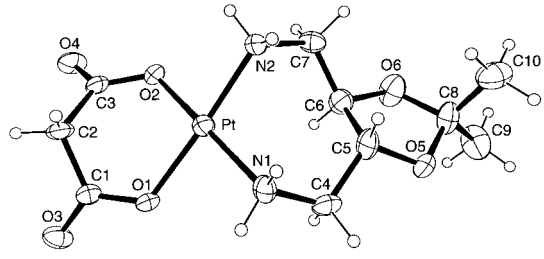


Figure 1
*ORTEP*III (Burnett & Johnson, 1996) view of one of the molecules of (I) with the numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

assumes the twist-chair conformation with the oxolane moiety orientated in the opposite direction with respect to the C2 atom. The oxolane ring substituted with a *trans* configuration assumes an envelope conformation with O5 at the tip of the flap.

Crystal packing consists of the extensive hydrogen-bonding networks in the two-dimensional molecular layers and weak van der Waals interactions between these layers. Both independent molecules have the same hydrogen-bonding scheme, each with four unique N—H···O hydrogen bonds between the amino and the malonate oxo groups, as listed in Table 2.

Experimental

The title compound was synthesized as reported previously (Kim *et al.*, 1994). Crystals were obtained from an aqueous ethanol solution by slow evaporation at 277 K.

Crystal data

$[Pt(C_3H_2O_4)(C_7H_{16}N_2O_2)]$
M_r = 457.35
Monoclinic, $P2_1$
a = 7.092 (8) Å
b = 30.78 (3) Å
c = 7.126 (7) Å
β = 116.96 (12)°
V = 1386 (2) Å^3
Z = 4
D_x = 2.191 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 45 reflections
θ = 7–20°
μ = 10.145 mm^{-1}
T = 293 (2) K
Prism, colorless
0.52 × 0.20 × 0.15 mm

Data collection

Rigaku AFC-4 diffractometer
ω scans
Absorption correction: empirical ψ scan (North *et al.*, 1968)
T_{min} = 0.054, T_{max} = 0.218
3891 measured reflections
3246 independent reflections (plus 219 Friedel-related reflections)
2954 reflections with $I > 2\sigma(I)$
R_{int} = 0.034
θ_{max} = 27.49°
$h = -9 \rightarrow 5$
$k = -39 \rightarrow 39$
$l = -8 \rightarrow 9$
3 standard reflections
every 100 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.108
S = 1.030
3465 reflections
343 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0511P)^2 + 10.8830P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 2.03 e Å^{-3} (0.82 Å from Pt)
$\Delta\rho_{min}$ = −2.54 e Å^{-3} (0.81 Å from Pt)
Absolute structure: Flack (1983)
Flack parameter = 0.07 (3)

The positions of the H atoms, except those in the methyl groups, were calculated and refined with constraints using the AFIX13 or 23 option in *SHELXL*97 with U_{iso} values 1.2 times those of the bonded atoms. All four methyl groups were modeled as idealized disordered groups with two positions rotated from each other by 60°, and the positions of the H atoms were refined with constraints and U_{iso} values 1.5 times those of the bonded atoms using the AFIX123 option. The absolute structure was assumed from the synthesis and the Flack (1983) parameter of 0.07 (3) indicates that it is correct.

Data collection, cell refinement and data reduction: local program (Yoon *et al.*, 1994); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *SHELXL*97.

Table 1
Selected geometric parameters (Å, °).

Pt—N2	2.002 (15)	Pt′—O2′	2.018 (13)
Pt—O2	2.024 (13)	Pt′—O1′	2.032 (12)
Pt—O1	2.024 (12)	Pt′—N2′	2.035 (13)
Pt—N1	2.029 (17)	Pt′—N1′	2.056 (14)
N2—Pt—O2	85.7 (6)	O2′—Pt′—O1′	92.1 (5)
O2—Pt—O1	92.2 (5)	O2′—Pt′—N2′	86.9 (6)
N2—Pt—N1	95.6 (7)	O1′—Pt′—N1′	86.4 (6)
O1—Pt—N1	86.8 (6)	N2′—Pt′—N1′	94.6 (6)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···O3^{i}	0.90	2.23	3.01 (2)	144
N1—H1B···O4^{ii}	0.90	2.03	2.93 (2)	172
N2—H2A···O3^{iii}	0.90	2.00	2.89 (2)	170
N2—H2B···O4^{i}	0.90	2.17	2.91 (3)	138
N1′—H1′A···O3′^{iv}	0.90	2.22	2.96 (2)	139
N1′—H1′B···O4′^{v}	0.90	2.01	2.91 (2)	174
N2′—H2′A···O3′^{vi}	0.90	1.98	2.87 (2)	176
N2′—H2′B···O4′^{iv}	0.90	2.16	2.93 (3)	143

Symmetry codes: (i) $1+x, y, 1+z$; (ii) $1+x, y, z$; (iii) $x, y, 1+z$; (iv) $x-1, y, z-1$; (v) $x, y, z-1$; (vi) $x-1, y, z$.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: OB1028). Services for accessing these data are described at the back of the journal.

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