

An X-ray powder diffraction study of *cis*-dichloridobis(2-methyl-2*H*-tetrazol-5-amine- κN^4)platinum(II), a tetrazole-containing analogue of cisplatin

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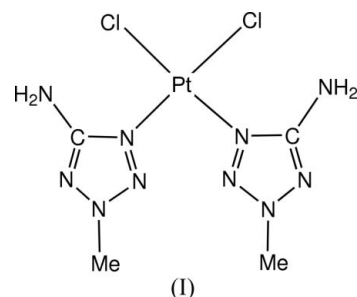
The structure of the title compound, *cis*-[PtCl₂(C₂H₅N₅)₂], was analysed using in-house X-ray powder diffraction data at room temperature. The structure was solved by direct methods and refined using Rietveld analysis. A slightly distorted square-planar coordination geometry is formed around the Pt atom by two Cl atoms and two ring N atoms of the 2-methyl-2*H*-tetrazol-5-amine ligands, which are in a *cis* configuration. The planes of the tetrazole rings are inclined at 79.7 (7) and 73.8 (6)° with respect to the coordination plane, with their substituents oriented in such a way that the complex as a whole has approximate C₂ symmetry. Intermolecular N—H...Cl hydrogen bonds mediate the formation of a three-dimensional supramolecular network.

Comment

Platinum complexes are the subject of a great deal of interest in connection with the search for new anticancer therapeutics showing better medical properties compared with those of cisplatin, carboplatin and oxaliplatin, which are widely used in clinical practice. It is known that these drugs exhibit side effects, and moreover their use is limited by inherent and acquired resistance. In this context, the synthesis and comprehensive characterization of Pt^{II} complexes with planar heterocyclic amine ligands are the subject of intense study, because such ligands are expected to ameliorate the toxic side effects of platinum-based antitumour drugs (Hotze *et al.*, 2002). To date, many Pt^{II} complexes with nitrogen-containing planar heterocycles, including pyridine and its derivatives, thiazole, imidazole, pyrazole and quinoline, have been studied (Kalinowska-Lis *et al.*, 2008). As for tetrazole-containing analogues, their systematic study began only recently (Voitekhovich *et al.*, 2009; Golovko *et al.*, 2010).

Scant information is present in the literature on the crystal structures of PtX₂L₂ complexes, with X being a halogen and L

a neutral substituted tetrazole. Crystal structures have been reported only for the *trans* isomer of the platinum(II) chloride complex with 2-*tert*-butyl-2*H*-tetrazol-5-amine (Voitekhovich *et al.*, 2009). The *cis* isomers of this class of complexes have not been structurally characterized yet, because many of them crystallize as fine powders, making structural investigations more difficult. We present here the structure of *cis*-dichloridobis(2-methyl-2*H*-tetrazol-5-amine- κN^4)platinum(II), (I), a tetrazole-containing analogue of cisplatin. Powder diffraction data were used, because all attempts to grow suitable single crystals to date have failed because of *cis*–*trans* isomerization during recrystallization.



Compound (I) (Fig. 1) is mononuclear *cis*-PtCl₂L₂, with space group *P*₂₁₂₁, which is not common for this class of compounds (see below). One molecule, with 17 non-H atoms, constitutes the asymmetric unit. The Pt atom exhibits a slightly distorted square-planar coordination formed by N4 and N44 of two tetrazole rings and by Cl1 and Cl2 in a *cis* arrangement [mean deviation of ligated atoms from the Pt1/Cl1/Cl2/N4/N44 plane = 0.037 (7) Å]. The Pt1–N4, Pt1–N44, Pt1–Cl1 and Pt1–Cl2 distances (Table 1) lie within expected ranges [Cambridge Structural Database (CSD), Version 5.32, November 2010; Allen, 2002]. The large ligands do not induce significant distortion from square-planar coordination geometry [N4–Pt1–N44 = 93.1 (5)°]. The geometry observed for both tetrazole ligands is similar to that of the free ligand (Bryden, 1956; Klapötke *et al.*, 2009).

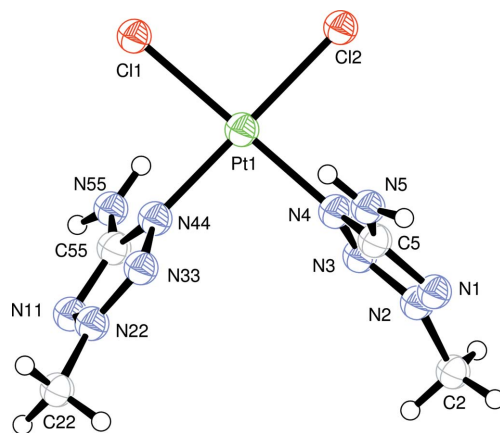


Figure 1

The molecular structure of (I), showing the atom-numbering scheme. Displacement spheres of the non-H atoms are shown at the 50% probability level and H atoms are shown as spheres of arbitrary radii.

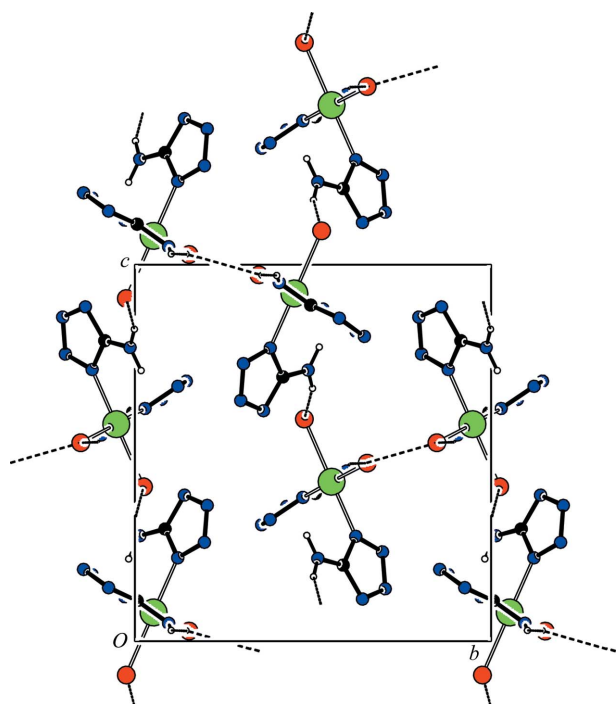


Figure 2
The structure of (I), viewed along the *a* axis. The methyl groups have been omitted for clarity. Dashed lines indicate hydrogen bonds.

The amino (and methyl) groups of the 2-methyl-2*H*-tetrazol-5-amine ligands lie on opposite sides of the coordination plane, giving approximate C_2 symmetry to the complex as a whole. The two tetrazole rings make dihedral angles of 79.7 (7)° (N1–N4/C5) and 73.8 (6)° (N11/N22/N33/N44/C55) with the coordination plane, with corresponding torsion angles Cl2–Pt1–N4–C5 and Cl1–Pt1–N44–C55 of 86.6 (14) and 82.3 (12)°, respectively.

The amino H atoms are involved in intermolecular N–H...Cl hydrogen bonds (Fig. 2 and Table 2). Both H atoms of the N5 amino group are donors to Cl1 atoms of different molecules, forming ribbons propagating along the *a* axis (Fig. 3*a*). Only one of the H atoms of the amino group at N55 participates in hydrogen bonding, linking the complex molecules into chains extending along the *c* axis (Fig. 3*b*), and connecting the above-mentioned ribbons into a three-dimensional network (Fig. 2).

Complex (I) belongs to 'structural class' $P2_12_12_1$, $Z = 4(1)$ (notation of Zorkii *et al.*, 1977), which is rare among the *cis* isomers of PtX_2L_2 . According to the analysis of Hansson *et al.* (2008), based on the CSD, the distribution of structural classes of *cis*- PtX_2L_2 complexes (*X* is a halogen and *L* is a ligand with a donor atom from group 14, 15 or 16) is dominated by $P2_1/c$, $Z = 4(1)$ (42% of compounds), followed by $P\bar{1}$, $Z = 2(1)$ (19%), and with a much lower representation for $P2_12_12_1$, $Z = 4(1)$ (5%).

Compound (I) is the first structurally characterized tetrazole-containing analogue of cisplatin. However, its cytotoxic activity, assayed *in vitro* against HeLa cells (Golovko *et al.*, 2010), is significantly lower than that of cisplatin. To begin to

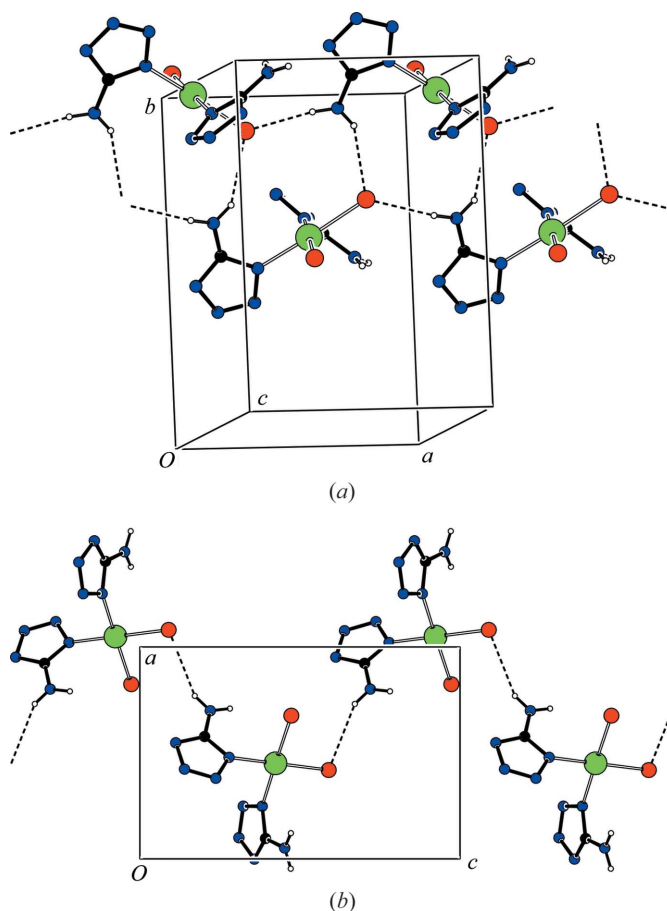


Figure 3
Hydrogen-bonded chains formed by hydrogen bonds involving (a) the N5 amino-group H atoms and (b) the N55 amino-group H atoms. Methyl groups have been omitted for clarity.

understand the molecular mechanisms underlying the anti-tumour activity of tetrazole-containing cisplatin analogues, and to develop a concept for the rational design of antitumour drugs based on a 'structure–cytotoxic activity' relationship, it will be necessary to accumulate more and diverse information for this class of complexes.

Experimental

A solution of 2-methyl-2*H*-tetrazol-5-amine (1 mmol, 0.099 g) in 1 *M* HCl (5 ml) was added to a solution of K_2PtCl_4 (0.5 mmol, 0.207 g) in 1 *M* HCl (5 ml), and the reaction mixture stirred for 24 h at room temperature. The resulting yellow precipitate was filtered off, washed with cold water and dried in air (yield 0.19 g, 82%). Analysis calculated: Pt 42.0, Cl 15.3%; found: Pt 42.2, Cl 15.1%.

Crystal data

[$PtCl_2(C_2H_5N_5)_2$]
 $M_r = 464.20$
Orthorhombic, $P2_12_12_1$
 $a = 8.37465$ (7) Å
 $b = 11.93209$ (10) Å
 $c = 12.61875$ (10) Å

$V = 1260.96$ (2) Å³
 $Z = 4$
Cu $K\alpha$ radiation
 $\lambda = 1.5418$ Å
 $T = 295$ K
Flat sheet, 30 × 30 mm

Data collection

HZG-4A (Carl Zeiss, Jena) diffractometer	Data collection mode: reflection
Specimen mounting: packed powder pellet	Scan method: step
	$2\theta_{\min} = 5.00^\circ$, $2\theta_{\max} = 120.00^\circ$,
	$2\theta_{\text{step}} = 0.02^\circ$

Refinement

$R_p = 0.036$	$\chi^2 = 2.690$
$R_{\text{wp}} = 0.046$	5751 data points
$R_{\text{exp}} = 0.028$	66 parameters
$R_{\text{Bragg}} = 0.045$	38 restraints
$R(F) = 0.033$	H-atom parameters not refined

Table 1

Selected bond lengths (Å).

Pt1—Cl1	2.313 (6)	N4—C5	1.346 (7)
Pt1—Cl2	2.304 (6)	N5—C5	1.352 (17)
Pt1—N4	2.021 (6)	N11—N22	1.337 (18)
Pt1—N44	2.016 (8)	N11—C55	1.330 (14)
N1—N2	1.338 (15)	N22—N33	1.291 (10)
N1—C5	1.330 (14)	N22—C22	1.48 (2)
N2—N3	1.288 (8)	N33—N44	1.324 (17)
N2—C2	1.49 (2)	N44—C55	1.336 (15)
N3—N4	1.329 (17)	N55—C55	1.35 (2)

Table 2

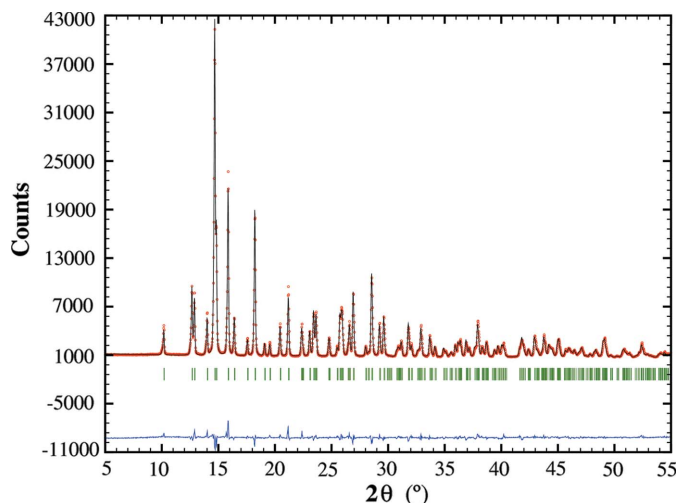
Hydrogen-bond geometry (Å, °).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N5—H51...Cl1 ⁱ	0.86	2.40	3.228 (17)	162
N5—H52...Cl1 ⁱⁱ	0.86	2.58	3.332 (12)	147
N55—H551...Cl2 ⁱⁱⁱ	0.86	2.82	3.596 (13)	151

 Symmetry codes: (i) $x + 1, y, z$; (ii) $x + \frac{1}{2}, -y + \frac{1}{2}, -z + 2$; (iii) $-x - \frac{1}{2}, -y + 1, z - \frac{1}{2}$.

The powder pattern was indexed with the program *TREOR90* (Werner *et al.*, 1985), giving an orthorhombic unit cell with $a = 8.373$ Å, $b = 11.935$ Å and $c = 12.618$ Å ($F_{20} = 86$, $M_{20} = 37$, $F_{40} = 88$, $M_{40} = 31$). Systematic absences $h00$ ($h = 2n$), $0k0$ ($k = 2n$) and $00l$ ($l = 2n$) are unique within the orthorhombic system to the space group $P2_12_12_1$, which was used for structure solution by direct methods using the program *EXPO* (Altomare *et al.*, 1999). The Pt and Cl atoms, all non-H atoms of one ligand, and most of the non-H atoms of the second ligand were located in the structure solution and subsequent Fourier recycling. For the second ligand, one N atom of the tetrazole ring and the C atom of the methyl group did not emerge, so they were located geometrically, with $R(F) = 0.106$ at this stage.

The structural model was refined with *FULLPROF* (Rodríguez-Carvajal, 2001). Background was approximated by a polynomial function. The pseudo-Voigt profile function was used to fit the pattern. A line-shape asymmetry correction was applied according to the Bérar-Baldinozzi function (Bérar & Baldinozzi, 1993). No preferred orientation was found. The displacement parameters of all non-H atoms were refined isotropically and were constrained to be the same. H atoms were placed at calculated positions (Sheldrick, 2008), with $C-H = 0.96$ Å for the methyl group and $N-H = 0.86$ Å for the amino group, and with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{iso}}(\text{C,N})$. Planar geometry was assigned to the amino groups, because 5-amino substituents of the tetrazole ring are typically planar and do not participate in coordination of metal cations (CSD; Allen, 2002). Only two compounds are exceptions, *viz.* the chloride and bromide complexes of copper(II) with 2-methyl-2*H*-tetrazol-5-amine, which


Figure 4

Experimental (dots), calculated (line) and difference (bottom) powder patterns for (I) in the range $2\theta = 5-55^\circ$. The positions of the Bragg reflections are shown by ticks above the difference pattern.

show semi-coordination of their 5-amino groups (Ivashkevich *et al.*, 2010).

Soft restraints were used for the bond lengths and angles in the ligands. The target values were based on an analysis of bond lengths and angles in the complexes of 2-substituted tetrazol-5-amines studied to date. These are the copper(II), palladium(II) and platinum(II) chloride complexes with 2-*tert*-butyl-2*H*-tetrazol-5-amine (Voitekhovich *et al.*, 2009), and the silver (Karaghiosoff *et al.*, 2009) and copper(II) (Ivashkevich *et al.*, 2010) complexes of 2-methyl-2*H*-tetrazol-5-amine. The bonds were restrained to 1.33 (N1—N2), 1.29 (N2—N3), 1.33 (N3—N4), 1.34 (N4—C5), 1.33 (N1—C5), 1.34 (C5—N5), 1.49 (N2—C2) and 2.00 Å (Pt1—N4), and the angles to 115.0 (N1—N2—N3), 105.0 (N2—N3—N4), 108.0 (N3—N4—C5), 110.0 (N4—C5—N1), 102.0 (C5—N1—N2), 124.0 (N4—C5—N5), 126.0 (N1—C5—N5), 122.5 (N1—N2—C2), 122.5 (N3—N2—C2), 123.0 (Pt—N4—N3) and 129.0° (Pt1—N4—C5). The same target values were applied independently for the two ligands. The values of σ , defining the weights of restraints, were set at 0.005 Å for bonds and at 0.05° for angles in the initial stages of the refinement, and at 0.01 Å and 0.1°, respectively, in the final refinement.

In view of the rather large number of atoms in the asymmetric unit, the restraints played a very important role in obtaining the structural parameters. As expected, full profile refinement failed without soft restraints. However, even with the restraints, the refinement was somewhat complicated. A stable decrease of discrepancy indices was achieved only when restrained parameters were gradually included in the refinement. In the first step, only the coordinates of Pt and Cl atoms were refined, and without any restraints. In subsequent steps, during refinement of the remaining atomic positions, the coordinates of the Pt and Cl atoms were kept fixed, otherwise the refinement was unstable. Refinement of C- and N-atom coordinates was performed first for one ligand. N4 was refined first, with soft restraints involving this atom only. Then C5 was included, with corresponding restraints. The remaining atoms of the first ligand were included in the order N3, N1, N2, N5 and C2. In the next step, atomic coordinates of the second ligand were added to the refinement in the same manner. Then the Pt and Cl atoms were refined together with all of the other atoms. After placement of H atoms in calculated positions, the final refinement was performed. This procedure reduced the discrepancy indices from $R_p =$

0.162, $R_{wp} = 0.261$, $R_{Bragg} = 0.284$ and $R_F = 0.131$ to $R_p = 0.036$, $R_{wp} = 0.046$, $R_{Bragg} = 0.045$ and $R_F = 0.032$, values indicative of an adequate result. The final Rietveld refinement plots are shown in Fig. 4.

Data collection: local program; cell refinement: *FULLPROF* (Rodríguez-Carvajal, 2001); data reduction: local program; program(s) used to solve structure: *EXPO* (Altomare *et al.*, 1999); program(s) used to refine structure: *FULLPROF*; molecular graphics: *PLATON* (Spek, 2009) and *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *FULLPROF* and *PLATON*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3255). Services for accessing these data are described at the back of the journal.

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