

***trans*-Bis(3-acetylpyridine- κ N)diiodo-
platinum(II)**

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In the square-planar title complex, $[\text{PtI}_2(\text{C}_7\text{H}_7\text{NO})_2]$, the Pt atom lies on a crystallographic inversion center, coinciding with an *anti* arrangement of the 3-acetylpyridine ligands. The dihedral angles between the pyridine rings and the Pt coordination plane are $67.5(2)^\circ$, while those between the pyridine rings and the acetyl planes are $20.8(5)^\circ$. The ^{195}Pt NMR resonance of the title complex (CD_2Cl_2) was observed at -3224 p.p.m. The major structural parameters are compared with those from previously reported related structures.

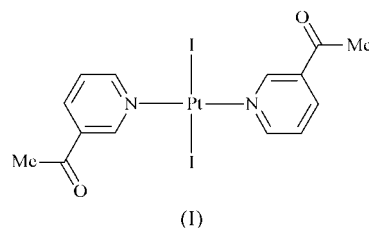
Comment

The anticancer drug cisplatin, *cis*- $\text{Pt}(\text{NH}_3)_2\text{Cl}_2$, and a few other platinum agents are widely used in the clinical treatment of testicular, ovarian, bladder, head and neck tumors (Farrell, 1989; O'Dwyer *et al.*, 1999). Structure–activity rules that emerged from early studies include the assessment that *trans* complexes are therapeutically inactive, as opposed to *cis* complexes – a rule based mainly on the lack of activity for transplatin. Some exceptions from this paradigm were found in 1989, including *trans*- $\text{Pt}(\text{pyridine})_2\text{Cl}_2$ (Farrell *et al.*, 1989), which is even active towards leukemia L1210 cisplatin-resistant cell lines (Van Beusichem & Farrell, 1992). A review of the cytotoxicity of *trans*-platinum complexes has been published recently (Natile & Coluccia, 2001).

Platinum–pyridine derivative compounds not only gained interest because of this rule-breaking finding, but also due to the recently reported anticancer complex *cis*- $\text{PtCl}_2(\text{NH}_3)(2\text{-picoline})$ (AMD473) (Chen *et al.*, 1998; Holford *et al.*, 1998). This compound, active both *via* oral administration and injection, is currently in phase II clinical trials. Other than AMD473 itself and its *trans* isomer (McGowan *et al.*, 2005), recent studies involving platinum complexes containing pyridine derivatives (Ypy) include $\text{Pt}(\text{ESDT})(\text{Ypy})(\text{NH}_3)\text{Cl}$ (Marzano *et al.*, 2002, 2004; Giovagnini *et al.*, 2005), in which the ethyl sarcosinedithiocarbamate ligand (ESDT) is used to reduce nephrotoxic effects, $\text{Pt}(\text{OAc})_2(\text{Ypy})_2$ and $\text{Pt}(\text{OAc})_2(\text{Ypy})(\text{NH}_3)$ (Ma *et al.*, 2005; Quiroga *et al.*, 2006), in which the

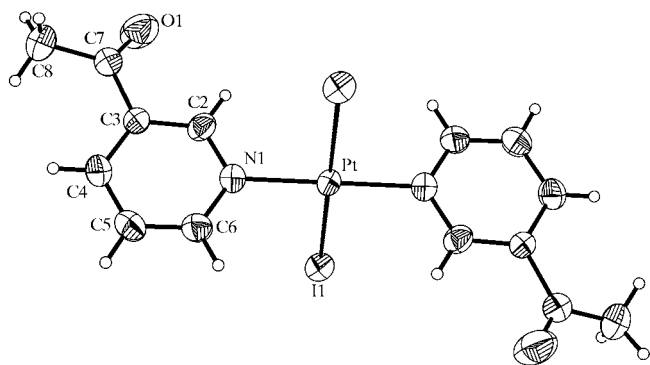
acetate ligands were used in order to obtain water-soluble complexes, and *trans*- $\text{PtCl}_2(4\text{-pic})L$ (Najajreh *et al.*, 2005), where *L* is a non-planar heterocyclic amine ligand. The cytotoxicity of this last compound is improved compared to transplatin (Khazanov *et al.*, 2002; Najajreh *et al.*, 2003), but the non-activity of *trans*- $\text{Pt}(\text{NH}_3)\text{Cl}_2(\text{hmpy})$, *trans*- $\text{Pt}(\text{hmpy})_2\text{Cl}_2$ and $[\text{Pt}(\text{hmpy})_3\text{Cl}]\text{Cl}$ (hmpy is 3- or 4-hydroxymethylpyridine) precludes any generalization.

A few years ago, we undertook a systematic and detailed study of complexes of the type *cis*- and *trans*- $\text{Pt}(\text{Ypy})_2X_2$ (*X* is Cl, I or NO_3) (Tessier & Rochon, 1999, 2001) and their hydrolysis products (Rochon & Tessier, 2002) by various techniques, including multinuclear NMR and X-ray crystallography. The pyridine derivatives included pyridine, the three picoline isomers, 2,4-lutidine and 3,5-lutidine. This series was used to study the steric and ligand basicity effects on the nature of the Pt–Ypy bond, as well as the number of hydrolyzed species in neutral media. As expected, the steric effects preclude formation of hydroxy-bridged oligomers (Rochon & Tessier, 2002). We also observed a relationship of the NMR chemical shifts with the $\text{p}K_a$ of the protonated ligands, indicating that the $\sigma(\text{Ypy} \rightarrow \text{Pt})$ bond is more important than the $\pi(\text{Pt} \leftarrow \text{Ypy})$ back-donation. We established the relative position of the ligands in the *trans*-influence series. In the course of the study, we obtained the title compound, (I), during an attempt to synthesize its *cis* isomer. Compound (I) is the first example of an acetylpyridine–platinum complex to be structurally characterized.



Complex (I) is the *trans* isomer. *Cis*→*trans* isomerization in $\text{Pt}(\text{Ypy})_2X_2$ complexes is not uncommon (Kong & Rochon, 1978; Tessier & Rochon, 1999). The Pt atom lies on a crystallographic inversion center, resulting in an *anti* arrangement of the 3-acetylpyridine ligands. Table 1 lists the geometric parameters. The Pt–N and Pt–I bond distances are identical to those obtained for other *trans*- $\text{Pt}(\text{Ypy})_2\text{I}_2$ complexes (Table 2). The bond angles and the coplanarity of the atoms indicate a square-planar geometry around the Pt center. The O atom in the acetyl group does not participate in any hydrogen bonding or long-range contact.

The dihedral angle between the pyridine ring and the Pt coordination plane is $67.5(2)^\circ$. Table 2 lists the dihedral angles for previously reported *trans*- $\text{Pt}(\text{Ypy})_2\text{I}_2$ complexes, while a more complete list for all square-planar complexes containing the *trans*- $\text{Pt}(\text{Ypy})_2$ moiety, as listed in the Cambridge Structural Database (CSD, Version 5.27; Allen, 2002), is provided in the supplementary material (Table S1). The value obtained for compound (I) lies between the values obtained for the 3-methylpyridine (63.5° ; CSD refcode KARVAA; Tessier & Rochon, 1999) and (3-pyridyl)methane-sulfonamide (69.1° ;

**Figure 1**

A view of the molecule of compound (I), showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level. Unlabeled atoms are generated by the symmetry operator $(-x, -y, -z)$.

ACAZOU; Dodoff *et al.*, 2004) complexes (Table 2). Various factors, such as steric hindrance, the other ligands and intermolecular interactions, could influence the orientation of the pyridine rings. As a general rule, *ortho*-substituted pyridine derivatives are almost perpendicular to the Pt coordination plane [for example, *trans*-Pt(2-Mepy)₂I₂ in Table 2]. The other ligands also seem to influence the dihedral angles. The order is as follows (from greater to smaller): I > Cl \simeq NH₃ \simeq C \equiv C > NO₃. The values obtained for the nitrato complexes are noticeably smaller (39–40°; Tessier & Rochon, 2001).

The acetyl group of (I) is not coplanar with the pyridine ring, as indicated by the dihedral angle of 20.8 (2)° (or see torsion angles in Table 1). This phenomenon is not uncommon for other platinum structures found in the CSD that contain at least one RC(O)–pyridine derivative (Table 3). The first five structures in Table 3 contain only one pyridine derivative, the four following are disubstituted and the rest are tetra-substituted. No general rule can be found, except that values seem to be smaller for monosubstituted complexes. The hydrogen-bonding pattern certainly plays an important role, as it occurs to some extent in all complexes in Table 3, with the exception of *trans*-Pt(4-(COOEt)py)₂Cl₂, where the ethoxy-carbonyl group is almost coplanar with the pyridine ring (1.2°; Camalli *et al.*, 1980). No hydrogen-bonding pattern is observed in (I).

The ¹⁹⁵Pt NMR resonance of compound (I) was observed at –3224 p.p.m. This observation is in the expected range for *trans*-Pt(Ypy)₂I₂ complexes (–3122 to –3264 p.p.m.; Tessier & Rochon, 1999). The reaction of compound (I) with silver nitrate in acetone (Souchard *et al.*, 1990; Tessier & Rochon, 2001) results in the formation of the *trans*-Pt(3-AcPy)₂(NO₃)₂ species, as indicated by the ¹⁹⁵Pt NMR signal (CDCl₃) observed at –1474 p.p.m. The expected values for *trans*-Pt(Ypy)₂(NO₃)₂ are from –1402 to –1481 p.p.m. (Tessier & Rochon, 2001).

Experimental

Compound (I) was prepared according to the published procedure for the preparation of *cis*-Pt(amine)₂I₂ complexes (Souchard *et al.*, 1990) using 3-acetylpyridine as a ligand [yield 75%; m.p. 523–528 K

(decomposition)]. Yellow crystals suitable for X-ray crystallographic analysis were obtained by recrystallization from dichloromethane.

Crystal data

[PtI₂(C₇H₇NO)₂]
 $M_r = 691.16$
 Monoclinic, $P2_1/c$
 $a = 4.632$ (1) Å
 $b = 16.456$ (5) Å
 $c = 11.483$ (3) Å
 $\beta = 98.57$ (3)°
 $V = 865.5$ (4) Å³

$Z = 2$
 $D_x = 2.652$ Mg m^{–3}
 Mo $K\alpha$ radiation
 $\mu = 11.68$ mm^{–1}
 $T = 292$ (2) K
 Platelet, yellow
 $0.31 \times 0.10 \times 0.04$ mm

Data collection

Siemens P4 diffractometer
 $2\theta/\omega$ scans
 Absorption correction: integration
 (XPREP; Bruker, 2003)
 $T_{\min} = 0.313$, $T_{\max} = 0.631$
 2206 measured reflections
 1970 independent reflections

1494 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.028$
 $\theta_{\max} = 27.5^\circ$
 3 standard reflections
 every 97 reflections
 intensity decay: none

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.035$
 $wR(F^2) = 0.078$
 $S = 1.00$
 1970 reflections
 98 parameters

H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0276P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.87$ e Å^{–3}
 $\Delta\rho_{\min} = -0.78$ e Å^{–3}

Table 1

Selected geometric parameters (Å, °).

Pt1–N1	2.026 (6)	C3–C7	1.503 (10)
Pt1–I1	2.6097 (10)	C7–C8	1.486 (11)
O1–C7	1.206 (9)		
N1–Pt1–I1	90.19 (17)	O1–C7–C3	119.5 (7)
N1–Pt1–I1 ⁱ	89.81 (17)	C8–C7–C3	118.8 (7)
O1–C7–C8	121.6 (8)		
C2–C3–C7–O1	19.7 (11)	C2–C3–C7–C8	–158.1 (8)
C4–C3–C7–O1	–161.5 (8)	C4–C3–C7–C8	20.6 (11)

Symmetry code: (i) $-x, -y, -z$.

Table 2

Bond distances (Å) and dihedral angles (°) for reported *trans*-Pt(Ypy)₂I₂ complexes.

CSD refcode	Ypy	Pt–N	Pt–I	Dihedral angle	Reference
KARVEE	2-Mepy	2.024	2.614	81.9	(a)
		2.055	2.616	89.9	(a)
DIPYPT	py	2.035	2.597	74.0	(b)
KARTUS	4-Mepy	2.017	2.603	70.4	(a)
ACAZOU	3-(NHSO ₂ Me)py	2.032	2.607	69.1	(c)
KARVAA	3-Mepy	2.020	2.604	63.5	(a)

References: (a) Tessier & Rochon (1999); (b) Thiele & Wagner (1978); (c) Dodoff *et al.* (2004).

H atoms were placed in idealized positions on C atoms, with C–H = 0.93 and 0.96 Å for aromatic and methyl H atoms, respectively. PLATON (Spek, 2003) was used to check missing symmetry or voids in the structure; none was found.

Data collection: XSCANS (Siemens, 1995); cell refinement: XSCANS; data reduction: XSCANS; program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: SHELXTL (Bruker, 2003); software used to prepare material for publication: SHELXTL.

Table 3

Dihedral angles (°) between the pyridine derivative rings and the planes formed by the $-C-C(O)-R$ atoms in square-planar platinum complexes containing at least one $RC(O)$ -pyridine derivative.

CSD refcode	Compound	Dihedral angle	Reference
MUYBEN	$[Pt\{4-(COOH)py\}(Ph_2MeP)_2-(Ph)(OTf)]$	3.9	(a)
MUYBIR	$[Pt\{4-(COOH)py\}(PEt_3)_2(Ph)]-(OTf)$	11.4	(a)
TEXFEH	$[Pt\{4-(COOH)py\}(2,6-(MeMet)-py)](ClO_4)^+$	5.6	(b)
XURDIX	$Pt\{3-(COO)2-hypp\}(PPh_3)_2Cl^{\ddagger}$	1.9	(c)
FOOXAK	$Pt\{2-(COO)3-hypp\}(PPh_3)_2Cl^{\S}$	3.7	(d)
CLPRPT	$trans-Pt\{4-(COOEt)py\}_2Cl_2$	1.2	(e)
NIXMIQ	$trans-Pt\{3-(CONHR)py\}_2Cl_2^{\P}$	33.4	(f)
XIKJEG	$cis-[Pt\{4-(CONH_2)py\}_2(PEt_3)_2]-(NO_3)_2$	21.0	(g)
JOSDAW01	$cis-[Pt\{4-(CONH_2)py\}_2(NH_3)_2]-(NO_3)_2$	33.5 25.7	(h)
GOKMOI	$Pt\{4-(COO)py\}_2\{4-(COOH)py\}_2$	3.2–21.0	(i)
GOKMIC	$[Pt\{4-(CONH_2)py\}_4]Cl_2^{\dagger\dagger}$	12.0 21.8	(i)
XAYKUD	$[Pt\{4-(CONH_2)py\}_4]Cl_2^{\ddagger\ddagger}$	33.9	(j)
XAYLAK	$[Pt\{4-(CONH_2)py\}_4](PF_6)_2$	7.6–38.4	(j)
JOQSOX	$[Pt\{3-(CONH_2)py\}_4]Cl_2$	20.0 40.4	(k)
JOQSUD	$[Pt\{3-(CONH_2)py\}_4](PF_6)_2$	1.8 8.4	(k)
QEXLAG	$[Pt\{3-(CONHBu)py\}_4](PF_6)_2$	14.0	(l)
QEXLEK	$[Pt\{3-(CONHBu)py\}_4](ReO_4)_2$	19.2	(l)

\dagger 2,6-(MeMet)py = 2,6-bis(methylthiomethyl)pyridine. \ddagger 3-(COO)2-hypp = 2-hydroxynicotinate. \S 2-(COO)3-hypp = 3-hydroxypicolinate. \P 3-(CONHR)py = N-nitroxyethylnicotinamide. $\dagger\dagger$ Tetrakis(4-aldoximepyridine) clathrate. $\ddagger\ddagger$ Heptahydrate. References: (a) Crisp *et al.* (2003); (b) Marangoni *et al.* (1996); (c) Quintal *et al.* (2002); (d) Quintal *et al.* (2000); (e) Camalli *et al.* (1980); (f) Eremenko *et al.* (1997); (g) Kuehl *et al.* (2001); (h) Minacheva *et al.* (1991); (i) Aakeroy *et al.* (1999); (j) Brammer *et al.* (2000); (k) Mareque Rivas & Brammer (1998); (l) Bondy *et al.* (2001).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3046). An additional comparative table is also available. Services for accessing these data are described at the back of the journal.

References

- Aakeroy, C. B., Beatty, A. M. & Leinen, D. S. (1999). *Angew. Chem. Int. Ed. Engl.* **38**, 1815–1819.
 Allen, F. H. (2002). *Acta Cryst.* **B58**, 380–388.
 Bondy, C. R., Loeb, S. J. & Gale, P. A. (2001). *Chem. Commun.* pp. 729–730.
 Brammer, L., Mareque Rivas, J. C., Atencio, R., Fang, S. & Pigge, F. C. (2000). *J. Chem. Soc. Dalton Trans.* pp. 3855–3867.
 Bruker (2003). *SHELXTL* (Version 6.14) and *XPREF* (Version 6.14). Bruker AXS Inc., Madison, Wisconsin, USA.

- Camalli, M., Caruso, F. & Zambonelli, L. (1980). *Cryst. Struct. Commun.* **9**, 721–724.
 Chen, Y., Guo, Z., Parsons, S. & Sadler, P. J. (1998). *Chem. Eur. J.* **4**, 672–676.
 Crisp, M. G., Tiekink, E. R. T. & Rendina, L. M. (2003). *Inorg. Chem.* **42**, 1057–1063.
 Dodoff, N. I., Varga, R. A. & Kovala-Demertzi, D. (2004). *Z. Naturforsch. Teil B*, **59**, 1070–1076.
 Eremenko, I. L., Golubnichaya, M. A., Nefedov, S. E., Sidorov, A. A., Nesterenko, D. A., Konovalova, N. P., Volkova, L. M. & Eremenko, L. T. (1997). *Russ. Chem. Bull.* **46**, 1595–1598.
 Farrell, N. (1989). *Transition Metal Complexes as Drugs and Chemotherapeutic Agents*, pp. 44–46. Dordrecht: Kluwer.
 Farrell, N., Ha, T. T. B., Souchard, J.-P., Wimmer, F. L., Cros, S. & Johnson, N. P. (1989). *J. Med. Chem.* **32**, 2240–2241.
 Giovagnini, L., Marzano, C., Bettio, F. & Fregona, D. (2005). *J. Inorg. Biochem.* **99**, 2139–2150.
 Holford, J., Raynaud, F., Murrer, B. A., Grimaldi, K., Hartley, J. A., Abrams, M. & Kelland, L. R. (1998). *Anti-Cancer Drug Des.* **13**, 1–18.
 Khazanov, E., Barenholz, Y., Gibson, D. & Najajreh, Y. (2002). *J. Med. Chem.* **45**, 5196–5204.
 Kong, P.-C. & Rochon, F. D. (1978). *Can. J. Chem.* **56**, 441–445.
 Kuehl, C. R. J., Tabellion, F. M., Arif, A. M. & Stang, P. J. (2001). *Organometallics*, **20**, 1956–1959.
 Ma, E. S. F., Bates, W. D., Edmunds, A., Kelland, L. R., Fojo, T. & Farrell, N. (2005). *J. Med. Chem.* **48**, 5651–5654.
 McGowan, G., Parsons, S. & Sadler, P. J. (2005). *Inorg. Chem.* **44**, 7459–7467.
 Marangoni, G., Pitteri, B., Bertolasi, V., Ferretti, V. & Gilli, P. (1996). *Polyhedron*, **15**, 2755–2761.
 Mareque Rivas, J. C. & Brammer, L. (1998). *New J. Chem.* **22**, 1315–1318.
 Marzano, C., Bettio, F., Baccichetti, F., Trevisan, A., Giovagnini, L. & Fregona, D. (2004). *Chem. Biol. Interact.* **148**, 37–48.
 Marzano, C., Trevisan, A., Giovagnini, L. & Fregona, D. (2002). *Toxicol. In Vitro*, **16**, 413–419.
 Minacheva, L. K., Golovaneva, I. F., Sakharova, V. G., Stetsenko, A. I., Tikhonova, L. S. & Porai-Koshits, M. A. (1991). *Koord. Khim.* **17**, 517–522. (In Russian.)
 Najajreh, Y., Kasparkova, J., Marini, V., Gibson, D. & Brabec, V. (2005). *J. Biol. Inorg. Chem.* **10**, 722–731.
 Najajreh, Y., Peleg-Shulman, T., Moshel, O., Farrell, N. & Gibson, D. (2003). *J. Biol. Inorg. Chem.* **8**, 167–175.
 Natile, G. & Coluccia, M. (2001). *Coord. Chem. Rev.* **216–217**, 383–410.
 O'Dwyer, P. J., Stevenson, J. P. & Johnson, S. W. (1999). *Clinical status of cisplatin, carboplatin, and other platinum-based antitumor drugs*, in *Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug*, edited by B. Lippert, pp. 31–72. Zurich: Verlag Helvetica Chimica Acta.
 Quintal, S. M. O., Nogueira, H. I. S., Felix, V. & Drew, M. G. B. (2000). *New J. Chem.* **24**, 511–517.
 Quintal, S. M. O., Nogueira, H. I. S., Felix, V. & Drew, M. G. B. (2002). *Polyhedron*, **21**, 2783–2791.
 Quiroga, A. G., Perez, J. M., Alonso, C., Navarro-Ranninger, C. & Farrell, N. (2006). *J. Med. Chem.* **49**, 224–231.
 Rochon, F. D. & Tessier, C. (2002). *Can. J. Chem.* **80**, 379–387.
 Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
 Siemens (1995). *XSCANS*. PC Version 2.20. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
 Souchard, J.-P., Wimmer, F. L., Ha, T. T. B. & Johnson, N. P. (1990). *J. Chem. Soc. Dalton Trans.* pp. 307–310.
 Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
 Tessier, C. & Rochon, F. D. (1999). *Inorg. Chim. Acta*, **295**, 25–38.
 Tessier, C. & Rochon, F. D. (2001). *Inorg. Chim. Acta*, **322**, 37–46.
 Thiele, G. & Wagner, D. (1978). *Chem. Ber.* **111**, 3162–70. (In German.)
 Van Beusichem, M. & Farrell, N. (1992). *Inorg. Chem.* **31**, 634–639.