

Short communication

# The Crystal Structure of a Novel Pt(II) Complex with 2-Hydroxy-6-methylpyridine (Hmhp), *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] · H<sub>2</sub>O

Sabina Grabner,\* and Peter Bukovec

<sup>1</sup> University of Ljubljana, Faculty of Chemistry and Chemical Technology, Večna pot 113, 1000 Ljubljana, Slovenia

\* Corresponding author: E-mail: sabina.grabner@fkt.uni-lj.si

Phone: + 386 (0)1 479 85 23

Received: 16-02-2015

Dedicated to the memory of Prof. Dr. Jurij V. Brenčič.

## Abstract

A novel platinum(II) complex with 2-hydroxy-6-methylpyridine (Hmhp), *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] · H<sub>2</sub>O, crystallizes in the space group *P* 2<sub>1</sub>/*n* with *a* = 11.5505(1) Å, *b* = 8.9467(1) Å, *c* = 14.6047(2) Å and  $\beta$  = 112.3919(6)°. The platinum ion is in the expected square-planar environment. The 2-hydroxy-6-methylpyridine ligand is coordinated to the metal ion in a monodentate manner *via* nitrogen. The plane of the aromatic ligand is nearly perpendicular to the platinum coordination plane. The Pt(II) ion is shielded with pyridine ortho substituents above and below the square coordination plane of platinum. Hydrogen bonding between the complex molecules and the H<sub>2</sub>O molecules of crystallization produces infinite two-dimensional layers. Weak intermolecular interactions of the C–H...Cl type link the layers into a three-dimensional structure.

**Keywords:** Crystal structure, Platinum(II) coordination chemistry, 2-Hydroxy-6-methylpyridine ligand, DmsO ligand, Hydrogen bonding

## 1. Introduction

Cisplatin, *cis*-[PtCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>], an effective anticancer drug, is of limited use in cancer treatment due to development of clinical resistance to cisplatin.<sup>1</sup> One of the crucial factors in resistance mechanisms is an increased inactivation of the drug by extracellular and intracellular thiol-containing scavengers such as glutathione and metallothionein.<sup>2</sup> Based on studies which have shown that steric hindrance towards an axial approach to the square-planar plane of the platinum(II) complexes can significantly slow down the rate of the substitution reaction, *cis*-[PtCl<sub>2</sub>(NH<sub>3</sub>)(2-pic)] (2-pic = 2-methylpyridine), known as picoplatin, was specifically designed to reduce reactivity of the platinum complex toward the sulfur-containing nucleophiles *e.g.* glutathione.<sup>3,4</sup> Substitution of one of the ammine ligands with sterically more demanding 2-methylpyridine has indeed proven to be helpful in overcoming resistance in small-cell lung cancer.<sup>5</sup> Studies have revealed that the hydrolysis of picoplatin is slower than

that of cisplatin which is in agreement with direct steric protection by the methyl group of 2-pic ligand towards an axial approach of nucleophile to Pt(II) ion from above (the pyridine ring is fairly perpendicular (103°) with respect to Pt square plane).<sup>6</sup> Very promising results concerning the cytotoxic activity *in vitro* against various tumor cells and resistant tumor cells have been obtained in the last two decades for *trans* platinum complexes with the general formula *trans*-[PtCl<sub>2</sub>(L)(L')] (L = N-donor aromatic heterocycle, L' = sulphoxide, ammine, N-donor aromatic heterocycle).<sup>7,8</sup>

Despite the extensive research on preparation of *cis* or *trans* Pt(II) complexes with diverse pyridine derivatives we found no reports referring to the use of 2-hydroxy-6-methylpyridine (6-methyl-2-pyridone) (Hmhp), a member of a large family of 2-pyridone ligands. Hmhp is a particularly interesting ligand in the architecture of platinum complexes because it has a hydroxyl substituent in its ortho position which can also serve as a hydrogen-bond acceptor or donor.

Herein, we report the synthesis and the crystal structure of *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] · H<sub>2</sub>O.

## 2. Experimental Section

### 2.1. General Remarks

Chemicals were purchased from Sigma-Aldrich and used as received. K[PtCl<sub>3</sub>(dmsO)] was prepared following a published procedure.<sup>9</sup> The infrared spectra were measured on Nujol using a Perkin Elmer 2000 Fourier Transform infrared spectrometer. Elemental analyses were performed on a Perkin Elmer 2400 CHN Analyzer.

### 2.2. Synthesis of *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] · H<sub>2</sub>O

K[PtCl<sub>3</sub>(dmsO)] (200 mg, 0.478 mmol) was dissolved in water (10 mL). To this solution, 2-hydroxy-6-methylpyridine dissolved in water (57.3 mg, 0.525 mmol) was added dropwise. The colour of the solution changed from yellow to green yellow. The obtained solution was left to stand in a refrigerator at 5 °C. The bright yellow block-shaped crystals of compound *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] · H<sub>2</sub>O that formed after 2 days were collected by filtration and washed with diethyl ether. Yield: 40% (87 mg). Analysis calculated for C<sub>8</sub>Cl<sub>2</sub>H<sub>15</sub>NO<sub>3</sub>SPt: C, 20.37; H, 3.18; N, 2.97%; found: C, 20.50; H, 3.29; N, 2.90%. IR (nujol, cm<sup>-1</sup>): 3596 s, 3408 s, 1615 vs, 1584 vs, 1500 vs, 1338 vs, 1305 vs, 1164 s, 1103 vs, 1028 vs, 985 m, 949 m, 925 m, 785vs, 745 vs, 704 m, 558w, 446 vs, 560w, 475m.

### 2.3. X-ray Crystallography

Data were collected on a Nonius Kappa CCD diffractometer using graphite monochromated Mo-K $\alpha$  radiation ( $\lambda = 0.71073$  Å). The data reduction and integration were performed with the software package DENZO-SMN.<sup>10</sup> Specific absorption corrections were not applied since the averaging of the symmetry-equivalent reflections largely compensated for any absorption effects. The coordinates of the majority of non-hydrogen atoms were found via direct methods using the structure solution program SHELXS.<sup>11</sup> The positions of the remaining non-hydrogen atoms were located by use of a combination of least-squares refinement and difference Fourier maps in the SHELXL-97 program.<sup>11</sup> The position of H<sub>2</sub>O hydrogen atoms could not be located from the residual electron density map. The remaining hydrogen atoms were included in the structure factor calculations at idealized positions. Figures depicting the structures were prepared by ORTEP and Mercury.<sup>12,13</sup> Cell parameters and refinement results are summarized in Table 1.

**Table 1.** Crystallographic data for *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] · H<sub>2</sub>O.

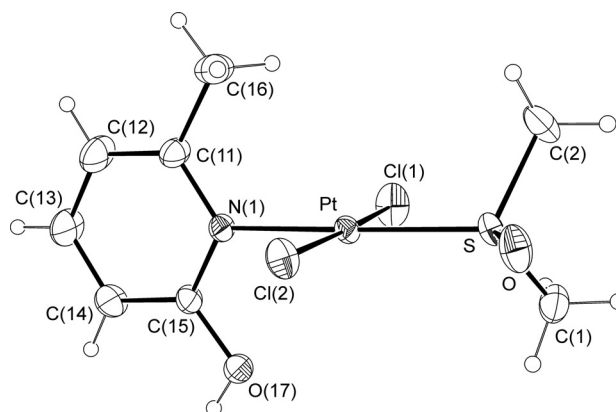
	<i>trans</i> -[PtCl <sub>2</sub> (dmsO)(Hmhp)] · H <sub>2</sub> O
Empirical formula	C <sub>18</sub> H <sub>15</sub> Cl <sub>2</sub> NO <sub>3</sub> PtS
Formula mass [g mol <sup>-1</sup> ]	471.26
Crystal system	monoclinic
Space group	<i>P</i> 2 <sub>1</sub> / <i>n</i>
<i>T</i> [K]	293(2)
<i>a</i> [Å]	11.5505(1)
<i>b</i> [Å]	8.9467(1)
<i>c</i> [Å]	14.6047(2)
$\alpha$ [°]	90
$\beta$ [°]	112.3919(6)
$\gamma$ [°]	90
<i>V</i> [Å <sup>3</sup> ]	1395.44(3)
<i>Z</i>	4
$\lambda$ [Å]	0.71073
$\mu$ [mm <sup>-1</sup> ]	10.579
Collected reflections	6055
Unique reflections, <i>R</i> <sub>int</sub>	3149, 0.0243
Observed reflections	3027
<i>R</i> 1 <sup>[a]</sup> [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	0.0310
<i>wR</i> 2 <sup>[b]</sup> [all data]	0.0809

$$^{\text{[a]}}R1 = \sum ||F_o| - |F_c|| / \sum |F_o|, \quad ^{\text{[b]}}wR2 = \{ \sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2] \}^{1/2}$$

## 3. Results and Discussion

To confirm the structure of our product unambiguously, a single-crystal structure determination was carried out on *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] · H<sub>2</sub>O. An ORTEP drawing of the complex molecule is shown in Figure 1 and relevant bond lengths and angles are given in Table 2. The title compound displays the expected square-planar configuration around platinum.

The four-fold coordination environment of platinum(II) consists of two *trans* positioned chlorides, a 2-hydroxy-6-methylpyridine ligand (Hmhp) and a dimethyl



**Fig. 1** ORTEP drawing of the *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] molecule with the displacement ellipsoids drawn at the 30% probability level.

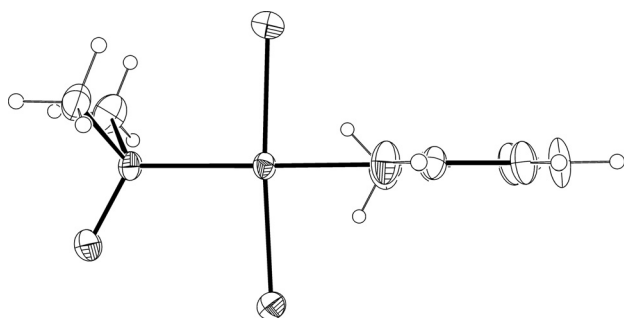
**Table 2.** Relevant structural parameters (Å, °) in the title compound.

Pt–Cl1	2.2984(10)	Pt–N1	2.067(4)
Pt–Cl2	2.2884(9)	Pt–S	2.213(1)
Cl1–Pt–N1	87.94(10)	S–Pt–Cl1	91.43(4)
N1–Pt–Cl2	87.83(10)	Cl1–Pt–Cl2	175.77(4)
Cl2–Pt–S	92.80(3)	N1–Pt–S	178.90(10)

sulfoxide ligand (dmsO) bound through the sulfur atom. The greatest deviation from the best plane defined by N(1), Cl(1), S and Cl(2) donor atoms is 0.011(1) Å. Both of the Cl–Pt–S angles are about 93°. The corresponding angles in other platinum complexes with sulfoxides were also slightly greater than 90°. <sup>14,15</sup> The Pt–S bond length of 2.213(1) Å is close to that found in *trans*-[PtCl(dmsO)(py)<sub>2</sub>]<sup>+</sup>. <sup>15</sup> Similar Pt–S bonds were observed also for *trans*-[PtCl<sub>2</sub>(dmsO)(HQ<sup>Ph</sup>)] (HQ<sup>Ph</sup> = 1-phenyl-3-methyl-4-benzoylpyrazol-5-one), *trans*-[PtCl<sub>2</sub>(dmsO)L] (L = 3-(pyridin-2-ylmethyl)oxazolidin-2-one) and *trans*-[PtCl<sub>2</sub>(dmsO)(2-pic)] (2-pic = 2-methylpyridine). <sup>16–18</sup>

The platinum coordination environment in the latter complexes is highly reminiscent of that in the title compound: two *trans* positioned chlorides, a dmsO ligand and an aromatic ligand bound *via* a nitrogen donor atom. The platinum-to-chloride bond lengths, 2.2884(9) and 2.2984(10) Å, are about the same as found in complexes with the same *trans* influence. For instance, in *trans*-[PtCl<sub>2</sub>(Tz)<sub>2</sub>] (where Tz stands for thiazole) the Pt–Cl bonds are 2.300(5) Å, whereas in *trans*-[PtCl<sub>2</sub>(dmsO)L] (L = 3-(pyridin-2-ylmethyl)oxazolidin-2-one) the Pt–Cl bonds are 2.2965(9) and 2.3025(8) Å. <sup>17,19</sup>

The 2-hydroxy-6-methylpyridine ligand is bound to the metal ion *via* a nitrogen at 2.067(4) Å, a slightly longer distance than 2-picoline in *trans*-[PtCl<sub>2</sub>(dmsO)(2-pic)] with the platinum-to-picoline bonds of 2.046(10) Å. <sup>18</sup> In the latter example, the aromatic ligand lies at an angle of 72.4° with the coordination plane of the platinum atom. Similarly, an almost perpendicular orientation of the aromatic ligand is observed also for *trans*-[PtCl<sub>2</sub>(dmsO)(HQ<sup>Ph</sup>)] and the title compound (see Figure 2). <sup>16</sup>

**Fig. 2.** Another drawing of the title complex emphasizing an almost perpendicular orientation of the Hmhp ligand relative to the platinum coordination plane.

The exact value of the dihedral angle between the plane of the Hmhp ligand and the platinum coordination plane is 88.8(1)°. The explanation lies in the nature of ortho substituents. Namely, minimal steric hindrance can be achieved only with the perpendicular orientation of the Hmhp ligand. In addition, with such an orientation the shielding of the platinum ion by the pair of ortho groups from above and below is achieved. The respective Pt···C(16) and Pt···O(17) contacts are 3.156(5) and 2.975(3) Å. The Hmhp ligand of *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)]·H<sub>2</sub>O displays a monodentate coordination through the nitrogen atom. In view of many coordination modes that either Hmhp or mhp<sup>−</sup> (a monoanion with a deprotonated OH functional group) were shown to adopt, the latter type is rather rare. <sup>20</sup>

Surprisingly, platinum(II) complexes with either form of this ligand are not known. The only structurally characterized platinum complexes are dinuclear metal–metal bonded Pt(III)–Pt(III) complexes with bidentate bridging mhp<sup>−</sup> ligands, [Pt<sup>III</sup><sub>2</sub>(CH<sub>3</sub>)<sub>4</sub>(mhp)<sub>2</sub>(Py)] and [Pt<sup>III</sup><sub>2</sub>(CH<sub>3</sub>)<sub>4</sub>(mhp)<sub>2</sub>(Et<sub>2</sub>S)]. <sup>21,22</sup> The complex molecules and the H<sub>2</sub>O molecules of crystallization in *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] · H<sub>2</sub>O are involved in an intricate pattern of hydrogen bonds (Table 3).

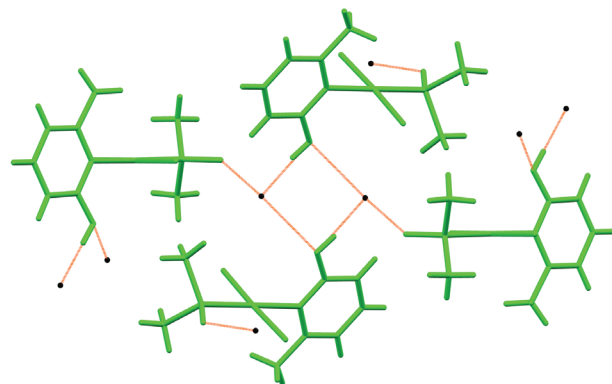
The connectivity pattern may be described as follows. Two H<sub>2</sub>O molecules, each forming three hydrogen

**Table 3.** Hydrogen-bonding interactions in the title compound.

Donor···acceptor <sup>[a]</sup>	Functions, involved in the interaction	Length [Å]
O1 <sup>[b]</sup> ···O	H <sub>2</sub> O···dmsO	2.861(5)
O17···O1	OH(Hmhp)···H <sub>2</sub> O	2.591(4)
O1 <sup>[c]</sup> ···O17	H <sub>2</sub> O···OH(Hmhp)	2.886(5)

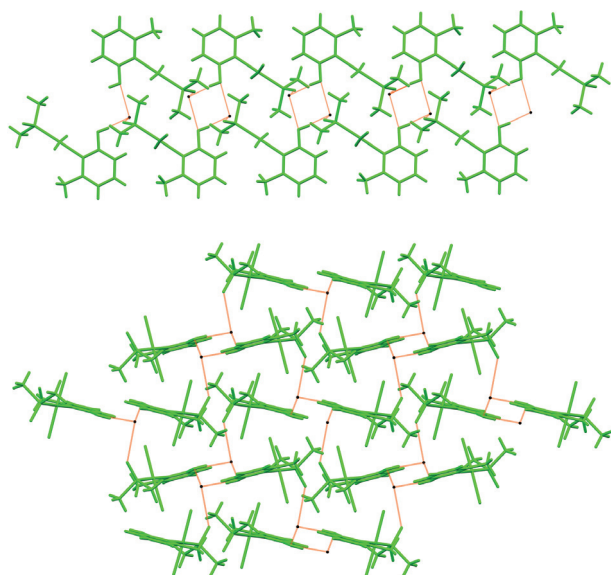
<sup>[a]</sup> O1 denotes a H<sub>2</sub>O oxygen atom and O17 a hydroxyl oxygen.

<sup>[b]</sup> Symmetry code: (i)  $x-0.5, -y-0.5, z-0.5$ . <sup>[c]</sup> Symmetry code: (ii)  $-x, -y, -z+2$ .

**Fig. 3.** Hydrogen-bonding pattern in *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] · H<sub>2</sub>O. The involved functions are: hydroxyl groups, dimethyl sulfoxide oxygen atoms and H<sub>2</sub>O molecules. Color code: black spheres = H<sub>2</sub>O molecules of crystallization, green = complex molecules.

bonding interactions, are bonded to four adjacent complex molecules (Figure 3).

As a result, bimolecular layers are formed (Figure 4). The layers are coplanar with the  $(-1\ 0\ 1)$  plane. The shortest hydrogen bond may be observed between the hydroxyl moiety which acts as a donor and a  $\text{H}_2\text{O}$  molecule acting as an acceptor of hydrogen bond, *i.e.*,  $2.591(4)\ \text{\AA}$ .<sup>23</sup> Weak intermolecular interactions of the  $\text{C}-\text{H}\cdots\text{Cl}$  type may be observed between adjacent layers.



**Fig. 4.** Section of an infinite layer: a view along *b*-axis (top) and along *a*-axis (bottom).

The specific  $\text{C1(a\ dmsol\ methyl\ group)}\cdots\text{Cl1}[-x-0.5, y-0.5, -z+1.5]$  contact is somewhat longer than the sum of the corresponding van der Waals radii,  $3.6059(5)$  *vs.*  $3.45\ \text{\AA}$ .<sup>23</sup> It is to be noted that the same methyl group also weakly interacts with dimethyl sulfoxide of an adjacent complex molecule, *i.e.*,  $\text{C1}\cdots\text{O}[-x-1, -y, -z+1] = 3.432(5)\ \text{\AA}$ .

## 4. Conclusion

The reaction of  $\text{K}[\text{PtCl}_3(\text{dmsol})]$  with 2-hydroxy-6-methylpyridine (Hmhp) in aqueous media gave the novel product  $\text{trans-}[\text{PtCl}_2(\text{dmsol})(\text{Hmhp})] \cdot \text{H}_2\text{O}$ . Platinum(II) complexes with either form of this ligand are not known. Hmhp is bound to the metal ion only *via* the nitrogen atom while its hydroxyl moiety is involved in the pattern of hydrogen bonds as a hydrogen donor. The dihedral angle between the  $\text{PtCl}_2\text{SN}$  plane and pyridine ring is  $88.8(1)^\circ$  and provides shielding of the Pt(II) ion with pyridine ortho substituents above and below the square coordination plane of platinum.

## 5. Supporting Information Available

Crystallographic data of the title compound were deposited at the Cambridge Crystallographic Data Centre (CCDC). The CCDC number is 1008235. Copies of the data can be obtained free of charge from CCDC via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

## 6. Acknowledgement

This work was supported by a grant from the Slovenian Ministry of Education, Science and Sport (grant P1-0134). We would like to express our gratitude to our colleague Barbara Modec for all her suggestions.

## 7. References

1. D. J. Stewart, *Crit. Rev. Oncol. Hematol.* **2007**, *63*, 12–31. <http://dx.doi.org/10.1016/j.critrevonc.2007.02.001>
2. B. Köberle, M. T. Tomcic, S. Usanova, B. Kaina, *Biochim. Biophys. Acta* **2010**, *1806*, 172–182.
3. R. Romeo, D. Minniti, M. Trozzi, *Inorg. Chem.* **1976**, *15*, 1134–1138. <http://dx.doi.org/10.1021/ic50159a031>
4. H. Krüger, R. van Eldik, *J. Chem. Soc. Chem. Commun.* **1990**, 330–331. <http://dx.doi.org/10.1039/c39900000330>
5. N. Patel, C. H. Tang, C. Parham, E. Shocron, G. McMahon, *Cancer Chemother. Pharmacol.* **2011**, *67*, 1389–1400. <http://dx.doi.org/10.1007/s00280-010-1435-5>
6. Y. Chen, Z. Guo, S. Parsons, P. Sadler, *Chem. Eur. J.* **1998**, *4*, 672–676. [http://dx.doi.org/10.1002/\(SICI\)1521-3765\(19980416\)4:4<672::AID-CHEM672>3.0.CO;2-8](http://dx.doi.org/10.1002/(SICI)1521-3765(19980416)4:4<672::AID-CHEM672>3.0.CO;2-8)
7. S. M. Aris, N. P. Farrell, *Eur. J. Inorg. Chem.* **2009**, 1293–1302. <http://dx.doi.org/10.1002/ejic.200801118>
8. M. Coluccia, G. Natile, *Anticancer Agents Med. Chem.* **2007**, *7*, 111–123. <http://dx.doi.org/10.2174/187152007779314080>
9. Y. N. Kukushkin, Y. E. Vyaz'menskii, L. I. Zorina, *Russ. J. Inorg. Chem.* **1968**, *13*, 1573–1576.
10. Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326. [http://dx.doi.org/10.1016/S0076-6879\(97\)76066-X](http://dx.doi.org/10.1016/S0076-6879(97)76066-X)
11. G. M. Sheldrick, SHELXS-97 and SHELXL-97, University of Göttingen, **1997**.
12. L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565. <http://dx.doi.org/10.1107/S0021889897003117>
13. C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler, J. van de Streek, *J. Appl. Cryst.* **2006**, *39*, 453–457. <http://dx.doi.org/10.1107/S002188980600731X>
14. S. G. de Almeida, J. L. Hubbard, N. Farrell, *Inorg. Chim. Acta* **1992**, *193*, 149–157. [http://dx.doi.org/10.1016/S0020-1693\(00\)80346-1](http://dx.doi.org/10.1016/S0020-1693(00)80346-1)
15. A. P. S. Fontes, Å. Oskarsson, K. Löqvist, N. Farrell, *Inorg. Chem.* **2001**, *40*, 1745–1750. <http://dx.doi.org/10.1021/ic000107n>

16. S. A. De Pascali, D. Migoni, M. Monari, C. Pettinari, F. Marchetti, A. Muscella, F. P. Fanizzi, *Eur. J. Inorg. Chem.* **2014**, 1249–1259. <http://dx.doi.org/10.1002/ejic.201301479>
17. A. Sarkar, S. Bhattacharyya, S. Kr Dey, S. Karmakar, A. Mukherjee, *New J. Chem.* **2014**, 38, 817–826. <http://dx.doi.org/10.1039/c3nj00990d>
18. R. Melanson, F. D. Rochon, *Acta Cryst* **1978**, B34, 1125–  
<http://dx.doi.org/10.1107/S0567740878005051>
19. M. Van Beusichem, N. Farrell, *Inorg. Chem.* **1992**, 31, 634–639. <http://dx.doi.org/10.1021/ic00030a021>
20. F. H. Allen, O. Kennard, O. Taylor, *Acc. Chem. Res.* **1983**, 16, 146–153. <http://dx.doi.org/10.1021/ar00089a001>
21. D. P. Bancroft, F. A. Cotton, L R. Falvello, W. Schwotzer, *Inorg. Chem.* **1986**, 25, 763–770. <http://dx.doi.org/10.1021/ic00226a010>
22. D. P. Bancroft, F. A. Cotton, *Inorg. Chem.* **1988**, 27, 4022–4025. <http://dx.doi.org/10.1021/ic00295a025>
23. The corresponding sum of the van der Waals radii is 3.04 Å. Data were taken from Douglas B, McDaniel D, Alexander J (1994) In: Concepts and models of inorganic chemistry, 3rd edn, John Wiley & Sons, Inc, New York.

## Povzetek

Nov Pt(II) kompleks z 2-hidroksi-6-metilpiridinom (Hmhp), *trans*-[PtCl<sub>2</sub>(dmsO)(Hmhp)] · H<sub>2</sub>O, kristalizira v prostorski skupini  $P 2_1/n$  z dimenzijami osnovne celice  $a = 11.5505(1) \text{ \AA}$ ,  $b = 8.9467(1) \text{ \AA}$ ,  $c = 14.6047(2) \text{ \AA}$  in  $\beta = 112.3919(6)^\circ$ . Kovinski ion ima kvadratno planarno razporeditev ligandov. 2-hidroksi-6-metilpiridin je koordiniran na kovinski ion enovezno preko dušikovega atoma. Ravnina aromatskega liganda je skoraj pravokotna na koordinacijsko ravnino platine. Orto substituenta na piridinskem obroču senčita kovinski ion tako nad kot pod kvadratno-planarno koordinacijsko ravnino platine. Vodikove vezi povezujejo molekule kompleksa in molekule vode v neskončne dvodimenzionalne plasti, šibke interakcije tipa C–H...Cl pa povezujejo plasti v tridimenzionalno strukturo.