Carboxylation of 2-Hydroxyethyl-Substituted Tetrachloro(ethane-1,2-diamine)-platinum(IV) Complexes — A New Synthetic Approach to Anticancer Platinum Compounds

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The present study has focused on a general reaction procedure for the derivatization of hydroxyethyl-substituted tetrachloro(ethane-1,2-diamine)platinum(IV) compounds at peripheral hydroxyl groups using acyl chlorides. A new class of platinum(IV) complexes could be synthesized which now opens the possibility for the first time to couple the cytotoxic platinum(IV) moiety to carrier molecules like proteins and antibodies in a very selective way. Moreover, it is now possible to synthesize platinum(IV) complexes with ligands in the equatorial plane which are not very stable in the presence of oxidizing agents.

Introduction

Since its discovery as a very effective antitumour compound, cisplatin,[1,2] *cis*-diamminedichloroplatinum(II), has become the dominant anticancer drug in clinics worldwide. Numerous platinum complexes have been synthesized and tested with respect to their cancerostatic activity so far, but only the second and third generation complexes carboplatin, *cis*-diammine(1,1-cyclobutanedicarboxylato)-platinum(II), and oxaliplatin, (*trans*-*R,R*-cyclohexane-1,2-diamine)oxalatoplatinum(II), are in clinical use today.[3] Because of severe side-effects and limitations of the platinum based drugs in use, research has focused on four major goals: (i) reduction of toxicity; (ii) expansion of platinum chemotherapy to a broader range of cancers; (iii) circumvention of resistance to Pt drugs; and (iv) synthesis of platinum compounds for oral administration. At the moment, only a few Pt complexes are in clinical trials.[4,5] Besides ZD0473[6] a sterically hindered compound and BBR3464[7] a trinuclear complex, satraplatin[8] (JM216) an orally available platinum(IV) compound is under development in the clinic.

The synthesis of JM216 is not only an approach to a new class of Pt^{IV} antitumour agents, but it also constitutes a new synthetic pathway in platinum chemistry, which was previously limited to ligand substitution or oxidation of platinum(II) species with hydrogen peroxide or chlorine gas to the corresponding Pt^{IV} complexes. Kinetically inert hydroxoplatinum(IV) complexes were used and carboxylated with anhydrides, acyl chlorides, pyrocarbonates and isocyanates to form carboxylates, carbonates and carbamates.[9–13] Unfortunately, the reactions are limited to a few carboxylating agents. Moreover, carboxylates will be lost again after reduction of the platinum(IV) species in the body. This would be a problem when linking of antitumour platinum fragments to carrier molecules is planned using the method described before. Therefore, we have focused on derivatization of kinetically inert tetrachloroplatinum(IV) complexes not directly at the metal centre but at peripheral functional groups. For this purpose, hydroxyethyl-substituted tetrachloro(ethane-1,2-diamine)platinum(IV) complexes and acyl chlorides have been used to set up a general reaction procedure.

Results and Discussion

The synthesis of the hydroxyethyl-substituted tetrachloro(ethane-1,2-diamine)platinum(IV) complexes *N*-(2-hydroxyethyl)ethane-1,2-diamine and *N,N′*-bis(2-hydroxyethyl)ethane-1,2-diamine which were selected for the carboxylation reactions starts from K_2PtCl_4 (Scheme 1). In the free diamine ligands there is no chiral atom. After coordination of *N,N′*-bis(2-hydroxyethyl)ethane-1,2-diamine to the platinum(II) centre, two chiral nitrogen atoms are produced resulting in the *trans*-*R,R*-, *trans*-*S,S*-, and *cis*-*R,S*-isomers.[14,15] The coordination of *N*-(2-hydroxyethyl)-ethane-1,2-diamine to platinum generates two isomers (*R* and *S*). The oxidation to the corresponding Pt^{IV} species

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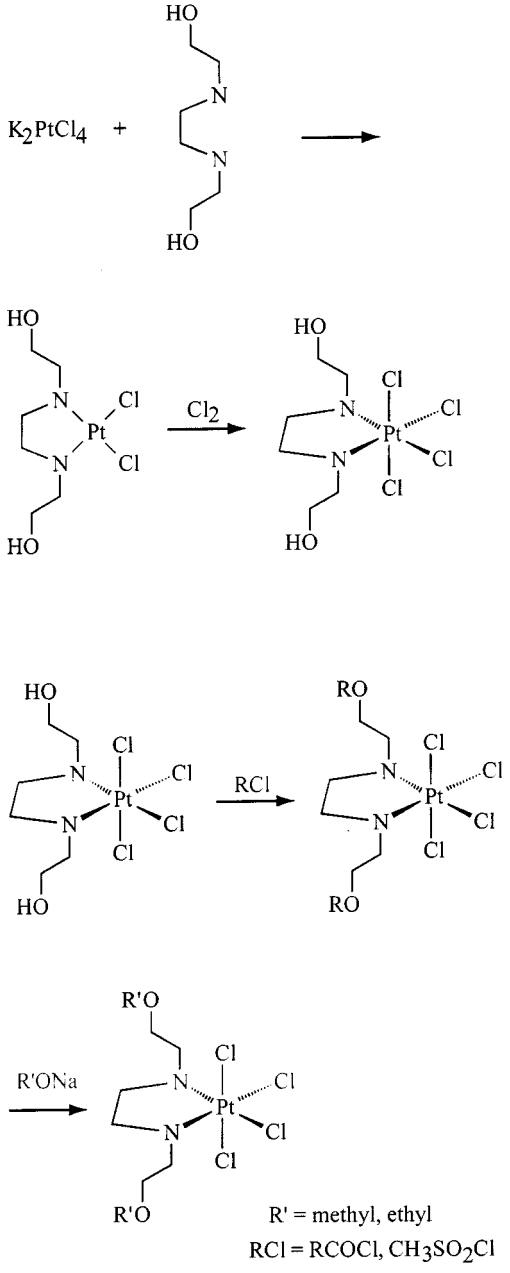

Scheme 1. Synthesis of the tetrachloro[*N,N'*-bis(2-hydroxyethyl)-ethane-1,2-diamine]platinum(IV) starting compound **2** and subsequent derivatization

was done in aqueous suspension with chlorine gas at room temperature.

For carboxylation of the peripheral OH groups, the tetrachloroplatinum(IV) compounds were suspended in dry acetone. After the addition of an excess of dry pyridine and acyl chloride, the mixture was stirred at room temperature and then under reflux. Water was added after cooling to room temperature. The precipitates were filtered off, dried, dissolved and precipitated with an appropriate organic solvent. The ether synthesis was carried out via sulfonation of the OH groups with mesyl chloride and subsequent reaction with sodium ethanolate or sodium methanolate without isolation of the intermediate ester.

The compounds were characterized by elemental analysis and, if soluble enough, by NMR spectroscopy. The theoretical values of the elemental analyses are in good agreement with those found experimentally. During the synthesis of the *N,N'*-bis(2-hydroxyethyl)-substituted (ethane-1,2-diamine)platinum(IV) complexes it was possible to isolate (*OC*-6-32)-*R,S*-tetrachloro[*N,N'*-bis(2-hydroxyethyl)ethane-1,2-diamine]platinum(IV) (**2**) and to resolve its structure by single crystal structure analysis (Figure 1).

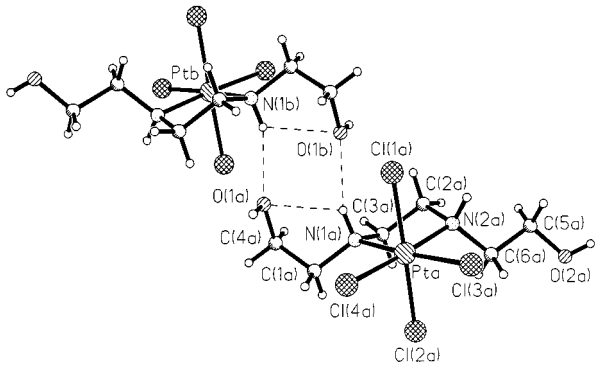

Figure 1. Structure of **2** in the crystal; selected distances (Å) and angles (°): Pt−N(1) 2.093(4), Pt−N(2) 2.086(4), Pt−Cl(1) 2.3094(13), Pt−Cl(2) 2.3202(13), Pt−Cl(3) 2.3227(13), Pt−Cl(4) 2.3259(12), C(2)−C(3) 1.499(7); N(1)−Pt−N(2) 84.57(17), N(1)−Pt−Cl(1) 87.68(12), N(2)−Pt−Cl(1) 86.47(13), N(1)−Pt−Cl(2) 90.54(12), N(2)−Pt−Cl(2) 93.56(13), Cl(1)−Pt−Cl(2) 178.20(5), N(1)−Pt−Cl(3) 174.31(12), N(2)−Pt−Cl(3) 89.87(12), Cl(1)−Pt−Cl(3) 90.81(5), Cl(2)−Pt−Cl(3) 90.99(5), N(1)−Pt−Cl(4) 94.75(12), N(2)−Pt−Cl(4) 176.98(13), Cl(1)−Pt−Cl(4) 90.56(5), Cl(2)−Pt−Cl(4) 89.38(5), Cl(3)−Pt−Cl(4) 90.75(5), C(3)−N(1)−Pt 105.5(3), C(2)−N(2)−Pt 106.9(3), N(2)−C(2)−C(3) 109.6(4), N(1)−C(3)−C(2) 109.2(4)

The O and N atoms are arranged in an octahedral manner around the platinum(IV) centre. The angular sum in the square planar plane (N1, N2, Cl3, Cl4) is 359.94°, with angles of 84.57(17)° (N2−Pt−N1), 90.75(5)° (Cl3−Pt−Cl4), 89.87(12)° (Cl3−Pt−N2) and 94.75(12)° (Cl4−Pt−N1). The Cl1−Pt−Cl2 axis is nearly linear with an angle of 178.20(5)°. The Pt−N and Pt−Cl distances [Pt−N1 2.093(4) Å, Pt−N2 2.086(4) Å, Pt−Cl1 2.3094(13) Å, Pt−Cl2 2.3202(13) Å, Pt−Cl3 2.3227(13), Å Pt−Cl4 2.3259(13) Å] are in the normal range for aminetetrachloroplatinum(IV) complexes. The bond lengths between the axial chloro ligands (Cl1 and Cl2) and Pt are significantly smaller than the corresponding Pt−Cl distances in the equatorial plane. The angular sum in the ethane-1,2-diamineplatinum(IV) chelate (five-membered ring) is 515.77°; the Pt−N1−C3−C2−N2 ring adopts a half-chair conformation with dihedral angles of 19.3, 44.7, 55.7, 35.9 and 8.9° at Pt−N1, N1−C3, C3−C2, C2−N2, and N2−Pt, respectively. The values found are in good agreement with those expected for cyclopentane in a half-chair conformation (13, 34, 42, 34 and 13°, respectively).

Furthermore, the structure of **2** is stabilized by intramolecular and intermolecular hydrogen bonds in the crystal. An intramolecular hydrogen bond is formed between N1 and O1, with a donor acceptor contact distance of 2.812 Å. O1

is also involved in the intermolecular hydrogen bond network with a very weak interaction to the proton at N1 (N1−H1···O1, N1−O1 3.186 Å). Moreover, intermolecular donor−acceptor contacts of 2.745 Å (O1−O2) and 3.254 Å (O2−Cl4), were found. A short intermolecular C−O contact of 3.195 Å (C2−O1, C2−H···O1) could be detected between O1 and C2 of the neighbouring ethane-1,2-diamine unit; this is in the typical range for C−H···O hydrogen bonds. It may indicate attractive interactions further stabilizing the structure of **2** in the crystal.

Besides the well-known procedures for the synthesis of platinum(IV) compounds, for example oxidation with H_2O_2 or Cl_2, or carboxylation of di- and tetrahydroxoplatinum(IV) complexes, a pathway to a new class of Pt^{IV} compounds is demonstrated.

In the present study simple acyl chlorides have been chosen for the carboxylation reaction, while hydroxyethyl-substituted tetrachloro(ethane-1,2-diamine)platinum(IV) complexes were used as the cytotoxic moiety. Tetrachloroplatinum(IV) compounds are kinetically inert so side products can be limited during the carboxylation. However, although it is known that tetrachloroplatinum(IV) complexes are easily reduced to their corresponding platinum(II) counterparts in vivo,[16] it occurs now without loss of the ester residue. Contrary to the limited possibilities of a carrier-mediated transport in platinum(IV) chemistry, a new synthetic approach to anticancer platinum(IV) compounds for drug targeting has been found. This new procedure is not only a completion of the synthesis of tumour inhibiting platinum-based drugs, but it also opens up the possibility for the first time of coupling the cytotoxic moiety to carrier molecules like proteins or antibodies in a very selective way. A platinum(IV) conjugate with albumine has recently been synthesized by us and will be published elsewhere. Moreover, it is now possible to synthesize platinum(IV) complexes with ligands (e.g. ethers, crown ethers) in the equatorial plane which are not very stable in the presence of oxidizing agents.

Conclusion

In conclusion it has been demonstrated that a new class of platinum(IV) complexes could be synthesized starting from tetrachloro[*N*-(2-hydroxyethyl)ethane-1,2-diamine]-platinum(IV) and tetrachloro[*N*,*N*′-bis(2-hydroxyethyl)-ethane-1,2-diamine]platinum(IV) by carboxylation of the peripheral hydroxyl groups with acyl chlorides.

Besides the synthesis of platinum(IV) compounds with ligands in the equatorial plane that are not very stable under oxidizing conditions, it is now possible for the first time to generate platinum(IV) conjugates with proteins or antibodies in a very selective way.

Experimental Section

General Remarks: All chemicals obtained from commercial suppliers were used as received and were of analytical grade. Water was doubly distilled. All synthetic procedures were carried out in the dark.

^1H and ^{13}C NMR experiments were performed at 200.13 MHz (^1H) and 50.32 MHz (^{13}C) on a Bruker Ac 200 MHz spectrometer at 24 °C with standard Bruker pulse programs.

Elemental analyses were performed by the microanalytical laboratory at the Universities of Heidelberg and Vienna.

Synthesis of Hydroxyethyl-Substituted (Ethane-1,2-diamine)platinum(II) and -(IV) Complexes. Dichloro[*N*,*N*′-bis(2-hydroxyethyl)-ethane-1,2-diamine]platinum(II) (1): A solution of *N*,*N*′-bis(2-hydroxyethyl)ethane-1,2-diamine (1.7916 g, 12.09 mmol) in 60 mL of ethanol was treated with K_2PtCl_4 (5.0176 g, 12.09 mmol). After addition of 115 mL of doubly distilled water the pH of the solution was adjusted to 7 using diluted hydrochloric acid and stirred at room temperature. The precipitate was collected over a period of 20 hours. During this time the pH was kept constant at 7 by addition of dilute NaOH. The yellow precipitate was washed with water and dried over P_4O_{10}. $C_6H_{16}Cl_2N_2O_2Pt$ (414.2): calcd. C 17.40, H 3.89, N 6.76, Cl 17.12, Pt 47.10; found C 17.45, H 3.63, N 6.62, Cl 17.45, Pt 47.23. Yield: 3.928 g, 78.5%.

Tetrachloro[*N*,*N*′-bis(2-hydroxyethyl)ethane-1,2-diamine]-platinum(IV) (2): Chlorine gas was bubbled through a suspension of dichloro[*N*,*N*′-bis(2-hydroxyethyl)ethane-1,2-diamine]platinum-(II) (2.000 g, 4.82 mmol) in 45 mL of water at room temperature. After 100 min the yellow precipitate was collected and washed with water (3 × 2 mL). The red filtrate thus obtained was then left to stand at room temperature for several days, after which time more product had precipitated. This precipitate was filtered off and washed with water. The precipitates were dried over P_4O_{10}. $C_6H_{16}Cl_4N_2O_2Pt$ (485.1): calcd. C 14.86, H 3.32, N 5.77, Cl 29.23, Pt 40.22; found C 14.74, H 3.35, N 5.75, Cl 28.94, Pt 40.16. Yield: 1.582 g, 68.0%.

Dichloro[*N*-(2-hydroxyethyl)ethane-1,2-diamine]platinum(II) (1a): A solution of *N*-(2-hydroxyethyl)ethane-1,2-diamine (2.514 g, 24.14 mmol) in 20 mL of water was treated with 150 mL of an aqueous solution of K_2PtCl_4 (10.006 g, 24.11 mmol). The pH was adjusted to 7 using diluted hydrochloric acid and stirred at room temperature. The precipitate was collected over a period of 20 hours. During this time the pH was kept constant at 7 by addition of dilute NaOH. The yellow precipitate was collected, washed with water and dried over P_4O_{10}. $C_4H_{12}Cl_2N_2O_2Pt$ (386.1): calcd. C 12.98, H 3.27, N 7.57, Cl 19.16, Pt 52.71; found C 12.94, H 3.24, N 7.54, Cl 19.28, Pt 52.75. Yield: 5.608 g, 63.0%.

Tetrachloro(*N*-(2-hydroxyethyl)ethane-1,2-diamine)platinum(IV) (2a): Synthesis and workup was performed as described for **2**. $C_4H_{12}Cl_4N_2O_2Pt$ (457.1): calcd. C 10.89, H 2.74, N 6.35, Cl 32.15, Pt 44.23; found C 10.87, H 2.77, N 6.31, Cl 32.09, Pt 44.15. Yield: 1.067 g, 45.0%.

Carboxylation Reactions and Ether Synthesis

Tetrachloro[*N*,*N*′-bis(2-octadecanoyloxyethyl)ethane-1,2-diamine]-platinum(IV) (3): Compound **2** (294.0 mg, 0.606 mmol) was suspended in dry acetone and mixed with dry pyridine (1.078 g, 13.63 mmol) and octadecanoic acid chloride (1.474 g, 4.87 mmol). The mixture was stirred at room temperature overnight and for 5 hours under reflux. After cooling to room temperature, 70 mL of water was added and the resulting mixture was stored overnight in the refrigerator. The precipitate was filtered off and washed thoroughly with water. After drying over P_4O_{10} the crude product was dissolved in 20 mL of chloroform and precipitated with diethyl

ether. The solid was washed several times with diethyl ether. After filtration the precipitate (light brownish) was dried over P_4O_{10}. $C_{42}H_{84}Cl_4N_2O_4Pt$ (1018.0): calcd. C 49.55, H 8.32, N 2.75, Pt 19.16; found C 49.18, H 8.06, N 2.83, Pt 19.52. Yield: 213 mg, 35%.

Tetrachloro[*N*,*N*′-*bis*(2-hexadecanoyloxyethyl)ethane-1,2-diamine]-platinum(IV) (4): The synthesis was carried out as described for **3**. $C_{38}H_{76}Cl_4N_2O_4Pt$ (961.9): calcd. C 47.45, H 7.96, N 2.91, Pt 20.28; found C 47.28, H 7.75, N 2.95, Pt 20.65. Yield: 181 mg, 47%.

{*N*,*N*′-Bis[2-(1-adamantanoyloxy)ethyl]ethane-1,2-diamine}-tetrachloroplatinum(IV) (5): The synthesis was carried out as described for **3**. ^{1}H NMR ($CDCl_3$): δ = 1.3−2.2 ($H_{adamantane}$), 2.7−4.6 (NC*H*$_2$, OC*H*$_2$), 6.3−8.9 (N*H*). ^{13}C NMR ($CDCl_3$): δ = 27.7 (C_{ad}), 36.3 (C_{ad}), 38.8 (C_{ad}), 40.9 (C_{ad}), 53.7 (N*C*H$_2$), 55.1 N*C*H$_2$), 60.7 (O*C*H$_2$), resonance for C=O was not found. $C_{28}H_{44}Cl_4N_2O_4Pt$ (809.6): calcd. C 41.54, H 5.48, N 3.46, Pt 24.10; found C 41.67, H 5.47, N 3.71, Pt 24.33. Yield: 302 mg, 60%.

{*N*,*N*′-Bis[2-(6,7,9,10,12,13,15,16-octahydrobenzo[*b*][1,4,7,10,13]-pentaoxacyclopentadecin-2-carbonyloxy)ethyl]ethane-1,2-diamine}-tetrachloroplatinum(IV) (6): The synthesis was carried out as described for **3**. The excess of free carboxylic acid is soluble in the water/acetone mixture; further workup is not necessary. $C_{36}H_{52}Cl_4N_2O_{14}Pt$ (1073.7): calcd. C 40.27, H 4.88, N 2.61, Pt 18.17; found C 39.96, H 4.84, N 2.71, Pt 18.37. Yield: 284 mg, 76%.

{*N*-[2-(1-Adamantanoyloxy)ethyl]ethane-1,2-diamine}tetrachloro-platinum(IV) (7): The synthesis was carried out as described for **3** with **2a** as starting compound. The precipitate was dried over P_4O_{10}. $C_{15}H_{26}Cl_4N_2O_2Pt$ (603.3): calcd. C 29.86, H 4.34, N 4.64, Pt 32.34; found C 30.28, H 4.39, N 4.39, Pt 32.23. Yield, 212 mg, 56%.

Tetrachloro[*N*,*N*′-*bis*(2-methoxyethyl)ethane-1,2-diamine]-platinum(IV) (8): Mesyl chloride (661 mg, 5.772 mmol) and dry pyridine (913 mg, 11.54 mmol) were added to a suspension of **2** (700 mg, 1.322 mmol) in dry chloroform. The mixture was stirred for 12 hours at room temperature and for 3 hours under reflux. After that, the suspension was evaporated to dryness and the resulting solid washed with ethanol and diethyl ether. The solid (yellow-brownish, 531 mg) was dried over P_4O_{10}. Some of the product (200 mg) was then reacted with an excess of $NaOCH_3$ (168 mg) in 10 mL of dry methanol. After stirring for eight hours at room temperature, the solution was reduced to 3 mL. Water (20 mL) was then added, and the precipitate was filtered off, washed with water and methanol and dried under reduced pressure. $C_8H_{20}Cl_4N_2O_2Pt$ (513.2): calcd. C 18.73, H 3.93, N 5.46, Pt 38.02; found C 18.26, H 4.02, N 5.53, Pt 37.96. Yield: 132 mg, 51%.

Tetrachloro[*N*-(2-ethoxyethyl)ethane-1,2-diamine]platinum(IV) (9): Mesyl chloride (727 mg, 6.348 mmol) and dry pyridine (1.004 g, 12.70 mmol) were added to a suspension of **2a** (700 mg, 1.587 mmol) in dry acetone. The mixture was stirred for 12 hours at room temperature and for 3 hours under reflux. After that, the suspension was filtered and reduced to 10 mL. Dry acetone (40 mL) and $NaOCH_2CH_3$ (2.159 g, 31.74 mmol) were then added. After stirring for eight hours at room temperature, the solution was reduced to 3 mL. Water (20 mL) was then added, and the precipitate was filtered off, washed with water and methanol and dried under reduced pressure. $C_6H_{16}Cl_4N_2O_1Pt$ (469.1): calcd. C 15.36, H 3.44, N 5.97, Pt 41.59; found C 14.79, H 3.40, N 5.72, Pt 41.67. Yield: 362 mg, 49%.

X-ray Crystallographic Study: X-ray diffraction measurements were performed on a Nonius Kappa instrument with a CCD detector at 293 K, using graphite-monochromated Mo-K_α radiation. Crystal data, data collection parameters and structure refinement details are given in Table 1. The structure was solved by direct methods and refined by full-matrix least-squares techniques. The non-H atoms were refined with anisotropic displacement parameters, while H atoms were calculated and allowed to ride. Details of the computer programs used are as follows: data reduction: DATAP;[17] structure solution: SHELXS-97;[18] structure refinement: SHELXL-97;[19] molecular diagram: ORTEP.[20] The scattering factors were obtained from a literature source.[21] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-162129. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Table 1. Crystal data and details of data collection for **2**

	2
Chemical formula	$C_6H_{16}Cl_4N_2O_2Pt$
M (g mol^{-1})	485.10
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	6.990(1)
b (Å)	9.723(1)
c (Å)	19.099(3)
β (°)	92.12(1)
V (Å^3)	1297.2(3)
Z	4
D_c (g cm^{-3})	2.484
μ (cm^{-1})	116.2
F(000)	912
θ range for data collection (°)	2.35−28.99
h range	−8/8
k range	−10/11
l range	−24/24
No. uniq. measd. refls.	2866
No. refls. used in refinement	2866
No. parameters	139
R_{int}	0.0137
R_1 (obs.)	0.0272
wR_2 (all data)	0.0752
S	1.111
Largest diff. peak and hole (eÅ^3)	1.282 and −1.730

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