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Synthesis and Characterization of [(1*R*,2*R*)-*trans*-Diaminocyclohexane]-platinum(II) Coordinated to Sulfur and Selenium Amino Acids

Claudia Rothenburger,[a] Markus Galanski,*[b] Vladimir B. Arion,[b] Helmar Görls,[a] Wolfgang Weigand,*[a] and Bernhard K. Keppler*[b]

Dedicated to Prof. Peter Schuster on the occasion of his 65th birthday

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Dichloro[(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) was activated with Ag_2CO_3 and then treated with (*S*)-methionine, *S*-methyl-(*S*)-cysteine, (*S*)-selenomethionine and *Se*-methyl-seleno-(*S*)-cysteine. The *N*,*S*- and *N*,*Se*-chelated platinum(II) species were isolated as hexafluorophosphate salts and characterized by multinuclear NMR spectroscopy, ESI-MS, IR, elemental analyses and, in the case of the (*S*)-methionine and (*S*)-selenomethionine complexes, by X-ray crystallography.

Introduction

Modern anticancer chemotherapy makes use of a variety of drugs, including metal-based agents. Cisplatin, *cis*-diamminedichloroplatinum(II), is one of the most effective anticancer drugs known to date.[1] It is widely used in the treatment of several solid tumors, including metastatic testicular germ-cell cancer, which has become a curable disease in more than 90% of cases.[2] In order to overcome the severe toxic side-effects of cisplatin-based therapy (nephrotoxicity, neurotoxicity, nausea, and vomiting), the second-generation platinum drug carboplatin, diammine(1,1-cyclobutanedicarboxylato)platinum(II), has been developed and approved for worldwide clinical use.[3,4]

Synthetic variations in the coordinating ligands have led to platinum complexes with 1,2-diaminocyclohexane (DACH) ligands.[5] The most prominent representative of this new class of third-generation platinum complexes is oxaliplatin (Figure 1), which was found to be active in primarily cisplatin- and carboplatin-resistant cell lines and tumors.[6] Recently, oxaliplatin (Eloxatin) has been approved in more than 60 countries all over the world for the treatment of metastatic colorectal cancer, which is the second most frequent cause of cancer death in developed countries.[7]

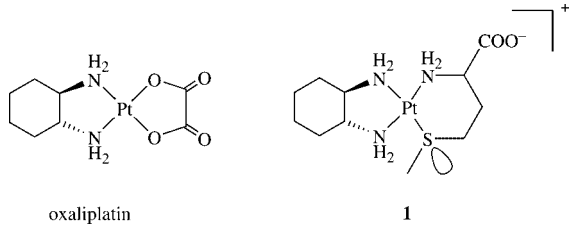

Figure 1. Chemical structures of oxaliplatin and of one of its metabolites (**1**) found in the plasma ultrafiltrate of cancer patients, both of which contain an (*S*)-methionine ligand.

It is widely accepted that cellular DNA is the crucial target for platinum anticancer drugs,[8] but how the drug reaches DNA is still puzzling. Platinum compounds display a high affinity for sulfur, in agreement with the hard/soft acid/base (HSAB) principle, therefore sulfur-containing biomolecules such as amino acids, peptides and proteins in the blood stream, the cytosol, and the nucleus should prevent anticancer platinum drugs from reaching the DNA.[9]

In plasma ultrafiltrate of rats and cancer patients treated with oxaliplatin, different kinds of metabolites, including those with (*S*)-methionine, have been detected in substantial amounts.[10,11] Whether these (*S*)-methionine species are produced from the organism just for detoxification and excretion purposes only, or themselves are involved in the anticancer process, is still a matter of some controversy. This is rather astonishing for a drug that is routinely used in

[a] Institut für Anorganische und Analytische Chemie, Friedrich-Schiller-Universität Jena,
August-Bebel-Strasse 2, 07743 Jena, Germany
Fax: +49-3641-948102
E-mail: c8wewo@uni-jena.de
[b] Institute of Inorganic Chemistry, University of Vienna,
Waehringer Strasse 42, 1090 Vienna, Austria
Fax: +43-1-4277-52680
E-mail: markus.galanski@univie.ac.at
bernhard.keppler@univie.ac.at

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clinical practice and which has reached blockbuster status. Consequently, we have focused on finding an appropriate synthetic procedure for the synthesis of the (*S*)-methionine derivative, which has also been used and extended to other sulfur- and selenium-containing amino acids. Interestingly, it is worthwhile to mention that (*S*)-selenomethionine as well as *Se*-methylseleno-(*S*)-cysteine are currently being evaluated in preclinical[12] and clinical settings[13,14] as chemopreventive agents (also called cytoprotective or rescue agents). Therefore, syntheses of [(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) coordinated to (*S*)-selenomethionine and *Se*-methylseleno-(*S*)-cysteine are of great interest in order to provide these complexes for evaluation of their pharmacological properties in the future.

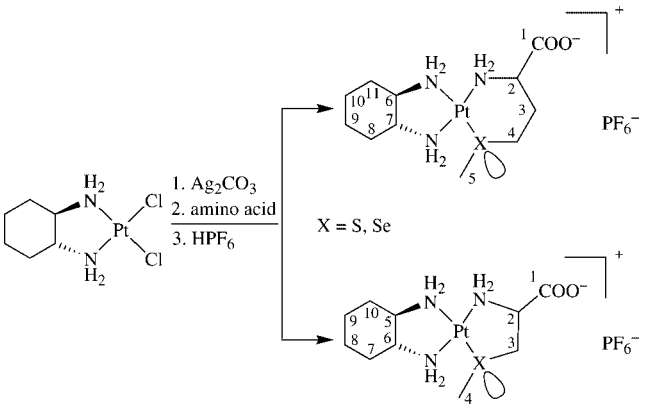

Figure 2. Syntheses of [(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) complexes containing (*S*)-methionine (**1**·PF_6), *S*-methyl-(*S*)-cysteine (**2**·PF_6), (*S*)-selenomethionine (**3**·PF_6), and *Se*-methylseleno-(*S*)-cysteine (**4**·PF_6) as amino acid ligands (stereochemistry at 2-C and X are omitted).

Results and Discussion

There are several reports in the literature dealing with the characterization of complexes like **1** (Figure 1), but in nearly all cases the target complexes were synthesized in small amounts in an NMR tube without isolation. In only one case was the synthesis of **1** described based on several laborious isolation steps, including two HPLC separations.[15] Additionally, the yield was very low (1.2%). In the present work, synthesis of the amino acid platinum(II) complex [(1*R*,2*R*)-*trans*-diaminocyclohexane][(*S*)-methionine-κ^2*N*,*S*]platinum(II) (**1**·PF_6) started from K_2PtCl_4 and (1*R*,2*R*)-*trans*-diaminocyclohexane. The resulting complex dichloro[(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) was treated with silver carbonate in order to remove the chloro ligands (Figure 2). Direct addition of (*S*)-methionine to the activated platinum species afforded a yellow crude product after lyophilization. After dissolution and addition of aqueous HPF_6, the target compound **1**·PF_6 was isolated as a white solid in moderate yield. The decisive steps towards the improved preparation of **1** are the use of Ag_2CO_3 for the activation of the dichloro[(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) complex and the addition of aqueous HPF_6 to this raw product. HPF_6 efficiently removes the carbonate counterions, while PF_6^- is known to be a beneficial partner in the crystallization process. The (*S*)-methionine complex **1**·PF_6 was intensively studied and characterized by ^{1}H, ^{13}C, ^{15}N, ^{31}P, and ^{195}Pt NMR spectroscopy, X-ray diffraction analysis, elemental analysis, IR spectroscopy, and ESI MS.

The ^{1}H NMR spectrum of **1**·PF_6, which was measured in H_2O/D_2O (9:1), can be divided into three spectral regions (Figure 3). The signals deriving from the cyclohexane ring (6-H to 11-H) are found in the upfield region (δ = 1.0–2.3 ppm). The signals of the diastereotopic protons of the CH_2 groups display a marked splitting of up to nearly 0.8 ppm, as could be deduced from the ^{1}H,^{13}C-COSY NMR spectrum. The 2-H, 3-H, and 4-H resonances of the coordinated (*S*)-methionine are found between δ = 2.1 and 3.5 ppm. All N*H* signals are detected most downfield (δ = 4.8–5.8 ppm) and are partly superimposed by the HDO resonance, which was suppressed by pre-saturation. Significant downfield shifts are observed for the signals of protons 4-H and 5-H. In uncoordinated (*S*)-methionine, 4-H and 5-H resonate at δ = 2.58 and 2.07 ppm, respectively. In the target complex, however, two sets of signals at δ = 2.87/2.94 (4-H) and 2.45/2.46 (5-H) ppm are detected. On the contrary, an upfield shift from δ = 3.80 ppm in the free ligand to δ = 3.35/3.44 ppm was found for the signal of the α-proton 2-H. Deconvolution of the ^{1}H NMR spectrum in the region at $\delta \approx$ 2.45 ppm allowed us to estimate the ratio between the two sets of signals: under the experimental conditions (298 K), a ratio of 2:3 was found.

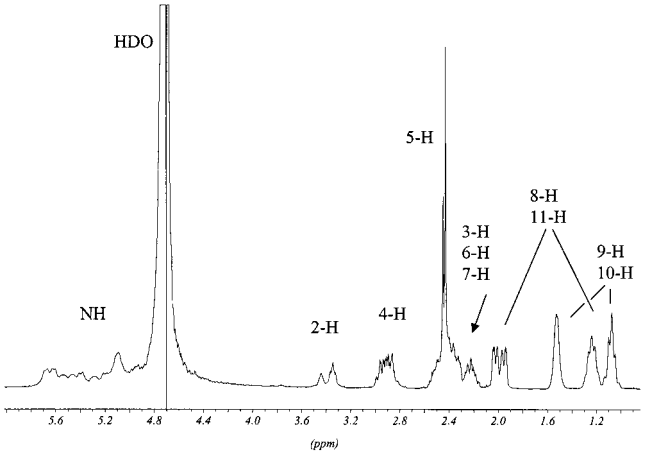

Figure 3. ^{1}H NMR spectrum of **1**·PF_6 with the HDO signal suppressed by pre-saturation.

The coordination sphere around the central platinum ion could be determined on the basis of the ^{195}Pt and ^{15}N chemical shifts. The ^{195}Pt NMR spectrum of **1**·PF_6 displays two signals at δ = –3313 and –3335 ppm for the two diastereoisomers (Figure 4), which is in accordance with a PtN_3S configuration. Deconvolution and integration resulted in the same ratio of 2:3. For PtN_3S-type complexes, ^{195}Pt chemical shifts in the range of δ = –3000 to –3300 ppm are expected,[16,17] whereas PtN_2SO and PtN_2S_2 complexes

resonate in the region af $\delta \approx -2700$ and -3700 ppm,[18] respectively. Besides ^{195}Pt NMR investigations, the ^{15}N chemical shifts were used to characterize the structure of the platinum complexes. Two-dimensional ^{1}H,^{15}N-correlated spectroscopy at natural abundance of the ^{15}N nuclei (spin 1/2, 0.37% natural abundance) has proven to be a powerful tool since the ^{15}N chemical shift of the nitrogen atom is diagnostic for ligands coordinated in *trans* position. Three ^{15}N chemical shifts could be detected for **1**·PF_6: the ^{1}H,^{15}N shift correlation peak at $\delta = -45$ ppm can be assigned to the 2-C*N*H_2 group of (*S*)-methionine *trans* to the nitrogen atom of the DACH ligand,[19] whereas the resonance at $\delta = -14$ ppm can be assigned to 7-C*N*H_2 *trans* to the nitrogen atom of the (*S*)-methionine ligand; the cross peak of 6-C*N*H_2 *trans* to the coordinated thioether group could be detected at $\delta = -4$ ppm.

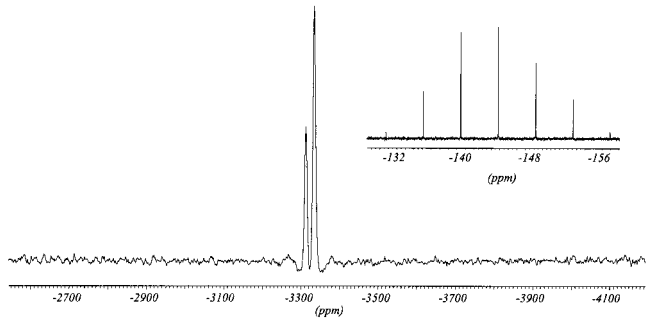

Figure 4. ^{195}Pt and ^{31}P (small inset) NMR spectra of **1**·PF_6.

The two sets of resonances for the (*S*)-methionine ligand in the ^{1}H NMR spectrum as well as two ^{195}Pt signals for **1**·PF_6 are a consequence of the coordination of (*S*)-methionine to the platinum(II) center through the sulfur and nitrogen atoms. As a result, another stereocenter which undergoes slow isomerization at the sulfur atom is formed. When the temperature was raised, the epimerization at the chiral sulfur center became faster, and at 333 K only one signal for the methyl protons 5-H was observed. This process was reversible (Figure S1, Supporting Information). In the case of the cyclohexane protons, the isomerization process seems to have no detectable influence on the proton signals. In the ^{13}C NMR spectra of the free and coordinated (*S*)-methionine ligand, the resonances of the carbonyl carbon atom C-1 are found in close proximity at $\delta = 174.6$ and 176.3/176.8 ppm, respectively. However, a distinct downfield shift of the signal of the *S*-methyl group from $\delta = 14.3$ to 19.6/19.7 ppm was detected. These features are in accordance with an *N*,*S* coordination of (*S*)-methionine to the platinum(II) center as well. The hexafluorophosphate counterion signal appears at $\delta = -143.9$ ppm in the ^{31}P NMR spectrum (Figure 4). Due to the coupling of the phosphorus nucleus with the six fluorine atoms, it appears as a septet with a coupling constant of 710 Hz.

X-ray diffraction quality single crystals were grown by slow concentration of a methanol solution of the complex. The structure of **1**·PF_6 consists of a complex cation **1** (Figure 5) and a complex anion $[PF_6]^-$, which interacts weakly through contacts of the type N−H···F (N1···F6 2.935, N2···F4 3.123, N2···F5 3.352, N2···F6 3.303 Å). The platinum(II) ion has a square-planar coordination geometry as it is chelated by two ligands: (1*R*,2*R*)-*trans*-diaminocyclohexane and (*S*)-methionine. (1*R*,2*R*)-*trans*-DACH acts as a neutral ligand and coordinates to the platinum(II) ion through nitrogen atoms N1 and N2 [Pt–N1 2.051(2), Pt–N2 2.051(2) Å]. These bond lengths are intermediate between those found in oxaliplatin [Pt−N1 2.06(2), Pt−N2 2.04(2) Å].[20] The second ligand, which is negatively charged due to the presence of the ionized carboxyl group, is bound to the platinum(II) ion through the nitrogen atom N3 and the thiomethyl sulfur atom S1. Coordination of the latter to the platinum(II) ion creates a new stereogenic center at the S atom, i.e. (*R*), in addition to the opposite configuration at atom C7. The Pt−N3 [2.062(2) Å] and Pt−S1 [2.2607(6) Å] bonds are markedly longer than the corresponding bonds in two independent molecules of dichloro[(*S*)-methionine-κ^2*N*,*S*)platinum(II)[21] [2.047(8), 2.029(8) and 2.246(2), 2.247(2) Å]. The deviation of the coordinated atoms from the mean plane through PtN1N2N3S1 does not exceed ±0.023 Å. The five-membered chelate ring has a distorted envelope conformation with a clear tendency towards a zigzag arrangement of C1 (+0.55 Å) and C6 (–0.14 Å). The torsion angle $\Theta_{N1–C1–C6–N2}$, which serves as a measure of the deviation of the chelate ring from planarity, is –54.3°. The cyclohexane ring adopts a chair conformation with the amino groups in equatorial positions.

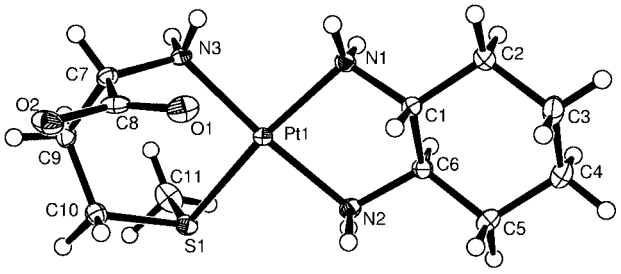

Figure 5. Structure of the cation in **1**·PF_6 with thermal ellipsoids at the 50% probability level. Selected bond lengths [Å] and angles [°]: Pt–N1 2.051(2), Pt–N2 2.051(2), Pt–N3 2.062(2), Pt–S1 2.2607(6), C10–S1 1.810(3), S1–C11 1.805(3), C8–O1 1.235(3), C8–O2 1.276(3); N1–Pt–N2 82.79(10), N3–Pt1–S1 95.35(7), C11–S1–C10–C9 –62.8, N3–C7–C8–O1 –2.2.

The six-membered metallocycle has a chair conformation, which is distorted because of the presence of heteroatoms. The methyl substituent at S1 and the COO^- group are placed on opposite sides of the PtN_3S plane. The orientation of the carboxylato group can be described by the torsion angle $\Theta_{N3–C7–C8–O1}$ (–2.2°). This angle is comparable with that observed on coordination of (*S*)-methionine to the palladium(II) ion in [$PdCl_2$(*S*-met)] (3.7°).[22]

The derivative **2**·PF_6, which contains an *S*-methyl-(*S*)-cysteine ligand, was synthesized in analogy to **1**·PF_6, thereby demonstrating the applicability of this reaction

pathway (Figure 2). Characterization was performed by elemental analysis, mass spectrometry, and IR, ^{1}H, and ^{13}C NMR spectroscopy. Besides the fact that one methylene unit is missing in **2**·PF_6, the ^{1}H and ^{13}C NMR spectra show a similar resonance pattern with respect to the (*S*)-methionine counterpart. The diastereoisomer ratio was found to be nearly 1:1. In **2**·PF_6, the proton signals are shifted to lower field in the amino acid ligand by 0.1 to 0.5 ppm. Comparison with the diastereoisomers of **1**·PF_6 revealed chemical shift differences smaller than 0.1 ppm. These differences are more pronounced in **2**·PF_6, with $\Delta\delta$ values of between 0.1 and 0.2 ppm. Remarkable $\Delta\delta$ values were observed especially in the case of the *S*-Me protons (**1**·PF_6: 0.01 ppm; **2**·PF_6: 0.1 ppm), thereby reflecting the change from the six-membered to the more strained five-membered platinacycle. The latter observation was also confirmed in the ^{13}C NMR spectrum, in which the *S*-Me carbon resonances are found at δ = 19.6 and 19.7 ppm for **1**·PF_6 and at δ = 20.6 and 21.8 ppm for the *S*-methyl-(*S*)-cysteine analog **2**·PF_6.

As mentioned in the introduction, (*S*)-selenomethionine and *Se*-methylseleno-(*S*)-cysteine are currently being evaluated as cytoprotective agents during the treatment with platinum-based anticancer complexes. Administration of either selenium agent results in a decreased platinum-induced toxicity without affecting the tumor-inhibiting properties of the platinum complexes. In the case of cis- and carboplatin (two monodentate ammine ligands), in-depth NMR spectroscopic and ESI-MS studies have been performed.[23,24] These showed that one or both ammine ligands are released from the platinum center upon coordination of (*S*)-selenomethionine. It is widely accepted that such types of complexes are not further involved in the anticancer process.[24] In contrast, for oxaliplatin, which contains the bidentate DACH ligand, release of the coordinated diamine is not expected due to the chelate effect. Therefore, the anticancer-active [(1*R*,2*R*)-*trans*-diaminocyclohexane]-platinum(II) fragment will still remain intact, thus opening up the possibility to selectively synthesize these types of metabolites and study their pharmacological properties.

Synthesis of the (*S*)-selenomethionine complex **3**·PF_6 was performed in analogy to the (*S*)-methionine counterpart (Figure 2). A comparable peak pattern to **1**·PF_6 as well as analogous shift differences with respect to the uncoordinated ligand were observed in the ^{1}H and ^{13}C NMR spectra of **3**·PF_6. The signals of protons 4-H and 5-H are significantly shifted to lower field in the complex, whereas the signal of the 2-H protons displays an upfield shift (e.g. the methyl resonances in **3**·PF_6 at δ = 2.31 and 2.34 ppm occur in the free ligand at δ = 1.93 ppm). The ^{13}C NMR resonances of **3**·PF_6 are equivalent to those observed for the (*S*)-methionine analog: the resonances for the carboxylate group in **3**·PF_6 appear at δ = 176.8 and 176.5 ppm and are slightly shifted in comparison to the free ligand (δ = 174.5 ppm); a distinct downfield shift of the signal of the *Se*-methyl group from δ = 3.6 ppm to δ = 11.7/11.6 ppm was also observed. The diastereoisomer ratio deduced from the ^{1}H NMR spectrum by deconvolution and integration was 2:3, which is the same as for the (*S*)-methionine analog. Comparison of the ^{1}H and ^{13}C NMR spectra of the *Se*-methylseleno-(*S*)-cysteine complex **4**·PF_6 with those of **3**·PF_6 revealed the same pattern as described above for **1**·PF_6 and **2**·PF_6. The ^{1}H chemical shift differences of the diastereoisomers (with respect to the amino acid ligand) were small in the case of **3**·PF_6 ($\Delta\delta < 0.05$ ppm), whereas the $\Delta\delta$ values of **4**·PF_6 were found to be between 0.05 and 0.16 ppm. This general behavior was also confirmed in the ^{13}C NMR spectra, in which the *Se*-Me carbon atom resonates at δ = 11.7 and 11.6 ppm in the case of **3**·PF_6 and at δ = 12.6 and 13.5 ppm for the *Se*-methylseleno-(*S*)-cysteine analog **4**·PF_6. For the latter, a converted diastereoisomer ratio of 3:2 with respect to **3**·PF_6 was found. As explained above, ^{195}Pt and ^{15}N NMR resonances are very indicative of the coordination sphere around the platinum center. Both the ^{195}Pt (Figure 6) and ^{15}N chemical shifts of **3**·PF_6 [^{195}Pt NMR: δ = –3381, –3351 ppm; ^{15}N NMR: δ = –48.0 (2-CNH_2), –18.0 (7-CNH_2), 3.5 (6-CNH_2) ppm] are similar to those observed for the (*S*)-methionine analog **1**·PF_6 (^{195}Pt NMR: δ = –3335, –3313 ppm;^{15}N NMR: δ = –45.2 (2-CNH_2), –14.0 (7-CNH_2), 4.0 (6-CNH_2) ppm] and are therefore in agreement with the structure presented in Figure 2.

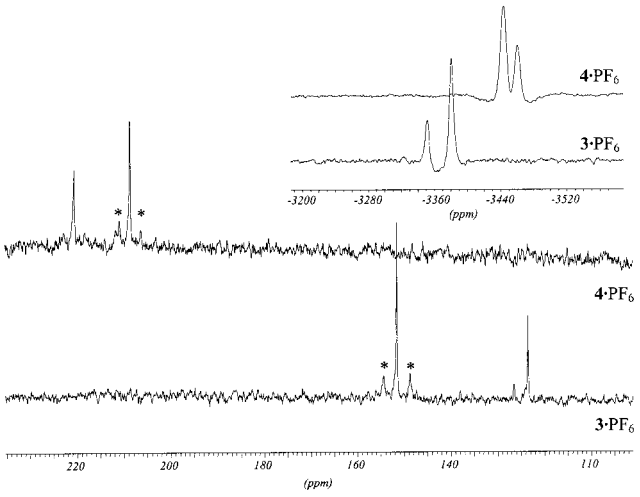

Figure 6. ^{77}Se and ^{195}Pt (small inset) NMR spectra of **3**·PF_6 and **4**·PF_6; ^{195}Pt satellites are marked with asterisks. In the case of the less intense signals, ^{195}Pt satellites could not unequivocally be detected.

From the analytical point of view, the selenium complexes offer an advantage since the selenium atom itself can be investigated by NMR spectroscopy (^{77}Se, spin 1/2, 7.6% natural abundance), thereby ultimately proving coordination of the selenium atom to the platinum center. Besides a remarkable downfield shift in comparison to the free ligand, coordination of the selenium atom is also reflected by the appearance of platinum satellites due to a $^1J_{^{77}Se,^{195}Pt}$ coupling (Figure 6).[25] In **3**·PF_6 and **4**·PF_6, the ^{77}Se chemical shifts of the diastereoisomers appear at δ = 123.5/151.5 and 208.6/220.5 ppm, respectively; the uncoordinated amino acids resonate at δ = 84.8 and 51.2 ppm, respectively.

Coupling of ^{77}Se with the ^{195}Pt central ion in the (*S*)-selenomethionine complex **3**·PF_6 (435 Hz) is thereby significantly larger than in the *Se*-methylseleno-(*S*)-cysteine analog **4**·PF_6 (355 Hz).

Finally, the structure of **3**·PF_6 in the solid state was determined by X-ray crystallography. Single crystals were grown by slow concentration of a methanol solution of the complex. The structural motif of the complex cation **3** is very similar to that of complex **1**. Again, the methyl and carboxylate groups are positioned on opposite sides of the PtN_3Se plane. However, it is worth noting that the Pt–Se distance [2.3777(10) Å] is more than 0.1 Å longer than the corresponding Pt–S distance in **1**. The Pt–Se bond length is comparable to that in dichloro[*O*-methyl-(*S*)-selenomethionine]platinum(II) [2.3697(8) Å].[26] Remarkably, the *Se*-methyl and COOMe groups lie on the same side of the $PtCl_2NSe$ plane in this complex (Figure 7).

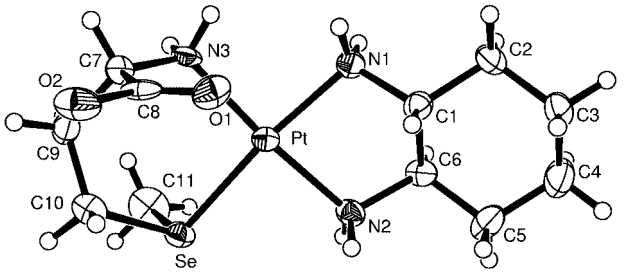

Figure 7. Structure of the cation in **3**·PF_6 with thermal ellipsoids at the 50% probability level. Selected bond lengths [Å] and angles [°]: Pt–N1 2.056(7), Pt–N2 2.061(7), Pt–N3 2.079(7), Pt–Se1 2.377(10), C10–Se1 1.948(9), Se1–C11 1.920(11), C8–O1 1.225(12), C8–O2 1.297(10); N1–Pt–N2 82.80(3), N3–Pt1–Se1 95.20(19), C11–Se1–C10–C9 –60.1, N3–C7–C8–O1 0.50.

Conclusions

[(1*R*,2*R*)-*trans*-Diaminocyclohexane]platinum(II) complexes with coordinated (*S*)-methionine, *S*-methyl-(*S*)-cysteine, (*S*)-selenomethionine, and *Se*-methylseleno-(*S*)-cysteine ligands have been synthesized and characterized by multinuclear NMR spectroscopy, ESI-MS, IR spectroscopy, and elemental analysis. The (*S*)-methionine (**1**·PF_6) and (*S*)-selenomethionine (**3**·PF_6) complexes were also studied by X-ray crystallography. The synthetic procedure resulting in the (*S*)-methionine complex by activation of the dichloro[(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) species with Ag_2CO_3 and isolation of the resulting complex as its hexafluorophosphate salt can also be extended to other sulfur- and selenium-containing amino acids. This is of central interest since three out of the four complexes synthesized are metabolites in cancer patients treated with oxaliplatin. These metabolites can now be evaluated with respect to their pharmacological properties.

Experimental Section

General: All chemicals and solvents used were obtained from commercial suppliers and were used as received. (*S*)-Methione was purchased from Roth and (*S*)-selenomethionine from Acros. *S*-Methyl-(*S*)-methionine, *Se*-methylseleno-(*S*)-cysteine, and HPF_6 (71% in water) were purchased from Fluka, and potassium tetrachloroplatinate(II) was obtained from Johnson Matthey. Dichloro[(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) was prepared according to a standard literature procedure.[27] The synthetic procedures were carried out in a light-protected environment in doubly distilled water and under argon using standard Schlenk-line techniques. Elemental analyses were performed by the microanalytical laboratory at the University of Vienna. ^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H}, ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-COSY, ^{1}H,^{15}N-COSY, ^{195}Pt, and ^{77}Se NMR spectra were recorded in D_2O or H_2O/D_2O (9:1) with a Bruker Avance DPX 400 instrument (UltraShield Magnet) using standard pulse programs at 400.13 (^{1}H), 162.0 (^{31}P), 100.63 (^{13}C), 85.99 (^{195}Pt), 76.32 (^{77}Se), and 40.55 (^{15}N) MHz. Two-dimensional spectra were measured in a gradient-enhanced mode. Chemical shifts were measured relative to the solvent peak (δ = 4.71 ppm), to external 85% H_3PO_4, to external $^{15}NH_4Cl$, to external Ph_2Se_2 at δ = 464 ppm, or to external $K_2[PtCl_4]$ at δ = –1630 ppm. Mass spectra (ESI-MS) were recorded with a Bruker ESQUIRE$_{3000}$ ion trap mass spectrometer. Infrared spectra (4000–400 cm^{-1}) were recorded in KBr pellets using a Perkin–Elmer FTIR instrument.

(*SP*-4-3)-[(1*R*,2*R*)-*trans*-Diaminocyclohexane][(*S*)-methionine-κ^2*N*,*S*]platinum(II)·Hexafluorophosphate (1·PF_6): Silver carbonate (355 mg, 1.29 mmol) was added in one portion to a suspension of dichloro[(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) (500 mg, 1.32 mmol) in 100 mL of water and the mixture was stirred at room temperature overnight. Silver chloride precipitated and was filtered off. (*S*)-Methionine (188 mg, 1.26 mmol) was then added to the bright-yellow solution and the mixture was stirred at room temperature for 8 h. Thereafter, the solution was lyophilized to give a slightly yellow crude product. The solid was dissolved in 5 mL of water in a 10-mL plastic vial and a solution of HPF_6 (146 μL, 1.26 mmol) in 1 mL of water was added. The mixture was lyophilized and the solid was washed with small portions of methanol. The target platinum(II) complex was obtained after filtration by removal of the solvent under reduced pressure and drying over P_2O_5. Yield: 380 mg (50%) [based on the amount of (*S*)-methionine]. $C_{11}H_{24}F_6N_3O_2PPtS$ (602.44): calcd. C 21.93, H 4.02, N 6.98, S 5.32; found C 21.62, H 4.05, N 6.76, S 5.30. ESI-MS (methanol): *m*/*z* = 457.3 [M$^+$]. FT-IR (KBr): $\tilde{\nu}$ = 3414 w (OH), 3080 w (NH), 1617 s (CO) cm^{-1}. Diastereoisomer 1: ^{1}H NMR (400.13 MHz, D_2O): δ = 4.8–5.8 (m, 6 H, NH_2), 3.35 (m, 1 H, 2-H), 2.94 (m, 2 H, 4-H), 2.45 (m, 2 H, 6-H, 7-H), 2.44 (s, 3 H, 5-H), 2.23 (m, 2 H, 3-H), 2.00 (m, 2 H, 8-H, 11-H), 1.54 (m, 2 H, 9-H, 10-H), 1.25 (m, 2 H, 8-H, 11-H), 1.09 (m, 2 H, 9-H, 10-H) ppm. ^{13}C NMR (100.63 MHz, D_2O): δ = 176.8 (1-C), 62.4 (6-C or 7-C), 61.0 (6-C or 7-C), 56.6 (2-C), 32.7 (2 C, 8-C, 11-C), 32.6 (4-C), 28.5 (3-C), 24.2 (2 C, 9-C, 10-C), 19.7 (5-C) ppm. ^{15}N NMR (40.55 MHz, H_2O/D_2O): δ = 4.0 (6-CNH_2), –14.0 (7-CNH_2), –45.2 (2-CNH_2) ppm. ^{31}P NMR (162.00 MHz, D_2O): δ = –143.9 (sept, $^1J_{P,F}$ = 710 Hz, PF_6) ppm. ^{195}Pt NMR (85.99 MHz, D_2O): δ = –3335 ppm. Diastereoisomer 2: ^{1}H NMR (400.13 MHz, D_2O): δ = 4.8–5.9 (m, 6 H, NH_2), 3.44 (m, 1 H, 2-H), 2.87 (m, 2 H, 4-H), 2.46 (m, 2 H, 6-H, 7-H), 2.45 (s, 3 H, 5-H), 2.33 (m, 2 H, 3-H), 2.00 (m, 2 H, 8-H, 11-H), 1.54 (m, 2 H, 9-H, 10-H), 1.25 (m, 2 H, 8-H, 11-H), 1.09 (m, 2 H, 9-H, 10-H) ppm. ^{13}C NMR (100.63 MHz, D_2O): δ = 176.3 (1-C), 62.2 (6-C or 7-C), 61.4 (6-C or 7-C), 55.6 (2-C), 32.7 (2 C, 8-C, 11-C), 31.0 (4-C), 27.7 (3-C), 24.1 (2 C, 9-C, 10-C), 19.6 (5-C) ppm. ^{15}N NMR (40.55 MHz, H_2O/D_2O): δ = 4.0 (6-CNH_2), –14.0 (7-CNH_2), –45.2 (2-CNH_2) ppm. ^{31}P NMR (162.00 MHz, D_2O): δ = –143.9 (sept, $^1J_{P,F}$ = 710 Hz, PF_6) ppm. ^{195}Pt NMR (85.99 MHz, D_2O): δ = –3313 ppm.

(*SP*-4-3)-[(1*R*,2*R*)-*trans*-Diaminocyclohexane][*S*-methyl-(*S*)-cysteine-κ²*N*,*S*]platinum(II)·Hexafluorophosphate (2·PF_6): Silver carbonate (238 mg, 0.86 mmol) was added in one portion to a suspension of dichloro[(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) (334 mg, 0.88 mmol) in 100 mL of water and the mixture was stirred at room temperature overnight. Silver chloride precipitated and was filtered off. *S*-Methyl-(*S*)-methionine (114 mg, 0.84 mmol) was then added to the bright-yellow solution and the mixture was stirred at room temperature for 8 h. Thereafter, the solution was lyophilized to give a slightly yellow crude product. The solid was dissolved in 2 mL of water in a 10-mL plastic vial and a solution of HPF_6 (98 μL, 0.84 mmol) in 1 mL of water was added. The mixture was lyophilized and the solid was washed with small portions of ethanol. The target platinum(II) complex was obtained after filtration by removal of the solvent under reduced pressure and drying over P_2O_5. Yield: 85 mg (17%) [based on the amount of *S*-methyl-(*S*)-cysteine]. $C_{10}H_{22}F_6N_3O_2PPtS$ (588.41): calcd. C 20.41, H 3.77, N 7.14, S 5.45; found C 20.85, H 3.97, N 7.04, S 5.51. ESI-MS (methanol): *m*/*z* = 443.3 [M^+]. FT-IR (KBr): $\tilde{\nu}$ = 3438 w (OH), 3224 w (NH), 1625 s (CO) cm^{-1}. Diastereoisomer 1: ^1H NMR (400.13 MHz, D_2O): δ = 5.0–6.1 (m, 6 H, NH_2), 3.68 (m, 1 H, 2-H), 2.92 (m, 2 H, 3-H), 2.58 (s, 3 H, 4-H), 2.43 (m, 2 H, 5-H, 6-H), 2.01 (m, 2 H, 7-H, 10-H), 1.54 (m, 2 H, 8-H, 9-H), 1.26 (m, 2 H, 7-H, 10-H), 1.09 (m, 2 H, 8-H, 9-H) ppm. ^{13}C NMR (100.63 MHz, D_2O): δ = 173.6 (1-C), 61.4 (2-C), 61.3 (2 C, 5-C, 6-C), 40.8 (3-C), 32.5 (2 C, 7-C, 10-C), 24.1 (2 C, 8-C, 9-C), 20.6 (4-C) ppm. Diastereoisomer 2: ^1H NMR (400.13 MHz, D_2O): δ = 5.0–6.1 (m, 6 H, NH_2), 3.48 (m, 1 H, 2-H), 3.06 (m, 2 H, 3-H), 2.48 (s, 3 H, 4-H), 2.43 (m, 2 H, 5-H, 6-H), 2.01 (m, 2 H, 7-H, 10-H), 1.54 (m, 2 H, 8-H, 9-H), 1.26 (m, 2 H, 7-H, 10-H), 1.09 (m, 2 H, 8-H, 9-H) ppm.^{13}C NMR (100.63 MHz, D_2O): δ = 173.8 (1-C), 62.2 (2-C), 61.3 (2 C, 6-C, 7-C), 40.8 (3-C), 32.5 (2 C, 7-C, 10-C), 24.1 (2 C, 8-C, 9-C), 21.8 (4-C) ppm.

(*SP*-4-3)-[(1*R*,2*R*)-*trans*-Diaminocyclohexane][(*S*)-selenomethionine-κ²*N*,*S*]platinum(II)·Hexafluorophosphate (3·PF_6): Silver carbonate (404 mg, 1.46 mmol) was added in one portion to a suspension of dichloro[(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) (569 mg, 1.50 mmol) in 100 mL of water and the mixture was stirred at room temperature overnight. Silver chloride precipitated and was filtered off. (*S*)-Selenomethionine (283 mg, 1.44 mmol) was then added to the bright-yellow solution and the mixture was stirred at room temperature for 8 h. Thereafter, the solution was lyophilized to give a slightly yellow crude product. The solid was dissolved in 5 mL of water in a 10-mL plastic vial and a solution of HPF_6 (167 μL, 1.44 mmol) in 1 mL of water was added. The mixture was lyophilized and the solid was washed with small portions of methanol and ethanol. The target platinum(II) complex was obtained after filtration by removal of the solvent under reduced pressure and drying over P_2O_5. Yield: 232 mg (25%) [based on the amount of (*S*)-selenomethionine]. $C_{11}H_{24}F_6N_3O_2PPtSe$ (649.33): calcd. C 20.35, H 3.72, N 6.47; found C 19.79, H 3.83, N 6.25. ESI-MS (methanol): *m*/*z* = 504.3 [M^+]. FT-IR: $\tilde{\nu}$ = 3414 w (OH), 3080 w (NH), 1615 s (CO) cm^{-1}. Diastereoisomer 1: ^1H NMR (400.13 MHz, D_2O): δ = 4.9–5.7 (m, 6 H, NH_2), 3.39 (m, 1 H, 2-H), 2.91 (m, 2 H, 4-H), 2.42 (m, 2 H, 6-H, 7-H), 2.37 (m, 2 H, 3-H), 2.31 (s, 3 H, 5-H), 2.00 (m, 2 H, 8-H, 11-H), 1.53 (m, 2 H, 9-H, 10-H), 1.25 (m, 2 H, 8-H, 11-H), 1.09 (m, 2 H, 9-H, 10-H) ppm. ^{13}C NMR (100.63 MHz, D_2O): δ = 176.8 (1-C), 63.0 (6-C or 7-C), 60.6 (6-C or 7-C), 56.9 (2-C), 32.7 (2 C, 8-C, 11-C), 30.9 (3-C), 26.3 (4-C), 24.4 (9-C or 10-C), 24.1 (9-C or 10-C), 11.4 (5-C) ppm. ^{15}N NMR (40.55 MHz, H_2O/D_2O): δ = 3.5 (6-CNH_2), –18.0 (7-CNH_2), –48.0 (2-CNH_2) ppm. ^{31}P NMR (162.00 MHz, D_2O): δ = –141.2 (sept, $^1J_{P,F}$ = 709 Hz, PF_6) ppm. ^{77}Se NMR (76.32 MHz, D_2O): δ = 151.5 (s, $^1J_{Se,Pt}$ = 435 Hz) ppm. ^{195}Pt NMR (85.99 MHz, D_2O): δ = –3381 ppm. Diastereoisomer 2: ^1H NMR (400.13 MHz, D_2O): δ = 4.7–5.7 (m, 6 H, NH_2), 3.39 (m, 1 H, 2-H), 2.87 (m, 2 H, 4-H), 2.42 (m, 2 H, 6-H, 7-H), 2.35 (m, 2 H, 3-H), 2.34 (s, 3 H, 5-H), 2.00 (m, 2 H, 8-H, 11-H), 1.53 (m, 2 H, 9-H, 10-H), 1.25 (m, 2 H, 8-H, 11-H), 1.09 (m, 2 H, 9-H, 10-H) ppm. ^{13}C NMR (100.63 MHz, D_2O): δ = 176.5 (1-C), 62.8 (6-C or 7-C), 61.2 (6-C or 7-C), 56.1 (2-C), 32.6 (2 C, 8-C, 11-C), 29.5 (3-C), 24.4 (4-C), 24.2 (9-C or 10-C), 24.1 (9-C or 10-C), 11.4 (5-C) ppm. ^{15}N NMR (40.55 MHz, H_2O/D_2O): δ = 3.5 (6-CNH_2), –18.0 (7-CNH_2), –48.0 (2-CNH_2) ppm. ^{31}P NMR (162.00 MHz, D_2O): δ = –141.2 (sept, $^1J_{P,F}$ = 709 Hz, PF_6) ppm. ^{77}Se NMR (76.32 MHz, D_2O): δ = 123.5 (s, $^1J_{Se,Pt}$ not detectable) ppm. ^{195}Pt NMR (85.99 MHz, D_2O): δ = –3351 ppm.

(*SP*-4-3)-[(1*R*,2*R*)-*trans*-Diaminocyclohexane][*Se*-methylseleno-(*S*)-cysteine-κ²*N*,*S*]platinum(II)·Hexafluorophosphate (4·PF_6): Silver carbonate (400 mg, 1.45 mmol) was added in one portion to a suspension of dichloro[(1*R*,2*R*)-*trans*-diaminocyclohexane]platinum(II) (560 mg, 1.47 mmol) in 100 mL of water and the mixture was stirred at room temperature overnight. Silver chloride precipitated and was filtered off. *Se*-Methylseleno-(*S*)-cysteine (260 mg, 1.43 mmol) was added to the bright-yellow solution and the mixture was stirred at room temperature for 8 h. Thereafter, the solution was lyophilized to give a slightly yellow crude product. The solid was dissolved in 5 mL of water in a 10-mL plastic vial and a solution of HPF_6 (166 μL, 1.43 mmol) in 1 mL of water was added. The mixture was lyophilized and the solid was washed with small portions of methanol and ethanol. The target platinum(II) complex was obtained after filtration by removal of the solvent under reduced pressure and drying over P_2O_5. Yield: 152 mg (17%) [based on the amount of *Se*-methylseleno-(*S*)-cysteine]. $C_{10}H_{22}F_6N_3O_2PPtSe$ (635.30): calcd. C 18.91, H 3.49, N 6.61; found C 18.53, H 3.82, N 6.33. ESI-MS (methanol): *m*/*z* = 490.2 [M^+]. FT-IR: $\tilde{\nu}$ = 3418 w (OH), 3079 w (NH), 1622 s (CO) cm^{-1}. Diastereoisomer 1: ^1H NMR (400.13 MHz, D_2O): δ = 4.9–6.1 (m, 6 H, NH_2), 3.60 (m, 1 H, 2-H), 2.82 (m, 2 H, 3-H), 2.45 (s, 3 H, 4-H), 2.41 (m, 2 H, 5-H, 6-H), 2.02 (m, 2 H, 7-H, 10-H), 1.53 (m, 2 H, 8-H, 9-H), 1.26 (m, 2 H, 7-H, 10-H), 1.09 (m, 2 H, 8-H, 9-H) ppm. ^{13}C NMR (100.63 MHz, D_2O): δ = 174.0 (1-C), 62.9 (6-C or 7-C), 62.8 (2-C), 61.1 (5-C or 6-C), 32.7 (7-C or 10-C), 32.6 (7-C or 10-C), 32.0 (3-C), 24.3 (8-C or 9-C), 24.2 (8-C or 9-C), 12.6 (4-C) ppm. ^{15}N NMR (40.55 MHz, H_2O/D_2O): δ = 5.2 (6-CNH_2), 0.5 (7-CNH_2), –21.2 (2-CNH_2) ppm. ^{31}P NMR (162.00 MHz, D_2O): δ = –141.2 (sept, $^1J_{P,F}$ = 709 Hz, PF_6) ppm. ^{77}Se NMR (76.32 MHz, D_2O): δ = 208.6 (s, $^1J_{Se,Pt}$ = 355 Hz) ppm. ^{195}Pt NMR (85.99 MHz, D_2O): δ = –3444 ppm. Diastereoisomer 2: ^1H NMR (400.13 MHz, D_2O): δ = 4.9–6.1 (m, 6 H, NH_2), 3.65 (m, 1 H, 2-H), 2.98 (m, 2 H, 3-H), 2.41 (m, 2 H, 5-H, 6-H), 2.37 (s, 3 H, 4-H), 2.02 (m, 2 H, 7-H, 10-H), 1.53 (m, 2 H, 8-H, 9-H), 1.26 (m, 2 H, 7-H, 10-H), 1.09 (m, 2 H, 8-H, 9-H) ppm. ^{13}C NMR (100.63 MHz, D_2O): δ = 174.0 (1-C), 62.7 (6-C or 7-C), 62.6 (2-C), 61.0 (5-C or 6-C), 32.7 (7-C or 10-C), 32.6 (7-C or 10-C), 32.1 (3-C), 24.3 (8-C or 9-C), 24.1 (8-C or 9-C), 13.5 (4-C) ppm. ^{15}N NMR (40.55 MHz, H_2O/D_2O): δ = 5.2 (6-CNH_2), 0.5 (7-CNH_2), –21.2 (2-CNH_2) ppm. ^{31}P NMR (162.00 MHz, D_2O): δ = –141.2 (sept, $^1J_{P,F}$ = 709 Hz, PF_6) ppm. ^{77}Se NMR (76.32 MHz, D_2O): δ = 220.5 (s, $^1J_{Se,Pt}$ not detectable) ppm. ^{195}Pt NMR (85.99 MHz, D_2O): δ = –3461 ppm.

Structure Determination: X-ray diffraction measurements were performed with Nonius Kappa CCD diffractometers. Single crystals were positioned at 35 and 29.1 mm from the detector and 591 and 256 frames were measured, each for 20 s over a 1.5 and 1.0° scan width (for complexes **1**·PF_6 and **3**·PF_6, respectively). The data were processed using the Denzo-SMN software package.[28] Crystal data,

data collection parameters, and structure-refinement details for **1**·PF_6 and **3**·PF_6 are given in Table 1. The structures were solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. H atoms of **1**·PF_6 were located on difference Fourier maps and isotropically refined. All hydrogen atoms of **3**·PF_6 were included at calculated positions with fixed thermal parameters. Computer programs: structure solution: SHELXS-97;[29] refinement: SHELXL-97;[30] molecular diagrams: ORTEP;[31] computer: Pentium II; scattering factors.[32] CCDC-606533 (**1**·PF_6) and -606879 (**3**·PF_6) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Crystal data and details of data collection for **1**·PF_6 and **3**·PF_6.

	1·PF_6	**3**·PF_6
Empirical formula	$C_{11}H_{24}F_6N_3O_2PPtS$	$C_{11}H_{24}F_6N_3O_2PPtSe$
Formula mass	602.45	649.35
Space group	$P2_12_12_1$	$P2_12_12_1$
a [Å]	6.5662(1)	6.6369(4)
b [Å]	12.4846(1)	12.5878(7)
c [Å]	22.1143(2)	22.0958(16)
V [Å^3]	1812.85(4)	1846.0(2)
Z	4	4
λ [Å]	0.71073	0.71073
$\rho_{calcd.}$ [g cm^{-3}]	2.207	2.336
Crystal size [mm]	0.29 × 0.17 × 0.14	0.32 × 0.30 × 0.28
T [K]	120	183
μ [cm^{-1}]	80.13	97.28
Flack parameter	0.006(4)	–0.017(14)
R_1[a]	0.0127	0.043l
wR_2[b]	0.0299	0.079
GOF[c]	1.110	1.030

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$. [c] GOF = $\{\Sigma[w(F_o^2 - F_c^2)^2]/(n - p)\}^{1/2}$, where n is the number of reflections and p is the total number of parameters refined.

Supporting Information (see footnote on the first page of this article): Temperature-dependent ^{1}H NMR spectra of **1**·PF_6.

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[1] *Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug* (Ed.: B. Lippert), Verlag Helvetica Chimica Acta, Zürich, Switzerland, and Wiley-VCH, Weinheim, Germany, **1999**.
[2] M. A. Jakupec, M. Galanski, B. K. Keppler, *Rev. Physiol. Biochem. Pharmacol.* **2003**, *146*, 1–54.
[3] P. J. O'Dwyer, J. P. Stevenson, S. W. Johnson, *Drugs* **2000**, *59*, 19–27.
[4] M. Galanski, M. A. Jakupec, B. K. Keppler, *Curr. Med. Chem.* **2005**, *12*, 2075–2094.
[5] E. Wong, C. M. Giandomenico, *Chem. Rev.* **1999**, *99*, 2451–2466.
[6] M. Galanski, M. A. Jakupec, B. K. Keppler, in *Metal Compounds in Cancer Chemotherapy* (Eds.: J. M. Pérez, M. A. Fuertes, C. Alonso), Research Signpost, Kerala, **2005**, p. 155–185.
[7] J. Graham, M. Muhsin, P. Kirkpatrick, *Nat. Rev. Drug Discovery* **2004**, *3*, 11–12.
[8] E. R. Jamieson, S. J. Lippard, *Chem. Rev.* **1999**, *99*, 2467–2498.
[9] J. Reedijk, *Chem. Rev.* **1999**, *99*, 2499–2510.
[10] F. R. Luo, S. D. Wyrick, S. G. Chaney, *Cancer Chemother. Pharmacol.* **1999**, *44*, 19–28.
[11] M. A. Graham, G. F. Lockwood, D. Greenslade, S. Brienza, M. Bayssas, E. Gamelin, *Clin. Cancer Res.* **2000**, *6*, 1205–1218.
[12] M. Rao, M. N. A. Rao, *J. Pharm. Pharmacol.* **1998**, *50*, 687–691.
[13] M. Fakih, S. Cao, F. A. Durrani, Y. M. Rustum, *Clin. Colorectal Cancer* **2005**, *5*, 132–135.
[14] S. Cao, F. A. Durrani, Y. M. Rustum, *Clin. Cancer Res.* **2004**, *10*, 2561–2569.
[15] S. K. Mauldin, M. Plescia, F. A. Richard, S. D. Wyrick, R. D. Voyksner, S. G. Chaney, *Biochem. Pharmacol.* **1988**, *37*, 3321–3333.
[16] T. G. Appleton, J. W. Connor, J. R. Hall, *Inorg. Chem.* **1988**, *27*, 130–137.
[17] M. El-Khateeb, T. G. Appleton, L. R. Gahan, B. G. Charles, S. J. Berners-Price, A. Bolton, *J. Inorg. Biochem.* **1999**, *77*, 13–21.
[18] K. M. Williams, C. Rowan, J. Mitchell, *Inorg. Chem.* **2004**, *43*, 1190–1196.
[19] Y. Chen, Z. Guo, P. Murdoch, E. Zang, P. J. Sadler, *J. Chem. Soc., Dalton Trans.* **1998**, *9*, 1503–1508.
[20] M. A. Bruck, R. Bun, M. Noji, K. Inagaki, Y. Kidani, *Inorg. Chim. Acta* **1984**, *92*, 279–284.
[21] C. Wilson, M. L. Scudder, T. W. Hambley, H. C. Freeman, *Acta Crystallogr., Sect. C* **1992**, *48*, 1012–1015.
[22] A. Caubet, V. Moreno, E. Molins, C. Miravitlles, *J. Inorg. Biochem.* **1992**, *48*, 135–152.
[23] Q. Liu, J. Zhang, X. Ke, Y. Mei, L. Zhu, Z. Guo, *J. Chem. Soc., Dalton Trans.* **2001**, *6*, 911–916.
[24] Q. Liu, J. Lin, P. Jiang, J. Zhang, L. Zhu, Z. Guo, *Eur. J. Inorg. Chem.* **2002**, *8*, 2170–2178.
[25] J. A. Beaty, M. M. Jones, L. Ma, *Chem. Res. Toxicol.* **1992**, *5*, 647–653.
[26] M. Carland, B. F. Abrahams, T. Rede, J. Stephenson, V. Murray, W. A. Denny, W. D. McFadyen, *Inorg. Chim. Acta* **2006**, *359*, 3252–3256.
[27] M. Galanski, A. Yasemi, S. Slaby, M. A. Jakupec, V. B. Arion, M. Rausch, A. A. Nazarov, B. K. Keppler, *Eur. J. Med. Chem.* **2004**, *39*, 707–714.
[28] Z. Otwinowski, W. Minor, in *Methods in Enzymology*, vol. 276 ("Macromolecular Crystallography", part A) (Eds.: C. W. Carter Jr, R. M. Sweet), Academic Press, New York, **1997**, p. 307–326.
[29] G. M. Sheldrick, *SHELXS-97, Program for Crystal Structure Solution*, University Göttingen, Germany, **1997**.
[30] G. M. Sheldrick, *SHELXL-97, Program for Crystal Structure Refinement*, University Göttingen, Germany, **1997**.
[31] C. K. Johnson, Rep. ORNL-5138, OAK Ridge National Laboratory, OAK Ridge, TN, **1976**.
[32] *International Tables for X-ray Crystallography* (Ed.: A. J. C. Wilson), Kluwer Academic Press, Dordrecht, The Netherlands, **1992**, vol. C, Tables 4.2.6.8 and 6.1.1.4.

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