



universität
wien

MASTERARBEIT

Titel der Masterarbeit

„Synthesis and Characterization of Novel Di- and
Tetracarboxylatoplatinum(IV) Complexes“

verfasst von

Doris Höfer, BSc

angestrebter akademischer Grad

Master of Science (MSc)

Wien, 2013

Studienkennzahl lt. Studienblatt: A 066 862

Studienrichtung lt. Studienblatt: Masterstudium Chemie

Betreut von: Ao. Univ.-Prof. Mag. Dr. Markus Galanski



universität
wien

MASTER THESIS

Title

„Synthesis and Characterization of Novel Di- and
Tetracarboxylatoplatinum(IV) Complexes“

Author

Doris Höfer, BSc

Submitted in partial fulfillment of the requirements for the degree of
Master of Science (MSc)

Vienna, 2013

Studienkennzahl lt. Studienblatt: A 066 862

Studienrichtung lt. Studienblatt: Masterstudium Chemie

Betreut von: Ao. Univ.-Prof. Mag. Dr. Markus Galanski

Acknowledgement

I would like to thank everybody who supported me during the time of this master thesis, especially:

O. Univ.-Prof. Dr. Dr. Bernhard Keppler for the great opportunity to work in his group.

Ao. Univ.-Prof. Mag. Dr. Markus Galanski for supervising this thesis, numerous NMR measurements, proofreading and his support whenever it was needed.

My colleague Mag. Dr. Hristo Varbanov for advice and discussions and for creating a pleasant working atmosphere.

The NMR service team (Dipl. Chem. Paul-Steffen Kuhn, Dr. Verena Pichler, DI Melanie Schmidlehner, Dr. Michael Primik, Dipl. Chem. Nadine Sommerfeld, Ao. Univ.-Prof Dr. Markus Galanski) for all NMR measurements.

Ao. Univ.-Prof. Dr. Vladimir Arion and Dipl.-Wirtschaftsing. (FH) Alexander Roller for measuring and refining the crystal structures and for always trying to find measurable crystals.

Mag. Theiner and his team of the microanalytical laboratory for all elemental analysis and Mag. Anatolie Dobrov for mass spectra measurements.

Mag. Elfriede Limberger for support in all administrative affairs and Mihai Odoleanu for supply of chemicals and glassware.

My colleagues from Lab 7 and 8 and all other members of the group for their help, the pleasant atmosphere and the nice coffee breaks and lunch times. In particular, I would like to thank Carmen Hackl for accompanying me throughout my studies and for being a great friend.

All my friends and my flat mates for the daily breakfasts and the countless hours spent together.

Finally, I want to express my gratitude to my parents and my sister for their great support in every possible way and to Mario Kapl for his encouragement and help.

Abstract

The origin of platinum chemotherapeutics goes back to the accidental discovery of B. Rosenberg who observed ceased cell proliferation exposing *E. coli* bacteria to transition metal compounds. Currently, cisplatin, carboplatin and oxaliplatin are in worldwide clinical use and applied in nearly 50% of all chemotherapies. Nevertheless, further research is driven to find complexes with milder toxicological profiles and activity in resistant tumor cells.

New strategies focus on platinum(IV) complexes which can be activated inside the tumor cells and possess therefore selectivity for malicious tissue. Platinum(IV) complexes are kinetically inert which makes them amenable to oral administration. Moreover, modifications of the additional axial ligands permit optimization of parameters which are of great importance for *prodrugs*. In particular, axial carboxylate ligands show promising results by conferring intermediate reduction potentials and providing a possibility to vary lipophilicity.

The scope of this work included the synthesis and characterization of different platinum(IV) complexes with axial carboxylate ligands. Therefore, three different (ethane-1,2-diamine)platinum(II) complexes with equatorial acetate, iodide and bromide ligands were generated. Subsequent oxidation with hydrogen peroxide afforded platinum(IV) analogs which were carboxylated exploiting the nucleophilic character of the coordinated hydroxide ligands.

Carboxylation was performed with anhydrides which were prepared using succinic anhydride as starting material. Succinic acid mono esters were obtained by stirring under reflux in selected alcohols, whereas anhydrous methanol, ethanol and pentanol were applied. Transesterification reactions with acetic anhydride delivered the desired anhydrides.

Finally, three tetracarboxylato(ethane-1,2-diamine) and two dicarboxylato(ethane-1,2-diamine)diiodido platinum(IV) complexes as well as one dibromidodicarboxylato(ethane-1,2-diamine)platinum(IV) complex were obtained with either two axial methoxy-, ethoxy-, or pentoxyoxobutanoato ligands.

The final compounds were characterized in detail with elemental analysis and multinuclear NMR spectroscopy including ^1H , ^{13}C , ^{195}Pt as well as $^1\text{H}^1\text{H}$ COSY, $^1\text{H}^{13}\text{C}$ HSQC, $^1\text{H}^{15}\text{N}$ HSQC and $^1\text{H}^{13}\text{C}$ HMBC measurements.

In addition, ESI-MS and IR spectra were recorded and X-ray crystallographic data were collected for the following three complexes:

- (OC-6-13)-Diacetato(ethane-1,2-diamine)bis((4-ethoxy)-4-oxobutanoato)platinum(IV)
- (OC-6-33)-(Ethane-1,2-diamine)bis((4-ethoxy)-4-oxobutanoato)diiodidoplatinum(IV)
- (OC-6-33)-Dibromido(ethane-1,2-diamine)bis((4-methoxy)-4-oxobutanoato)platinum(IV).

Zusammenfassung

Den Grundstein für die derzeitigen Platinchemotherapeutika hat B. Rosenberg gelegt als er zufällig beobachtete, dass Übergangsmetallverbindungen die Zellteilung von *E. coli* Bakterien stoppen. Heute sind Cisplatin, Carboplatin und Oxaliplatin weltweit zugelassen und finden in fast 50% aller Chemotherapien Anwendung. Aktuelle Forschungsarbeiten verfolgen das Ziel, Komplexe zu entwickeln, die ein milderes toxikologisches Profil und Aktivität in resistenten Tumorzellen aufweisen.

Neue Strategien haben den Fokus auf Platin(IV) Verbindungen gelegt. Diese können in den Tumorzellen aktiviert werden und besitzen somit eine Selektivität für Krebsgewebe. Platin(IV) Komplexe sind kinetisch inert und ermöglichen daher eine orale Applikation. Außerdem können, durch Veränderungen an den axialen Liganden, Parameter angepasst werden, die für *Prodrugs* von großer Bedeutung sind. Vor allem axiale Carboxylatliganden zeigen dabei vielversprechende Erfolge, da sie den Komplexen ein mittleres Reduktionspotential verleihen und somit die Möglichkeit bieten, die Lipophilie anzupassen.

Diese Arbeit beschäftigt sich mit der Synthese und Charakterisierung verschiedener Platin(IV) Komplexe mit axialen Carboxylatliganden. Als Ausgangsmaterial wurden drei (Ethan-1,2-diamin)platin(II) Komplexe mit äquatorialen Acetat-, Iodido- oder Bromidoliganden synthetisiert. Die darauffolgende Oxidation mit Wasserstoffperoxid lieferte die entsprechenden Platin(IV) Analoga, die aufgrund des nukleophilen Charakters ihrer Hydroxidliganden eine weitere Carboxylierung ermöglichten.

Die Carboxylierungsreaktionen wurden mit Anhydriden durchgeführt welche im Vorhinein hergestellt wurden. Durch Refluxieren von Bernsteinsäureanhydrid in den entsprechenden Alkoholen wurden Bernsteinsäuremonoester erhalten. Bei diesen Reaktionen wurden wasserfreies Methanol, Ethanol und Pentanol eingesetzt. Eine anschließende Umesterung mit Essigsäureanhydrid lieferte dann die gewünschten Anhydride.

Im Zuge dieser Arbeit wurden drei Tetracarboxylato(ethan-1,2-diamin)platin(IV) und zwei Dicarboxylato(ethan-1,2-diamin)diiodidoplatin(IV) Komplexe sowie ein Dibromidodicarboxylato(ethan-1,2-diamin)platin(IV) Komplex hergestellt, welche jeweils zwei axiale Methoxy-, Ethoxy-, oder Pentoxyoxobutanoatoliganden aufwiesen.

Die Endprodukte wurden eingehend mit Elementaranalyse und multinuklearer NMR Spektroskopie untersucht, wobei ^1H , ^{13}C , ^{195}Pt sowie $^1\text{H}^1\text{H}$ COSY, $^1\text{H}^{13}\text{C}$ HSQC, $^1\text{H}^{15}\text{N}$ HSQC und $^1\text{H}^{13}\text{C}$ HMBC Messungen durchgeführt wurden.

Des Weiteren wurden ESI-MS und IR Spektren aufgenommen; Kristallstrukturen konnten für folgende drei Komplexe erhalten werden:

- (OC-6-13)-Diacetato(ethan-1,2-diamin)bis((4-ethoxy)-4-oxobutanoato)platin(IV)
- (OC-6-33)-(Ethan-1,2-diamin)bis((4-ethoxy)-4-oxobutanoato)diiodidoplatin(IV)
- (OC-6-33)-Dibromido(ethan-1,2-diamin)bis((4-methoxy)-4-oxobutanoato)platin(IV).

Table of Contents

Acknowledgement	I
Abstract.....	III
Zusammenfassung.....	V
Table of Contents	VII
1 Introduction.....	1
1.1 A short history about platinum chemotherapeutics	1
1.2 Platinum(II) complexes	2
1.2.1 Platinum complexes in clinical use	2
1.2.2 Cisplatin – mode of action	3
1.2.3 Drawbacks.....	4
1.2.4 Structure activity relationships of platinum(II) complexes.....	5
1.2.5 Strategies to overcome resistance and side effects	6
1.3 Platinum(IV) complexes	9
1.3.1 Activation by reduction.....	9
1.3.2 Structure activity relationships of platinum(IV) complexes	10
1.3.3 Novel platinum(IV) complexes.....	11
1.4 Synthesis	13
1.4.1 Platinum(II) complexes.....	13
1.4.2 Oxidation	14
1.4.3 Carboxylation.....	15
1.5 Research Objective and Achievements	16
2 Results and Discussion.....	17
2.1 Synthesis	17
2.1.1 Platinum(II) complexes.....	19
2.1.2 Oxidation	20

2.1.3	Carboxylation.....	20
2.1.4	Anhydrides.....	20
2.2	Characterization.....	21
2.2.1	Elemental analysis.....	21
2.2.2	ESI-MS	22
2.2.3	NMR	23
2.2.4	IR.....	27
2.2.5	Crystal structures.....	29
3	Experimental.....	35
3.1	General remarks	35
3.2	Chemicals	35
3.3	Instrumental analysis.....	36
3.4	Platinum(II) complexes	37
3.5	Oxidation.....	41
3.6	Carboxylation	47
3.7	Synthesis of the anhydrides.....	61
	List of Abbreviations.....	67
	Bibliography	69
	Curriculum Vitae	73

1 Introduction

1.1 A short history about platinum chemotherapeutics

In 1965 Barnett Rosenberg [1] reported for the first time the inhibiting effect of transition metal compounds on cell division processes. He investigated the effect of electromagnetic radiation on *E. coli* bacteria and discovered that electrolysis products ceased the cell proliferation. Detailed studies showed that platinum complexes like *cis*-[Pt(NH₃)₂Cl₂] and *cis*-[Pt(NH₃)₂Cl₄], which were formed through electrolysis of the rather inert platinum electrodes, were responsible for this observation. Thereby *cis*-[Pt(NH₃)₂Cl₂] was already known since 1844 as Peyrone's Chloride. In 1969 first *in vivo* studies of *cis*-[Pt(NH₃)₂Cl₂] with solid sarcoma-180 tumors revealed the outrageous potential of cisplatin as anticancer agent [2]. Only 13 years after the accidental discovery, cisplatin (Figure 1.1 1) was approved by the FDA for testicular and bladder cancer. Nevertheless, dose limiting side effects and the restricted spectrum of activity in other cancer types pushed further investigations on platinum drugs. In 1989 carboplatin (Figure 1.1 2) was admitted for ovarian cancer. The exchange of chlorides with a 1,1-cyclobutanedicarboxylato chelating ligand resulted in a less toxic pharmacological profile. To expand the therapeutic spectrum of platinum drugs, a third generation platinum drug, oxaliplatin (Figure 1.1 3), was approved by the FDA in 2004 [3]. Oxaliplatin is applied in combination with 5-fluoracil in metastatic colorectal cancer [4]. Nowadays cisplatin, carboplatin and oxaliplatin are used in nearly 50% of all chemotherapies [5]. The development of improved platinum complexes, which is still in progress, generated countless compounds of which only few reached clinical trials and none further admission. An overview of complexes which entered clinical trials can be found in [5, 6].

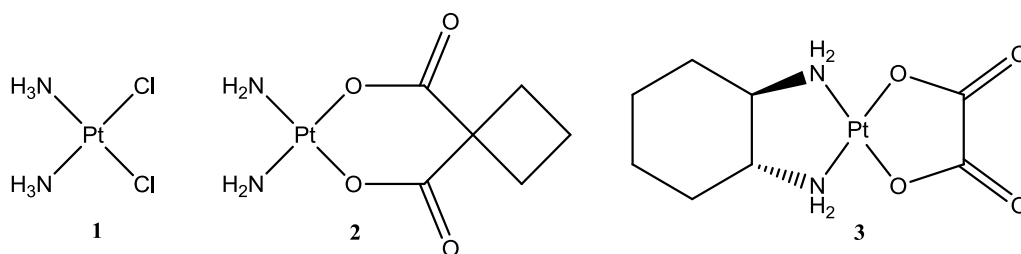


Figure 1.1. Cisplatin 1, carboplatin 2, oxaliplatin 3 – the only platinum complexes which are in worldwide clinical use.

1.2 Platinum(II) complexes

1.2.1 Platinum complexes in clinical use

Cisplatin

In general, cisplatin, *cis*-diamminedichloridoplatinum(II), is used in combination with other cytostatic agents. It is administered intravenously in chloride solution to avoid hydrolysis of the ligands. The best results with cisplatin are achieved in testicular cancer with a cure rate of 90%. Further application fields are ovarian and bladder cancer, non-small cell lung cancer, small cell lung cancer, esophageal cancer and individually other solid tumors [6]. During the treatment severe side effects occur including nausea, vomiting, nephrotoxicity, ototoxicity, neuropathy and myelosuppression [7]. Even with hydration and diuretics, nephrotoxicity is dose limiting in most cases [8]. Emetogenesis is treated by administration of serotonin-receptor antagonists [7].

Carboplatin

Carboplatin, *cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II), exhibits a milder toxicological profile than cisplatin which can be ascribed to the less reactive chelate ligand. Since cisplatin and carboplatin have the same ammine carrier ligands, they form the same platinum-DNA adducts and show activity in same tumor cells [5]. The main application of carboplatin is ovarian cancer, whereat myelosuppression represents its dose limiting side effect [5, 7].

Oxaliplatin

Oxaliplatin, *trans*-(*R,R*)-(cyclohexane-1,2-diamine)oxalatoplatinum(II), succeeded in overcoming cisplatin resistance in several cell lines through introduction of the bidentate (*R,R*)-cyclohexane-1,2-diamine (DACH) ligand. Oxaliplatin is approved for metastatic colorectal cancer in combination with 5-fluoracil. While sensory neuropathy is dose limiting, oxaliplatin treatment shows no nephrotoxicity or ototoxicity. Nausea and vomiting are treated with antiemetics [7].

Cisplatin, carboplatin and oxaliplatin are in worldwide use, while nedaplatin (Figure 1.2 4) is only approved in Japan, lobaplatin (Figure 1.2 5) in China and heptaplatin (Figure 1.2 6) in the Republic of Korea [5].

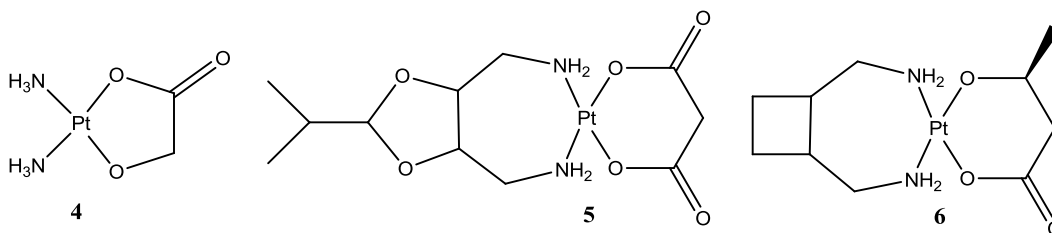


Figure 1.2. Regionally approved platinum complexes – nedaplatin 4 (Japan), lobaplatin 5 (China), heptaplatin 6 (Republic of Korea).

1.2.2 Cisplatin – mode of action

Cisplatin enters the cell via passive diffusion and active transport mechanisms [9], which are effected mainly by copper transport receptors CTR1 [10]. Inside the cell, cisplatin hydrolyzes and the chloride leaving groups are replaced by water, forming more reactive mono $[\text{Pt}(\text{NH}_3)_2\text{Cl}(\text{OH}_2)]^+$ and diaqua species $[\text{Pt}(\text{NH}_3)_2(\text{OH}_2)_2]^{2+}$ [11]. It is supposed that the ligand exchange occurs primarily inside the cells as a result of the higher chloride concentration in the blood which impedes hydrolysis (4 mM versus 100 mM) [6]. The aquated platinum species enter the nucleus and the labile aqua ligands are replaced by N7 of purine bases [12, 13]. Thereby monoaquaplatinum species are responsible for most DNA binding [14]. The resulting platinum-DNA adducts introduce a distortion in the DNA scaffold and proteins, which recognize this event, may trigger apoptosis pathways or cause other cellular responses like replication arrest, transcription inhibition or cell-cycle arrest [10, 12, 13] (Figure 1.3). The distortion in double helix is mainly caused by 1,2-intrastrand GpG crosslinks (60-65%), but also ApG (20-25%) and GpXpG intrastrand crosslinks (2%) as well as interstrand and DNA-protein crosslinks were found [6]. The highest platinum-DNA adduct levels are observed in dividing cells as a consequence of the reduced histone methylation which induces relaxation of the condensed chromatin and increases the accessibility of the DNA [14]. Finally, less than 1% of the administered cisplatin reaches the DNA. The greater part reacts with proteins and low molecular weight biomolecules. Moreover, platinum is excreted very fast and efficiently through the kidneys [6].

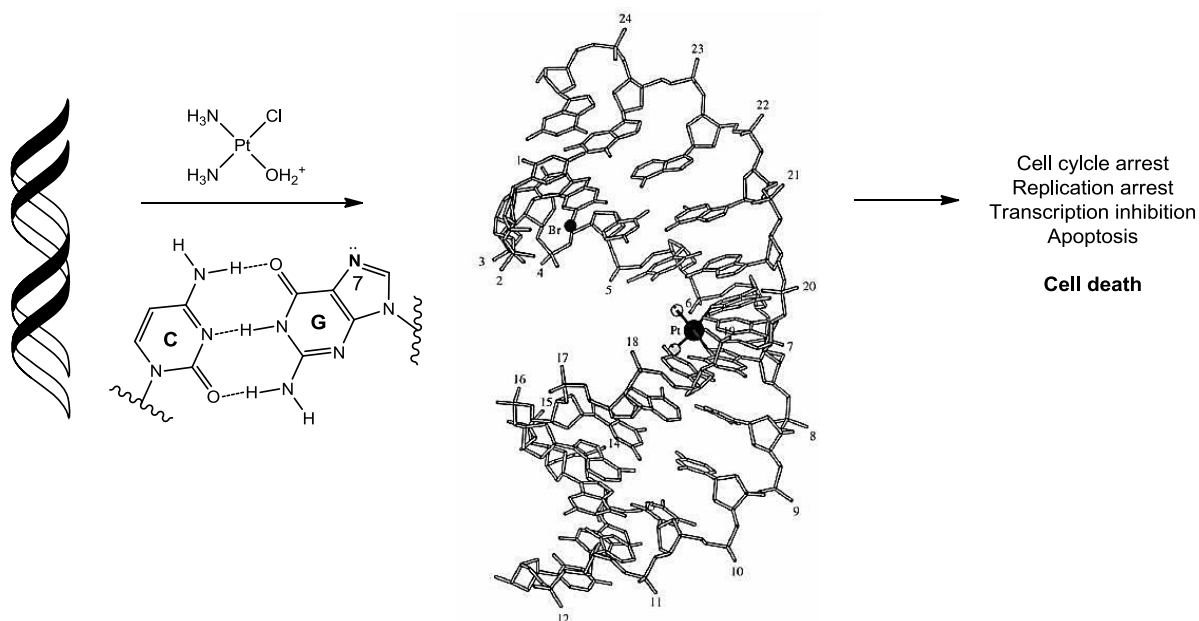


Figure 1.3. Cisplatin's mode of action. Hydrolyzed cisplatin binds to the N7 of purine bases and causes distortion in DNA scaffold. The crystal structure from Takahara et al. [15] shows the major platinum-DNA adduct – a 1,2-GpG crosslink, cf. [10].

1.2.3 Drawbacks

One of the major drawbacks of platinum chemotherapy are the severe side effects. Platinum complexes do not discriminate between tumor cells and healthy tissue and show uptake in all readily proliferating cells, causing severe damages. The coordination to proteins in the kidneys and the inner ear is related to the typical nephro- and ototoxicity. As electrophiles, the intravenously administered platinum compounds also react with all kinds of nucleophiles and bind to plasma proteins leading to severe side effects or inactivation. The high affinity of platinum(II) to sulfur can be explained by the HSAB principle [5, 6, 16].

Many cancer cells show resistance to platinum based chemotherapy, whereas a difference can be made between acquired and intrinsic resistance. The rapid adaptation of cells to chemotherapeutic damages and the inhibition of apoptosis signaling pathways during the treatment are known as acquired resistance. In contrast, the intrinsic resistance is a result of inherited characteristics from healthy tissue which developed sophisticated defense mechanisms as protection against toxins [17].

The mechanisms of resistance for cisplatin are excessively investigated and important effects have been discovered. Some events are controversially discussed and still new processes are found. In this section an overview of the main resistance mechanisms will be given (Figure 1.4). A more detailed disquisition can be found in the literature, eg. [3, 10, 14, 17].

Reduced accumulation

The cellular uptake of cisplatin depends on the extracellular environment. Studies showed that a low extracellular pH and salts like CaCl_2 and CuCl often increase cisplatin uptake while other reagents like NaCl , mannitol or KCl impede accumulation. Another important role plays the interaction with plasma proteins, since protein-bound platinum is less cytotoxic and cellular uptake decreases. CTR1 deficiency is also involved in resistance as cisplatin uptake is partly mediated by these copper transporters. An increased efflux either from the cells or from the nucleus into the cytoplasm is also related to reduced cisplatin accumulation. Copper-transporting P-type adenosine triphosphatases ATP7A and ATP7B are involved in this event [10, 14].

Cytosolic detoxification

Inside the cells, platinum(II) readily reacts with sulfur containing species such metallothioneins and glutathione, a cysteine containing tripeptide. An increased glutathione level is frequently observed in resistant cell lines [10]. The resistance is based on inactivation through binding and in context of glutathione also enhanced DNA repair and reduction of cisplatin induced oxidative stress was observed [14].

DNA repair

The outrageous activity of cisplatin in testicular carcinoma results from its low capacity to repair platinum-DNA adducts. Platinum damages are primarily repaired by the nucleotide excision repair system (NER). Another important pathway is the DNA mismatch repair (MMR). During MMR, defective cells undergo several ineffective repair cycles until a finally apoptotic response is triggered. Cells which are deficient in MMR or have a reduced content of MMR proteins show increased resistance and reduced apoptosis [3].

Reduced apoptotic response

The recognition of platinum-DNA adducts triggers different transduction pathways which decide over the cell's fate. Evidence suggests that altered apoptotic pathways and abnormalities of apoptosis inhibitors or apoptotic factors like p53 are involved in platinum resistance [3, 10, 14].

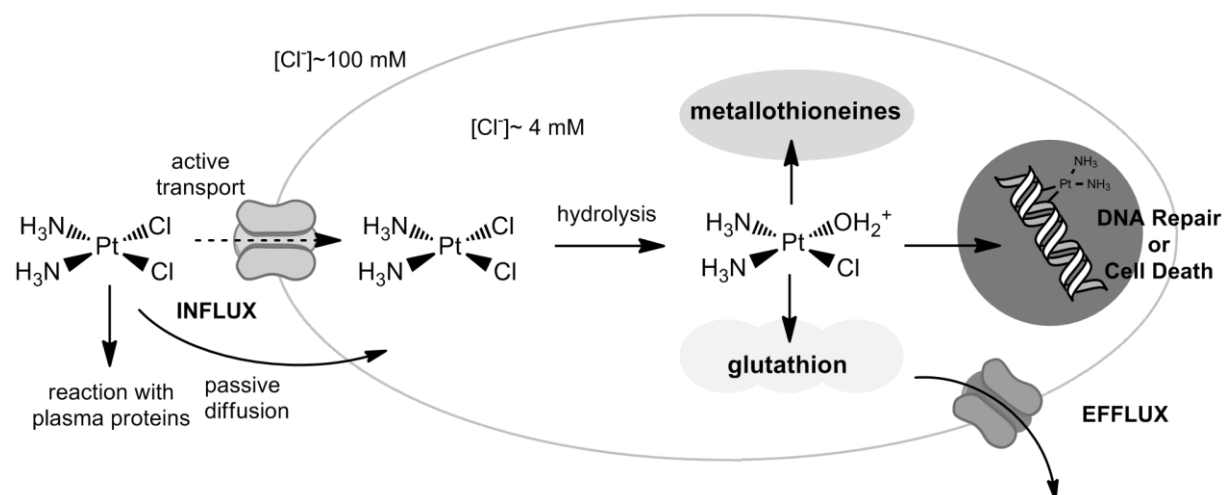


Figure 1.4. Cisplatin – mode of action and resistance mechanisms. Cisplatin enters the cell through passive diffusion and active transport mechanisms. Inside the cell cisplatin is subjected to hydrolysis and the reactive aqua species form platinum-DNA adducts which trigger apoptotic pathways. Resistance may be caused by decreased uptake or increased efflux, detoxification through binding to proteins metallothioneines and glutathione or DNA repair mechanisms. Figure according to [3].

1.2.4 Structure activity relationships of platinum(II) complexes

All platinum complexes in clinical use follow the structure activity relationships which were defined by Hoeschele et al. [18] in 1973. Thus active platinum complexes are uncharged, have square planar geometry and provide *cis*-configuration with a A_2Y_2 coordination sphere. A_2 are inert non-leaving groups represented as strongly bound mono or bidentate am(m)ine ligands with at least one proton. Y_2 stands for anionic mono or bidentate leaving groups like chloride or carboxylate ligands [6].

Investigations showed that an exchange of the leaving groups has an impact on the biodistribution and toxicological profile. In general, complexes with highly reactive leaving groups cause systematic toxicity through protein binding in organs while inert complexes exhibit milder general toxicity. An alteration of the am(m)ines has an impact on the anticancer activity of platinum drugs since variation in DNA adducts induce different cell responses. A good water solubility and lipophilicity also has a positive impact on the side effects. While stable water soluble compounds can be excreted in large part intact and cause therefore less harm to the kidneys, lipophilic compounds show reduced side effects as renal excretion is decreased [8].

1.2.5 Strategies to overcome resistance and side effects

The improved knowledge of resistance and mode of action initiated the development of new design strategies. Recent approaches can be divided into four classes. The first class is represented by improved *rationally designed platinum complexes* (i) whereat non classical complexes like charged and multinuclear complexes as well as complexes with trans-configuration were brought into focus [16]. Further, the attention shifted to *drug delivering* concepts (ii). This concept is also known as passive targeting because special tumor characteristics are exploited to achieve selective accumulation of the drug in the malicious tissue [5]. Another group is based on active *targeted drugs* (iii). These complexes are armed with moieties for selective organ or receptor binding [8]. The last class contains platinum complexes which can be *activated inside the tumor* tissue (iv). Representative for a big amount of platinum(II) complexes, some examples will be described in this section. A more detailed insight can be found in several reviews, e.g. [5, 6, 8, 19].

Oxaliplatin, BBR3464 and picoplatin are examples for *rationally designed drugs* (i), whereat BBR3464 and picoplatin violate the classical structure activity rules. Next to oxaliplatin, which is worldwide approved, BBR3464 and picoplatin managed access to clinical trials.

- *Oxaliplatin* (Figure 1.1 3) was the first drug designed to overcome cisplatin resistance. The goal was attained by introduction of the DACH chelate ligand. The bulky hydrophobic DACH ligand points into the DNA major groove and prevents therefore binding of DNA repair proteins in GpG intrastrand adducts [20].
- *BBR3464* (Figure 1.5 7), a multinuclear platinum(II) complex, followed the strategy to overcome resistance by formation of different DNA adducts. The trinuclear complex causes flexible and long range platinum-DNA adducts with a high degree of interstrand cross links [21].

- *Picoplatin* (Figure 1.5 **8**) exhibits a bulky methylpyridine ring which sterically blocks the platinum nucleus and hinders reactions with glutathione and metallothioneins, which may cause resistance due to inactivation [22].

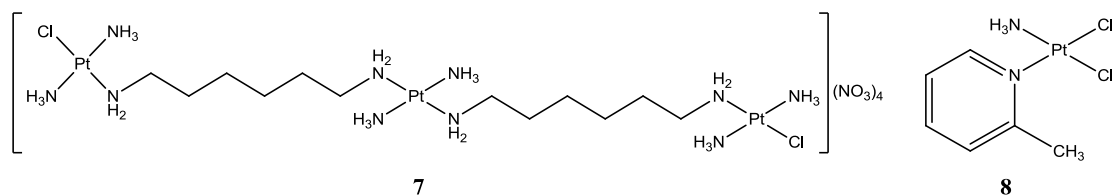


Figure 1.5. BBR3464 **7** - a trinuclear Pt(II) complex; picoplatin **8** - reactions with glutathione are impeded as a result of the sterically blocked Pt(II) nucleus.

ProLindac and Lipolatin follow the *drug delivering concept* (ii). This concept implies long lifetime in the blood in combination with a preference to accumulate in the tumor tissue. This preference is provided by the EPR effect. The EPR effect results from the rapid division of mutated cells. The extensive angiogenesis causes a high vascular density and chaotic formation of blood vessels which leads to large gaps in the vascular endothelium. Macromolecules and lipids are likely to accumulate in these gaps, since lymphatic drainage is impaired and clearance from the interstitial space is less probable [8].

- *ProLindac*TM (Figure 1.6 **9**) is a nanopolymer which consists of the active form of oxaliplatin bound to the biodegradable and water soluble polymer hydroxypropylmethacrylamide (HPMA) [23].
- *Lipoplatin*TM is a liposomal encapsulated form of cisplatin. The liposomal shell increases the stability of cisplatin which has a positive impact on the general toxicity and allows administration in higher doses. Moreover, the circulation time in the body fluid is enhanced and the accumulation in the tumor tissue more likely because of the EPR effect. Further, the nature of the liposomes (reversed miscelles) enables unhampered passing through cell membranes [8]

Targeted drugs (iii) usually receive their selectivity through receptor mediated uptake, but also moieties with tissue selectivity are known.

- Platinum complexes with attached folic acid (Figure 1.6 **10**, **10a**) show affinity to folate receptors which play an important role in receptor-mediated endocytosis. Tumor selectivity is acquired, since folate receptors are ubiquitous expressed in tumor cells but rare in healthy tissue [24].

- Another example for targeted drugs are platinum complexes with bone-seeking properties (Figure 1.6 **11**). The treatment of osteosarcoma (bone tumors) and of their metastasis is very difficult due to the limited blood supply. To reach the tumors, bisphosphonates with osteotropic properties were linked to platinum complexes [25].

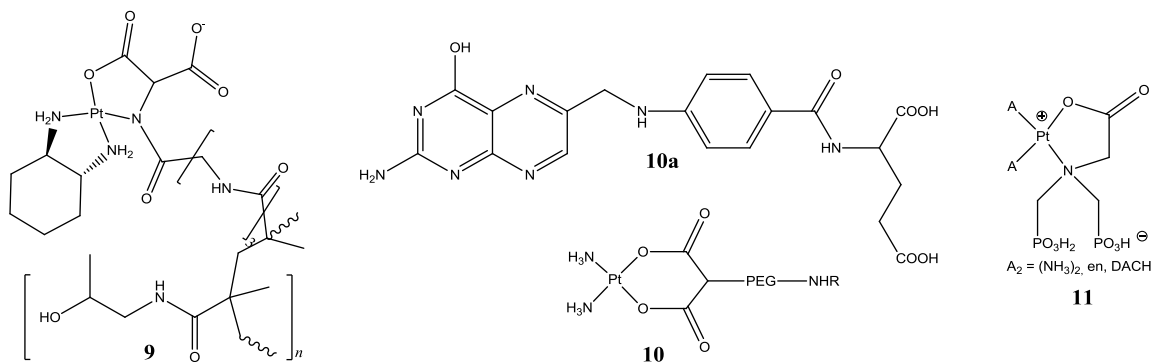


Figure 1.6. ProLindac **9** active form of oxaliplatin bound to a HPMA polymer; Pt(II) complexes **10** with folic acid **10a** show affinity to folate receptors; osteotropic platinum complexes with bisphosphonate moieties **11**.

Another very promising approach is *activation by reduction* (iv) which is employed for platinum(IV) complexes. This concept will be described in the following sections.

1.3 Platinum(IV) complexes

Expansion of the platinum(II) coordination sphere by additional axial ligands brings along a series of benefits. Platinum(IV) complexes with d6 low-spin octahedral coordination geometry [26] are kinetically inert, hence substitution reactions with biological nucleophiles occur only slowly. Accordingly, interactions with proteins which are responsible for drug loss and severe side effects, are reduced. Another consequence of the inertness is an increased circulation lifetime in body fluids, which results in an enhanced probability to accumulate in the tumor tissue [6, 8, 26].

The inertness of platinum(IV) complexes makes them amenable to oral administration, since degradation in the gastrointestinal tract is less probable. An oral administration is capable to enhance the quality of life of patients and lowers therapy costs [6, 8, 26].

Through insertion of the axial ligands, structural modifications are easily accomplished. With changes in the axial moieties, pharmacological properties, which are important for platinum(IV) complexes such as lipophilicity and reduction potentials, can be adjusted. The lipophilicity plays an important role during oral administration and in overcoming platinum resistance. The reduction potential is crucial considering the concept of *activation by reduction* [6, 8, 26].

1.3.1 Activation by reduction

Platinum(IV) complexes behave as pro-drugs which permits activation inside the tumor tissue. Activation is based on the reduction to the more reactive platinum(II) species which implies loss of the axial ligands. Reduction is facilitated due to the hypoxic milieu which is often found in solid tumors. The reductive environment is caused by an insufficient blood supply due to the defective architecture of the fast spreading malicious cells [6, 8, 26].

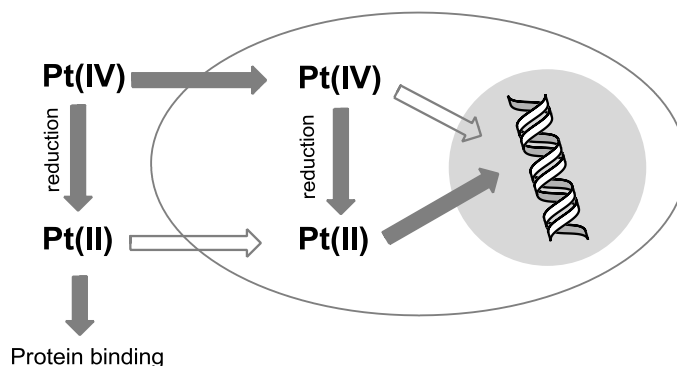


Figure 1.7. Activation by reduction. Platinum(IV) drugs are activated by reduction to the more reactive Pt(II) species which form platinum-DNA adducts. According to the properties of the drug the reduction succeeds extra or intracellularly. Figure according to [6].

According to the chemical properties of the drugs, activation occurs extra- or intracellularly [6, 8, 26] and the resulting platinum(II) species further react as described in Section 1.2.2 (Figure 1.7).

1.3.2 Structure activity relationships of platinum(IV) complexes

One of the most important parameter for determining the platinum(IV) drug's efficacy is the rate of reduction [26], since activation inside the tumor cell is crucial.

It was supposed that the reduction potential correlates with the rate of reduction. The reduction potential of diam(m)ine complexes depends on the whole coordination sphere, but is mainly influenced by the axial ligands [27]. For dichlorido(ethane-1,2-diamine)platinum(IV) complexes the redox potential decreases with the rate of reduction for the following axial ligands Cl (-160 ± 53 mV), CH_3OCO (-546 mV) and OH (-884 mV). Therefore, reduction should be facilitated with axial chloride and hampered with hydroxide ligands [28].

Correlations between reduction potential and cytotoxicity can be deduced, observing the well investigated drugs tetraplatin **12**, iproplatin **13** and satraplatin **14** (Figure 1.8). Tetraplatin exhibits a high reduction potential with two axial chloride ligands and is therefore already activated in the blood stream. It is assumed that the high reactivity is responsible for the severe side effects which caused exclusion from clinical trials. Iproplatin on the other hand possesses a low reduction potential with two hydroxide ligands and is found in large extent unchanged in the cells. The insufficient reduction is attributed to the low activity of iproplatin. Satraplatin exhibits an intermediate reduction potential with axial acetate ligands. As a consequence satraplatin shows high cytotoxicity as well as a milder toxicological profile [27].

Another important parameter for drug design is the lipophilicity which correlates with the accumulation in tumor cells and has therefore an impact on the cytotoxicity and resistance. Reithofer et al. [29] synthesized a series of complexes with the same equatorial core and axial carboxylate ligands of different length. Investigating the cytotoxic activity, a correlation with lipophilicity was shown.

Reduction potential and lipophilicity are important factors which determine the pharmacological profile of platinum(IV) complexes. Another important parameter is given by the biological activity of the corresponding platinum(II) species which in the end induce the DNA lesions [27].

1.3.3 Novel platinum(IV) complexes

The axial ligands, which are lost during the activation can be adjusted to achieve favorable pharmacological properties for prodrugs like suitable reduction potentials or lipophilicity. The axial ligands can be hydroxides, chlorides or acetates, but may contain moieties with biological activity [26]. Representative for countless platinum(IV) complexes, some examples will be given in this section, which gained attention because of their high biological activity and their underlying concepts.

- *Tetraplatin* **12** and *Iproplatin* **13** (Figure 1.8) were the first platinum(IV) complexes that entered clinical trials. Iproplatin was selected because of its high solubility, but showed no better activity than cisplatin during the trials. On the other hand tetraplatin caused severe cumulative neurotoxicity [26].
- *Satraplatin* (JM-216) (Figure 1.8 **14**) possesses a redox potential between iproplatin and tetraplatin. The high stability and lipophilicity enable oral administration and circumvention of resistance mechanisms. At the moment, satraplatin is in clinical trials for different combination therapies [6].
- *LA-12* (Figure 1.8 **15**), a satraplatin analog with a bulky 1-adamantylamine ligand is the last platinum(IV) complex that entered clinical trials up to date [5].
- Since carboxylato ligands showed good results, a series of tetracarboxylato(trans-cyclohexan-1,2-diamine)platinum(IV) complexes were investigated and showed higher *in vitro* and *in vivo* activity than satraplatin [30, 31].

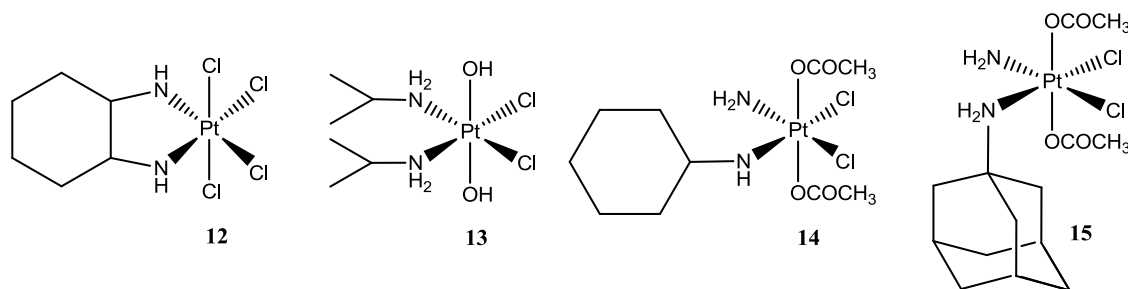


Figure 1.8. Tetraplatin (**12**) , iproplatin (**13**) , satraplatin (**14**), LA-12 (**15**), platinum(IV) complexes in clinical trials.

The concept of targeted drugs is also applied based on platinum(IV) complexes. Several compounds were produced with biological active ligands tethered to the axial positions.

- One of the first examples was presented by Lippard et al. [32] who chose estrogen derivatives as axial ligands (Figure 1.9 **16**). The idea was that the released estrogen upregulates the

expression of HMGB1 proteins which protect platinum-DNA adducts from NER mechanisms, cf. [8, 32].

- Another approach attaching bioactive ligands was performed with cantharidins, a class of traditional Chinese medicine agents (TCM). These TCM agents were used for the treatment of liver, lung and digestive tract cancer. Cantharidin and its derivatives show inhibition of the protein phosphatase 2A which is involved in phosphorylation and dephosphorylation processes. Attached cantharidins were supposed to show a synergistic effect during platinum therapy [33, 34] (Figure 1.9 17).

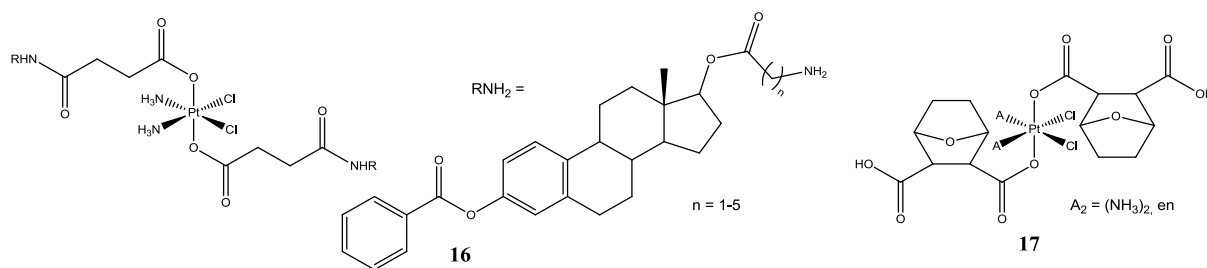


Figure 1.9. Estrogen tethered to the axial position of a platinum(IV) complex. After reduction, estrogen is released and upregulates the expression of HMGB1 proteins which circumvent DNA repair mechanisms.

The EPR effect can also be exploited to accumulate platinum(IV) complexes in the tumor tissue.

- Lippard et al. [35] applied single-walled carbon nanotubes (SWNT) as delivery systems which allow cell uptake via endocytosis. The SWNT-shuttle was attached to one of the axial ligands of the platinum(IV) complexes. To obtain only one axial hydroxide ligand, the oxidation was performed in ethanol, giving an alkoxide as second axial ligand. The free hydroxide ligand was further carboxylated with succinic anhydride and derivatized with the amine-functionalized nanotubes (Figure 1.10). The SWNT tethered platinum complexes showed an enhanced cytotoxicity in comparison to the free complexes which is attributed to the EPR effect and an improved uptake via endocytosis.

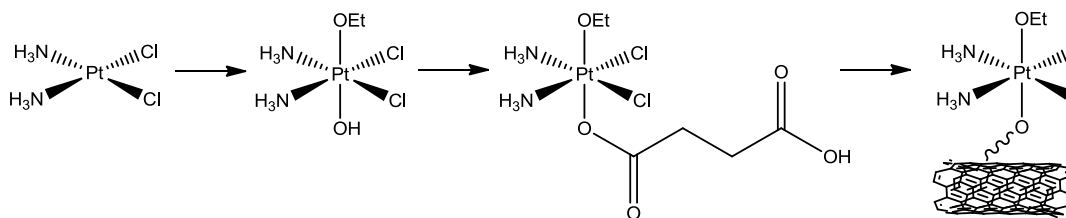


Figure 1.10. Cisplatin was oxidized in ethanol, carboxylated with succinic anhydride and derivatized with amine-functionalized single-walled carbon nanotubes which serve as shuttle for drug uptake.

1.4 Synthesis

1.4.1 Platinum(II) complexes

The chemistry of platinum(II) complexes is affected by ligand substitution reactions in which complexes of $[\text{PtA}_2\text{X}_2]$ configuration show *cis-trans*-isomerism. The stereochemistry of the square planar complexes is determined by the *trans*-effect. This effect was excessively studied on platinum(II) complexes which were very attractive for this purpose because they are not too labile, easy to synthesize and they participate in ligand exchange reactions which can be easily followed [36]. First observations of the *trans*-effect were reported by Peyrone and Jorgensen, synthesizing $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$. Peyrone obtained the *cis* isomer by treating tetrahalogenated platinum(II) with amines, while Jorgensen gained the *trans* stereoisomer by adding halide ions to tetraamine platinum(II) complexes [37]. These observations are ascribed to the *trans*-effect, defined as labialization of ligands which are in *trans* position to *trans*-directing ligands. The stereoselective synthesis of *trans*- and *cis*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ can be explained since chloride has a larger *trans* effect than NH_3 (Figure 1.11) [36].

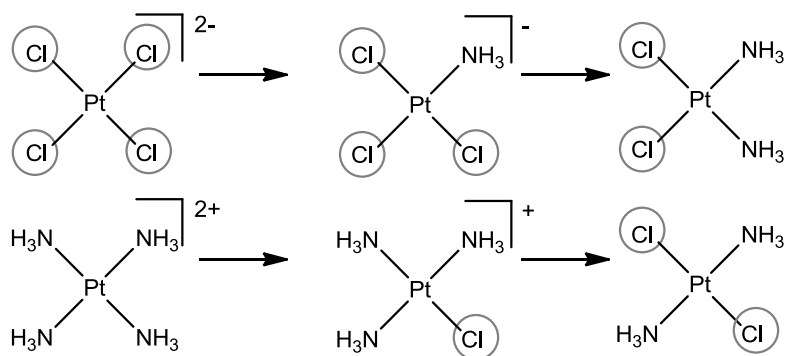


Figure 1.11. Chloride labilizes the bond in *trans* position therefore the *cis* configuration is obtained starting with $[\text{PtCl}_4]^{2-}$ and the *trans* isomer with $[\text{Pt}(\text{NH}_3)_4]^{2+}$ as starting material.

After discovery of the cytotoxic activity, it was of great importance to obtain pure cisplatin in high yields. Since addition of ammonium hydroxide to $[\text{PtCl}_4]^{2-}$ leads to formation of salts and small amounts of *trans*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$, Dhara [38] developed an improved synthetic strategy. First $[\text{PtCl}_4]^{2-}$ was transformed into $[\text{PtI}_4]^{2-}$ with potassium iodide and subsequent addition of ammonium hydroxide lead to the formation of *cis*- $[\text{Pt}(\text{NH}_3)_2\text{I}_2]$ which can be isolated as yellow solid. Since iodide shows a higher *trans*-effect than chloride only the *cis*-isomer is formed in this reaction. The exchange of iodide was performed with AgNO_3 and KCl . AgNO_3 leads to formation of the aqua species $[\text{Pt}(\text{OH}_2)_2(\text{NH}_3)_2]^{2+}$ and the labile aqua ligands can be substituted with chlorides (Figure 1.12).

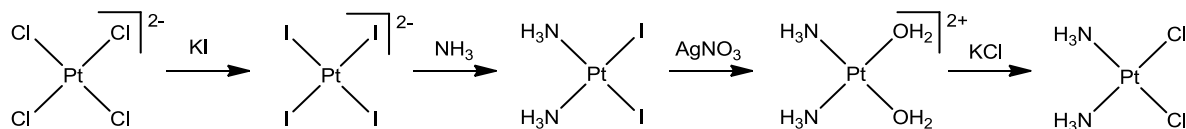


Figure 1.12. Synthetic strategy by Dhara [38]. $[\text{PtCl}_4]^{2-}$ is first converted into $[\text{Pt}(\text{NH}_3)_2\text{I}_2]$ to obtain only *cis*-configuration due to the higher trans-effect of iodide. The iodides are subsequently exchanged by chlorides with AgNO_3 and KCl .

Exchange of the equatorial chloride ligands by carboxylate moieties generated complexes with less toxic effects, higher solubility and conserved cytotoxic activity. In the literature, several methods are reported to prepare dicarboxylatoplatinum(II) complexes, eg. [39–41] (Figure 1.13). Precursor for all synthetic strategies is $[\text{PtA}_2\text{I}_2]$. During the first synthetic pathway (a) the diaqua species is obtained by adding silver sulfate. Barium carboxylate, prepared *in situ* with the corresponding carboxylic acid and barium hydroxide, is subsequently added to the diaqua complex and the dicarboxylatoplatinum(II) complex is formed. In the second strategy (b) silvercarboxylate is prepared in advance and directly added to the diiodidoplatinum(II) complex. During the third strategy (c) the aqua complex is obtained after the addition of AgNO_3 and sodiumcarboxylate is added to receive the final carboxylato complex.

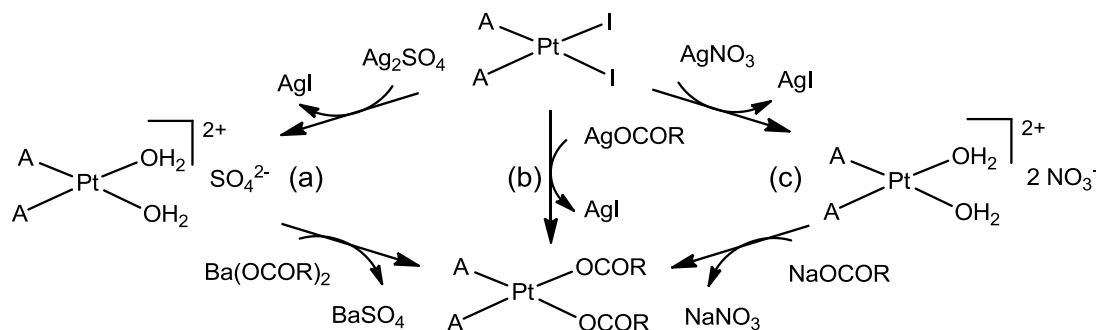


Figure 1.13. Three synthetic routes leading to platinum(II) carboxylate complexes using $[\text{Pt}(\text{NH}_3)_2\text{I}_2]$ as starting material.

1.4.2 Oxidation

Oxidation to platinum(IV) species is usually performed with hydrogen peroxide [42] or chlorine gas. Chloride in the axial positions can also be obtained by reaction of the axial hydroxide ligands with hydrochloric acid [6] (Figure 1.14)

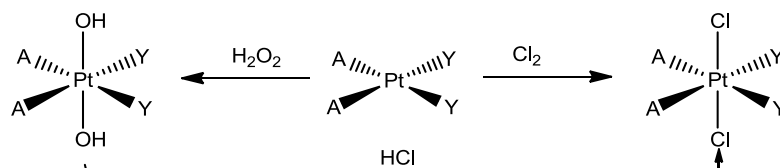


Figure 1.14. Oxidation to platinum(IV) with H_2O_2 or Cl_2 . Chlorides in the axial positions are accessible by reaction of the axial hydroxido ligand with HCl .

1.4.3 Carboxylation

Axially bound hydroxide ligands act as nucleophiles and can be derivatized with common strategies known from organic chemistry. The first carboxylation was reported by Giandomenico et al. [43] with anhydrides, pyrocarbonates and isocyanates. A fourth class of carboxylation agents, the acylchlorides, was introduced by Galanski et al. [44]. The carboxylation was performed with acyl chlorides in combination with pyridine to reduce the concentration of free HCl which caused difficulties in former approaches. Ang et al. [45] used these strategies for the synthesis of platinum(IV) arylcarboxylates with acidchlorides and acid anhydrides.

Carboxylation with cyclic anhydrides was first reported by Navarro-Ranninger et al. [46], who used succinic anhydride, maleic anhydride and glutaric anhydride. The carboxylation with cyclic anhydrides revealed a big advantage, since functional groups were introduced which allowed further derivatization. Such attempts were first reported by Lippard et al. [32], who tethered estradiol to the axial ligands with the help of diisopropylcarbodiimid (Figure 1.9).

Vast improvements of the carboxylation with cyclic anhydrides and further derivatizations were reported by Reithofer et al. [47]. With DMF as solvent, improved reaction times and yields were achieved. The free carboxylic acids were further derivatized with alcohols and amines, using CDI, a common peptide coupling reagent. Reaction with the alcohol required further activation; therefore sodium alkoxides were prepared in advance. The synthetic strategies are visualized in Figure 1.15.

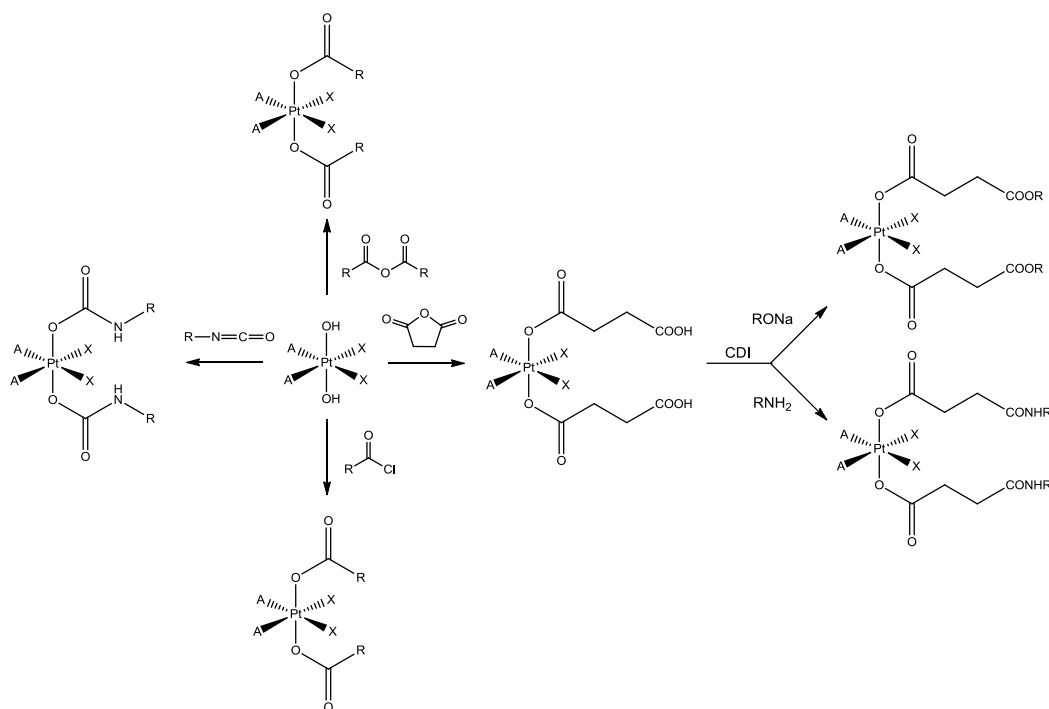


Figure 1.15. Carboxylation of the nucleophilic hydroxo ligands with anhydrides, isocyanates [43], acyl chlorides [44] and cyclic anhydrides [46]. The free functional carboxylic acids can further be derivatized with alcohols and amines [47].

1.5 Research Objective and Achievements

The aim of this master thesis was the development and characterization of novel platinum(IV) complexes. This included the synthesis of different platinum(II) complexes, their oxidation and further derivatization with different carboxylic anhydrides. Main focus of the work was the carboxylation of the complexes with self-prepared anhydrides.

Three (ethane-1,2-diamine)platinum(II) complexes were synthesized with equatorial acetate, bromide and iodide ligands. The complexes were oxidized with hydrogen peroxide and the axial hydroxide ligands were carboxylated with different anhydrides to obtain tetracarboxylatoplatinum(IV) complexes as well as diiodido- and dibromidodicarboxylatoplatinum(IV) complexes. The equatorial carboxylate ligands confer high water solubility to the complexes. By using anhydrides with variable chain length, complexes with different lipophilicity were generated.

As described before, Giandomenico et al. [43] first published the derivatization of the free hydroxide ligands with simple anhydrides. After the first report of carboxylation reactions with cyclic anhydrides by Navarro-Ranninger et al. [46], Reithofer et al. [47] established a synthetic strategy for the carboxylation with succinic anhydride and subsequent derivatization with alcohols. A disadvantage of this very useful method is that the isolation of the carboxylated compound is often challenging and subsequent derivatization with CDI and alcohols leads in general to low yields.

Therefore, one subject of this work was to improve the synthesis by preparing the desired carboxylate moieties in advance. For that purpose succinic anhydride was mono-esterified with the corresponding alcohol and by stirring under reflux in acetic anhydride the corresponding anhydrides were obtained. The carboxylation can easily be performed with the prepared anhydrides which provides directly the final products. Thus one time- and substance consuming step is saved and the overall yield can be improved.

The new platinum(IV) complexes were characterized with elemental analysis, one- and two dimensional NMR, ESI-MS and IR spectroscopy. In some cases it was possible to perform X-ray crystallographic analyses.

2 Results and Discussion

2.1 Synthesis

The work is based on the following three ethane-1,2-diamineplatinum(II) complexes (Figure 2.1).

- (SP-4-2)-(Ethane-1,2-diamine)diiodidoplatinum(II) (**A**)
- (SP-4-2)-Dibromido(ethane-1,2-diamine)platinum(II) (**B**)
- (SP-4-2)-Diacetato(ethane-1,2-diamine)platinum(II) (**C**)

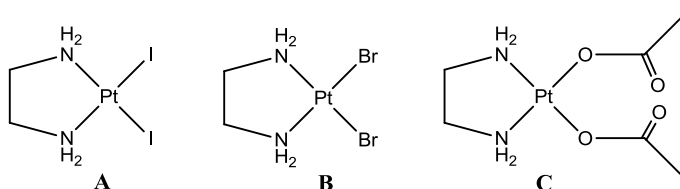


Figure 2.1. Ethane(1,2)diamineplatinum(II) complexes used as precursors in this work.

Starting from potassium tetrachloridoplatinate, compound **A** was synthesized, which acted as precursor for **B** and **C**. With these three platinum(II) complexes the reaction in Figure 2.2 was accomplished.

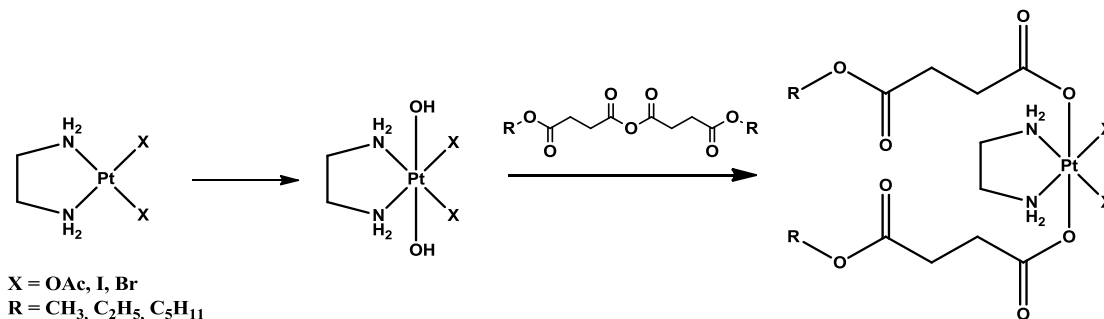


Figure 2.2. Reaction sequence which was accomplished with different anhydrides and compounds **A-C**.

Complexes **A-C** were oxidized with hydrogen peroxide and subsequently carboxylated with different anhydrides:

- 3-(Methoxycarbonyl)propanoic anhydride (**a**)
- 3-(Ethoxycarbonyl)propanoic anhydride (**b**)
- 3-(Pentoxycarbonyl)propanoic anhydride (**c**)

Complex **A** was also used for the synthesis of (ethane-1,2-diamine)dihydroxidoplatinum(II) (**D**) which was attained *in situ* and immediately oxidized to its platinum(IV) analog. The resulting tetrahydroxidoplatinum(IV) complex (**D-1**) was further carboxylated with acetic anhydride (**d**). The whole reaction sequence is illustrated in Figure 2.3 and the final products are listed in Table 2.1.

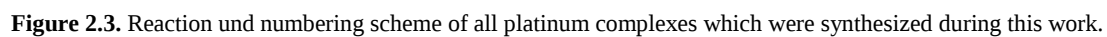
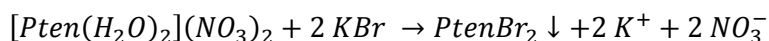


Table 2.1. Final compounds of the master thesis with numbering system. All compounds are illustrated in Figure 2.3.

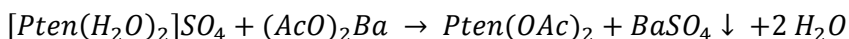
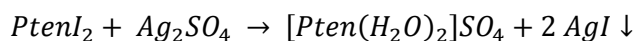
compound	no.
enPtI ₂ (C ₅ H ₇ O ₄) ₂	A-2a
enPtI ₂ (C ₆ H ₉ O ₄) ₂	A-2b
enPtBr ₂ (C ₅ H ₇ O ₄) ₂	B-2a
enPt(OAc) ₂ (C ₅ H ₇ O ₄) ₂	C-2a
enPt(OAc) ₂ (C ₆ H ₉ O ₄) ₂	C-2b
enPt(OAc) ₂ (C ₉ H ₁₁ O ₄) ₂	C-2c
enPt(OAc) ₄	D-2d

2.1.1 Platinum(II) complexes

The starting compound **A** was synthesized according to the literature [38] with some modifications. It was not possible to produce the corresponding dibromidoplatinum(II) complex **B** directly from K₂PtCl₄, even with longer reaction time and double excess of potassium bromide. Due to the minor *trans*-effect of bromide only a mixture of [enPtCl₂], [enPtBrCl] and [enPtBr₂] was gained by this reaction. Consequently, it was necessary to apply **A** as precursor and exchange the iodide ligands by bromides. Therefore AgNO₃ was added to induce precipitation of AgI which could be easily removed by filtration. The subsequent addition of potassium bromide to the aqua species lead to the formation of the desired product. The reactions of the described steps were as follows:



Complex **A** also served as starting material for **C**. The reaction was performed as recorded by Rochon et. al. [39]. Initially, the diaqua species was achieved by adding silver sulfate. The silver iodide was removed by filtration and barium acetate, which was prepared *in situ*, was added to cause precipitation of barium sulfate and formation of the product.



Since free silver ions lead to side reactions and impurities, it was applied as limiting reactant in the following ratios: Pt:Ag₂SO₄ 1:0.95 and Pt:AgNO₃ 1:1.95. It was possible to obtain the platinum(II) precursors in good to excellent yields (73-98%).

2.1.2 Oxidation

The platinum(II) precursors were oxidized in a 15% solution of hydrogen peroxide. On account of the limited stability of **C**, complex **C-1** could be isolated only in poor yields (35%). As described by Kratochwil et. al. [48], the oxidized compounds **A-1** and **B-1** were suspended in pyridine and heated for one hour at 70°C after the oxidation. This represents a convenient method to remove remaining starting material. The platinum(II) species form soluble complexes with the pyridine and the insoluble platinum(IV) compounds can be easily collected by filtration. Complex **A-1** and **B-2** could be isolated in 67-76% yields.

2.1.3 Carboxylation

The carboxylation was performed via common Schlenk technique. Using moisture sensitive anhydrides, the exclusion of air and the use of anhydrous solvents was required. *N,N*-Dimethylformamide was selected as solvent because it allows the observation of the reaction progress. Unlike the starting materials, the formed products are soluble in DMF. Therefore, clear solutions indicated the completion of the reactions. The procedures only differed in time and temperature. Complex **C-1** was heated to 35-45°C (4-8 h) while **B-1** required heating to 60°C (26 h) and **A-2** to 70°C (2 h). The colors varied from pale yellow (**C-2**) to orange (**B-2**) and dark red (**A-2**). All final products needed purification by column chromatography with solvent mixtures of methanol and ethyl acetate. The compounds could be isolated in yields from 22 to 61%. The tetraacetatoplatinum(IV) complex **D-2** was obtained by stirring **D-1** in acetic anhydride over 10 days and was isolated in 51% yield.

2.1.4 Anhydrides

For synthesis of the anhydrides, the corresponding monoesters of succinic acid were prepared based on the procedure described in [49]. Succinic anhydride was suspended in the corresponding alcohol and heated under reflux until a clear solution was formed. Excess of solvent was removed *in vacuo* and the monoesters were further transformed into the anhydrides by heating under reflux in acetic anhydride. The reaction sequence is visualized in Figure 2.4.

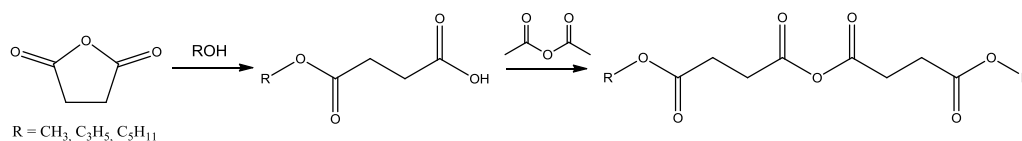


Figure 2.4. Reaction sequence for the synthesis of different carboxylic anhydrides starting from succinic anhydride.

2.2 Characterization

All new compounds were characterized with elemental analysis, one- and two-dimensional NMR (*nuclear magnetic resonance*) spectroscopy, ESI-MS (*electrospray ionization mass spectrometry*) and IR (*infrared*) spectroscopy. In the case of **A-2b**, **B-2a** and **C-2b** X-ray diffraction studies could be performed. Known products were identified by ^1H -NMR spectroscopy or by elemental analysis, if NMR measurements were not possible as a consequence of low solubility. In the following subsections the different spectroscopic characterizations will be introduced.

2.2.1 Elemental analysis

All compounds were generated to achieve a purity of at least 95%. This implicates that the allowed deviation of $\pm 0.4\text{wt}\%$ for C, H and N is not exceeded. Table 2.2 shows the elemental analysis of the final complexes. Each entry contains the theoretical and found weight percentage of carbon, hydrogen and nitrogen as well as their deviations.

Table 2.2 Elemental analysis for the synthesized compounds. All values are within the max. allowed deviation of $\pm 0.4\text{wt}\%$.

no.	molecular formula		w-% C	w-% H	w-% N
A-2a	$\text{C}_{12}\text{H}_{22}\text{I}_2\text{N}_2\text{O}_8\text{Pt}$	Found	18.60	2.87	3.64
		Calculated	18.69	2.88	3.63
		Difference	-0.09	-0.01	0.01
A-2b	$\text{C}_{14}\text{H}_{26}\text{I}_2\text{N}_2\text{O}_8\text{Pt}$	Found	21.02	3.32	3.46
		Calculated	21.04	3.28	3.50
		Difference	-0.02	0.04	-0.04
B-2a	$\text{C}_{12}\text{H}_{22}\text{Br}_2\text{N}_2\text{O}_8\text{Pt}$	Found	21.47	3.30	4.04
		Calculated	21.28	3.27	4.14
		Difference	0.19	0.03	-0.01
C-2a	$\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_{12}\text{Pt} \cdot 0.5\text{H}_2\text{O}$	Found	29.87	4.40	4.38
		Calculated	29.82	4.54	4.35
		Difference	0.05	-0.14	0.03
C-2b	$\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_{12}\text{Pt} \cdot 0.5\text{H}_2\text{O}$	Found	32.15	4.95	4.16
		Calculated	32.15	4.95	4.17
		Difference	0.00	0.00	-0.01
C-2c	$\text{C}_{24}\text{H}_{44}\text{N}_2\text{O}_{12}\text{Pt}$	Found	38.66	6.26	3.96
		Calculated	38.55	5.93	3.75
		Difference	0.11	0.33	0.21
D-2d	$\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_8\text{Pt}$	Found	24.33	4.14	5.61
		Calculated	24.44	4.10	5.70
		Difference	-0.11	0.04	-0.09

2.2.2 ESI-MS

ESI-MS measurements were recorded in the positive as well as in the negative mode. Since ESI represents a soft ionization technique and avoids fragmentation in large part, monoadducts of $[M+Na^+]^+$ caused the most intensive peaks in the positive mode. Acetato complexes (series **C** and **D**) also showed loss of acetic acid (Table 2.3). The dominant signals in the negative mode derived from $[M-H]^+$ ions (Table 2.4). For the acetato complexes **C-2a**, **C-2b** and **C-2c** also $[M+Cl]^+$ adducts were detected. The isotopic distribution of the signals coincides with the theoretical patterns.

Table 2.3. Found $[M+Na^+]^+$ and $[M-CH_3COOH+Na^+]^+$ adducts for all final compounds detected in the positive mode of ESI-MS measurements.

no.	compound	$[M+Na^+]^+$	$[M-CH_3COOH+Na^+]^+$
A-2a	enPtI ₂ (C ₅ H ₇ O ₄) ₂	793.4	
A-2b	enPtI ₂ (C ₆ H ₉ O ₄) ₂	821.4	
B-2a	enPtBr ₂ (C ₅ H ₇ O ₄) ₂	699.3	
C-2a	enPt(OAc) ₂ (C ₅ H ₇ O ₄) ₂	656.5	596.5
C-2b	enPt(OAc) ₂ (C ₆ H ₉ O ₄) ₂	685.2	625.0
C-2c	enPt(OAc) ₂ (C ₉ H ₁₁ O ₄) ₂	769.3	710.2
D-2d	enPt(OAc) ₄	513.1	453.1

Table 2.4. Found $[M-H]^+$ and $[M+Cl]^+$ ions for all final compounds detected in the negative mode of ESI-MS measurements.

no.	compound	$[M-H]^+$	$[M+Cl]^+$
A-2a	enPtI ₂ (C ₅ H ₇ O ₄) ₂	769.9	
A-2b	enPtI ₂ (C ₆ H ₉ O ₄) ₂	798	
B-2a	enPtBr ₂ (C ₅ H ₇ O ₄) ₂	676.0	
C-2a	enPt(OAc) ₂ (C ₅ H ₇ O ₄) ₂	632.2	668.4
C-2b	enPt(OAc) ₂ (C ₆ H ₉ O ₄) ₂	663.2	699.4
C-2c	enPt(OAc) ₂ (C ₉ H ₁₁ O ₄) ₂	745.3	782.3
D-2d	enPt(OAc) ₄	489.0	

2.2.3 NMR

The final compounds were characterized with ^1H , ^{13}C and ^{195}Pt NMR spectroscopy. Moreover two-dimensional $^1\text{H}^{13}\text{C}$ -HSQC (*heteronuclear single quantum correlation*), $^1\text{H}^{15}\text{N}$ -HSQC, $^1\text{H}^{13}\text{C}$ -HMBC (*heteronuclear multiple bond correlation*) and $^1\text{H}^1\text{H}$ -COSY (*correlation spectroscopy*) measurements were performed to allow assigning of ambiguous signals. Nevertheless, it was not always possible to analyze all signals with certainty.

The interpretation of the NMR spectra is shown in detail on the example of complex **C-2c**.

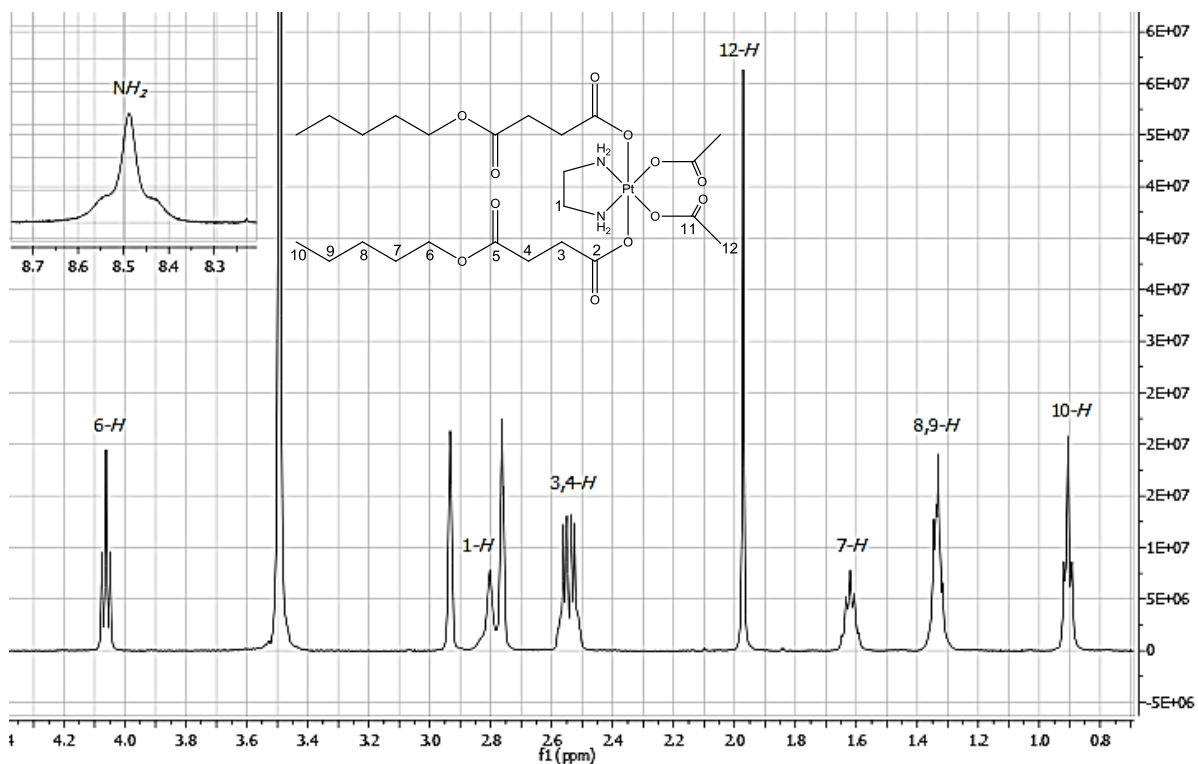


Figure 2.5. ^1H NMR in DMF-d_7 and structure with numbering scheme of complex **C-2c**. All signals are denoted with the corresponding protons in the complex.

Figure 2.5 shows the ^1H NMR and structure of complex **C-2c**. The assignment of NH_2 protons as well as of 1-*H*, 3/4-*H*, 6-*H* and 10-*H* was achieved by means of their spin multiplicities, chemical shifts and intensities. Protons 7-, 8- and 9-*H* were assigned with the help of COSY (Figure 2.6). The multiplet from 1.65-1.59 ppm shows a cross peak with 6-*H* alluding that the multiplet is generated by 7-*H*. The subsequent multiplet (1.36-1.30 ppm) shows correlations with the multiplet of 7-*H* and the triplet of 10-*H*. The intensity of 8 indicates that the signal is generated by 8-*H* and 9-*H*.

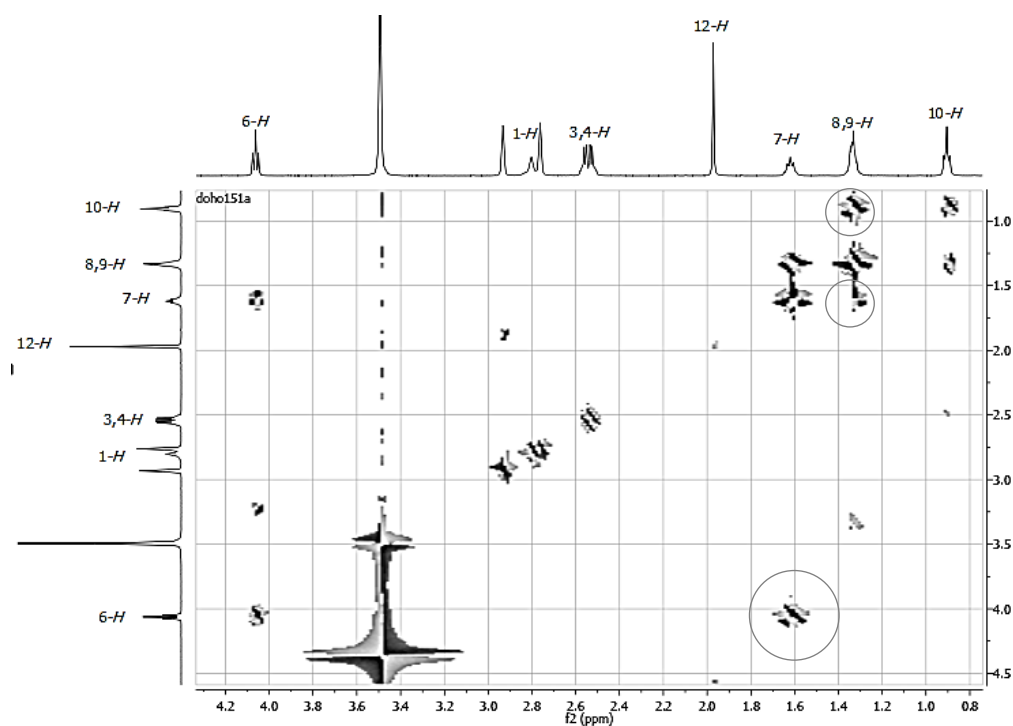


Figure 2.6. Assigned COSY spectrum for complex **C-2a**. The encircled signals allowed determination of the signals for 7-*H* and 8,9-*H*.

HSQC and HMBC spectra turned out to be very useful for assigning of ^{13}C NMR spectra. By knowing the signals of the protons, the corresponding carbons could be easily identified by HSQC spectroscopy (Figure 2.7).

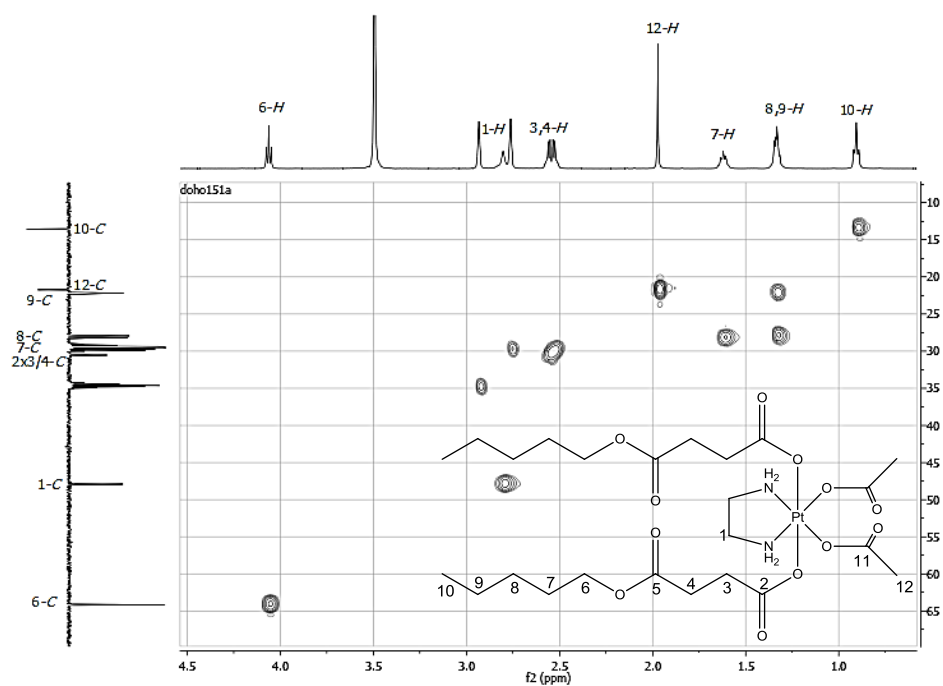


Figure 2.7. HSQC spectrum of complex **C-2c** used for assigning of the ^{13}C NMR spectrum.

HMBC spectra (Figure 2.8) were recorded for the assignment of carbonyl carbon atoms. The first carbon at 180.1 ppm correlates only with the multiplet of 3- and 4-*H* which implies that the signal is generated by 2-*C*. The next carbon shows a cross peak with the protons from 12-*H*, therefore it is determined to be 11-*C*. The third carbon was identified to be 5-*C* because of the cross peaks with 6-*H* and with 3,4-*H*. The fully assigned ^{13}C NMR is shown in Figure 2.9. In all series one signal of 3- and 4-*H* is superimposed by DMF.

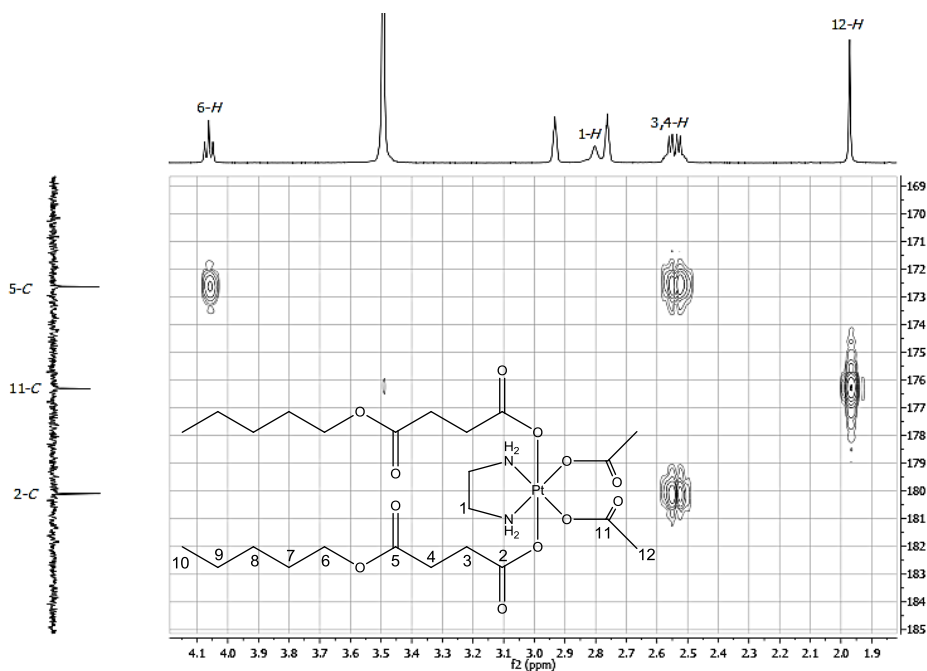


Figure 2.8. Part of the HMBC spectrum which was used for the identification of carbonyl signals in the ^{13}C NMR.

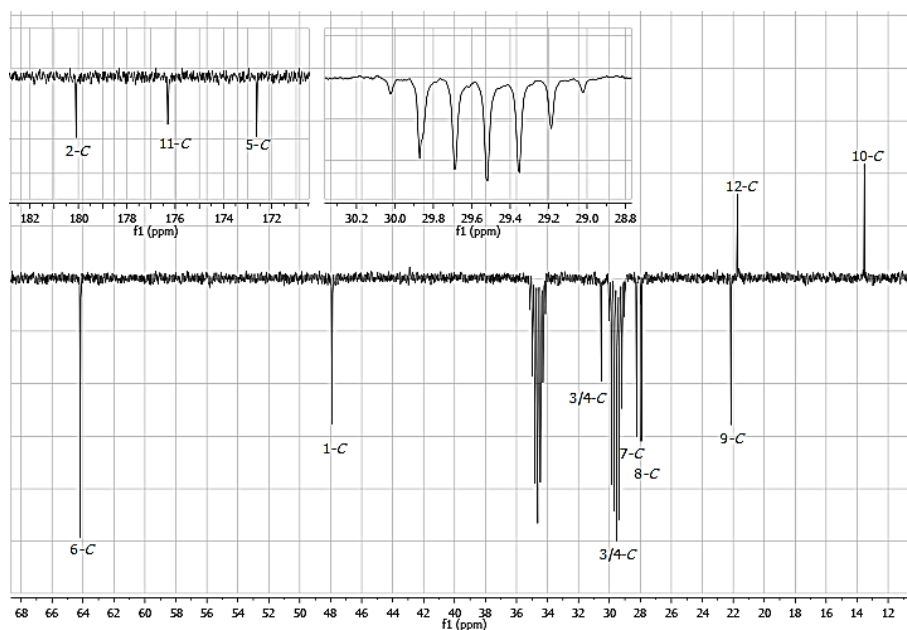


Figure 2.9. Fully assigned ^{13}C NMR for C-2c. One of the signal of 3-*H*/4-*H* is superimposed by DMF.

For the complexes **C-2a** and **C-2b** it was also possible to determine the protons 3-*H* and 4-*H*. Figure 2.10 shows that one of the two signals which belong to 3-*C* and 4-*C* exhibits platinum satellites with a coupling constant of $^3J_{\text{Pt,C}}=39$ Hz. These satellites arise from a vicinal carbon platinum coupling which can only be the case for 3-*C*. Carbon platinum coupling was also observed for 8-*C* in **C-2a**.

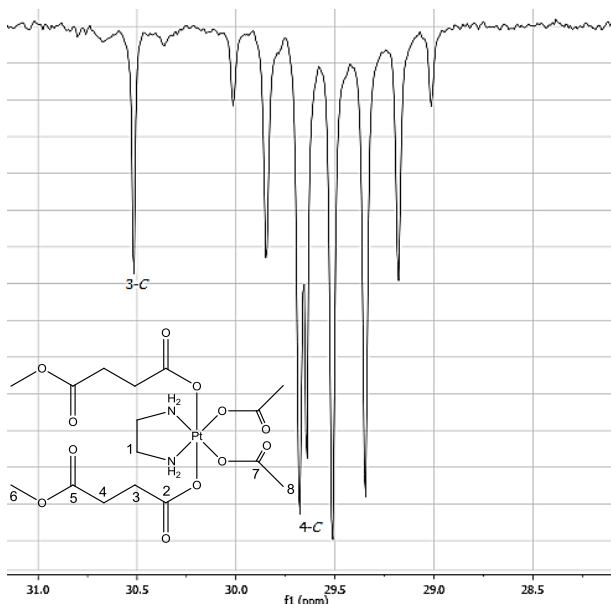


Figure 2.10. Part of the ^{13}C NMR from **C-2a**. Platinum satellites allow assigning of 3-*H* and 4-*H*.

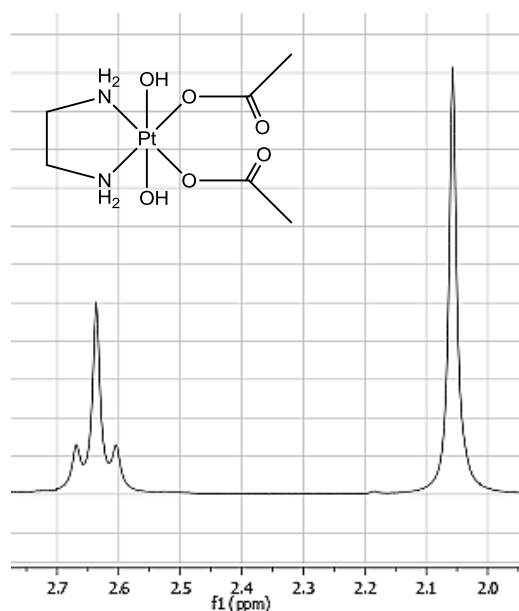


Figure 2.11. ^1H NMR of **B-1**. Pt-*H* coupling is responsible for platinum satellites.

Platinum satellites also appear in ^1H NMR such as for complex **C-1** (Figure 2.11). The singlet from the protons of the methylene groups is flanked by satellites ($^3J_{\text{Pt,H}} = 32.5$ Hz) which results from Pt-*H* coupling. In many cases it is not possible to determine the coupling constant since coupling leads often to broad signals. This is especially observed for protons (CH_2 and NH_2) within the ethanediamine chelate ligand (see Figure 2.5).

During the reaction sequence striking differences in the chemical shifts of NH_2 could be observed. This signal was found for the platinum(II) acetato complex **C-1** at 5.24 ppm and at around 8.50 ppm for the carboxylated platinum(IV) analog. ^{195}Pt NMR spectroscopy also allows following changes in the oxidation state. The transformation from the platinum(II) **C** to the platinum(IV) acetato complex **C-1** causes a significant change in the chemical shift of nearly 3500 ppm. The subsequent carboxylation has only a very little effect on the chemical shift (Δ 300 ppm), noting that ^{195}Pt spectra range over several thousand ppm. Additionally, it can be observed that the ligand sphere has a big influence on the metal center. In the ^{195}Pt spectra, the didiodido complexes (**A-2a**, **A-2b**) exhibited peaks at 1372 ppm, the dibromido complex (**B-2a**) at 2230 ppm and the diacetato complexes (**C-2a**, **C-2b**, **C-2c**) at an average of 3494 ppm. On the other hand the lengths of the carboxyl chains have no effect on the platinum nucleus. These observations can be seen in Table 2.5.

Table 2.5. Chemical shifts in ^1H , ^{13}C and ^{195}Pt NMR of selected atoms of the final compounds.

no.	compound	^{195}Pt	^1H	^1H	^{13}C	^{13}C
			NH_{2en}	CH_{2en}	$\text{C}(2)=\text{O}$	$\text{C}(5)=\text{O}$
D-2d	$\text{enPt}(\text{OAc})_4$	3496	8.52	2.80		
C-2a	$\text{entPt}(\text{OAc})_2(\text{C}_5\text{H}_7\text{O}_2)_2$	3494	8.48	2.80	180.0	173.0
C-2b	$\text{enPt}(\text{OAc})_2(\text{C}_6\text{H}_9\text{O}_4)_2$	3494	8.49	2.80	180.1	172.5
C-2c	$\text{enPt}(\text{OAc})_2(\text{C}_9\text{H}_{15}\text{O}_4)_2$	3495	8.49	2.80	180.1	172.6
B-2a	$\text{entPtBr}_2(\text{C}_5\text{H}_7\text{O}_2)_2$	2230	8.73	2.93	181.5	172.9
A-2a	$\text{entPtI}_2(\text{C}_5\text{H}_7\text{O}_2)_2$	1372	8.47	2.76	181.8	172.9

2.2.4 IR

IR spectroscopy allows following the reaction by means of significant changes in the absorption properties. Moreover, IR turned out to be especially useful to prove oxidation of complexes **A-1** and **B-1** since they were not accessible to NMR spectroscopy as a result of their limited solubility. Hence, IR spectroscopy was besides elemental analysis the only characterization method for complexes **A**, **B**, **A-1** and **B-1**. The interpretation of IR spectra is discussed on the basis of the oxidation and subsequent carboxylation of the diiodidoplatinum(II) complex **A**. The IR spectrum of **A** is illustrated in Figure 2.12.

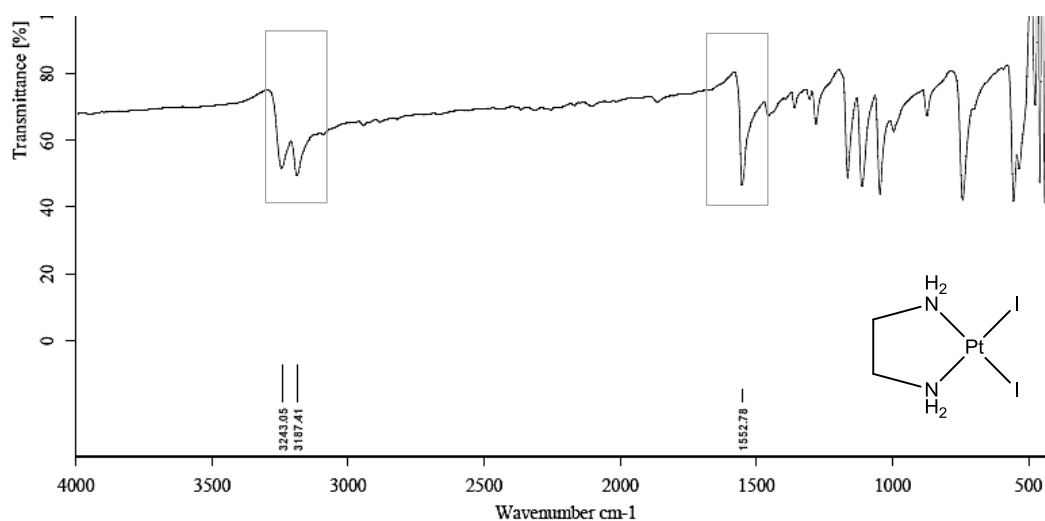


Figure 2.12. IR spectrum and structure of compound **A**. ($\nu_{\text{N-H}}$) stretch can be observed at 3243 cm^{-1} and 3187 cm^{-1} and ($\delta_{\text{N-H}}$) bend at 1553 cm^{-1} .

Distinctive N-H stretching vibrations were found for all complexes in the range from 3261 to 3113 cm^{-1} . This characteristic absorption is usually represented as a broad signal consisting of two peaks. In the platinum(II) and dihydroxidoplatinum(IV) compounds further N-H bend vibrations were observed in the region from 1594-1552 cm^{-1} . The oxidation is accompanied by sharp PtO-H absorption bands from 3412 to 3475 cm^{-1} (Figure 2.13).

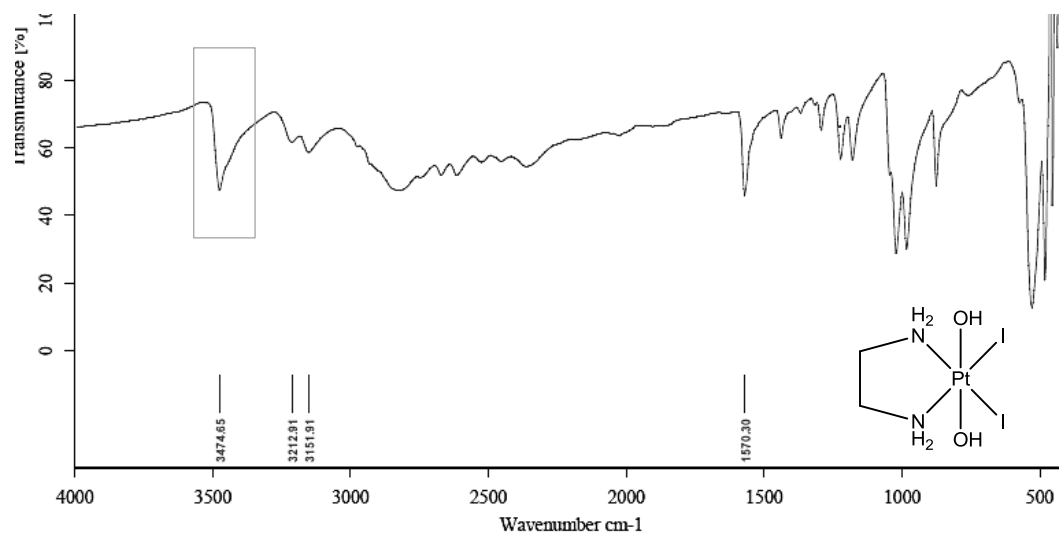


Figure 2.13. IR spectrum and structure of compound **A-1**. Oxidation gives rise to a ($\nu_{\text{Pt-OH}}$) stretch at 3475 cm^{-1} .

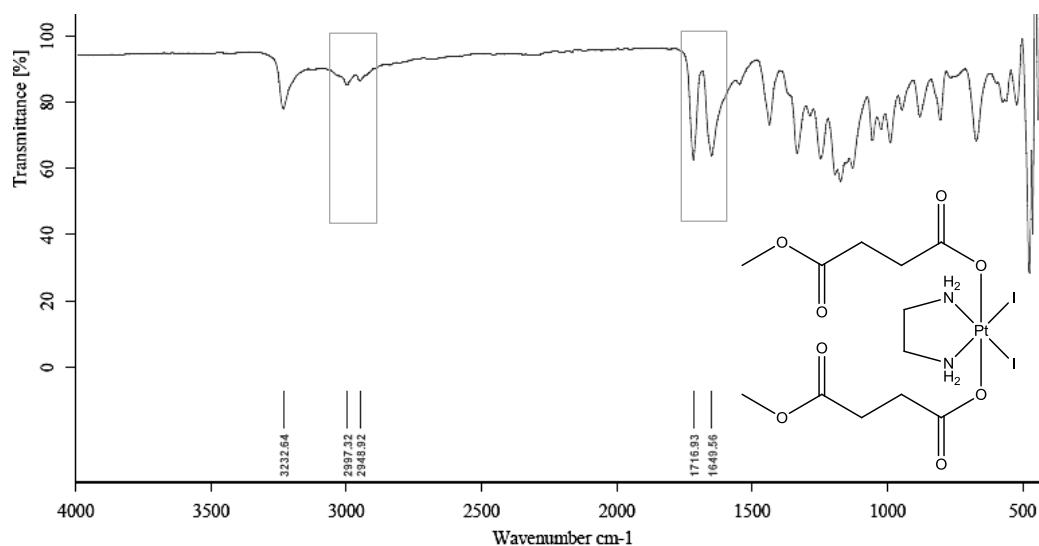


Figure 2.14. IR spectrum and structure of compound **A-2a**. Carboxylation leads to a ($\nu_{\text{C-H}}$) stretch at 2997 cm^{-1} and 2949 cm^{-1} .

The following carboxylation gives rise to further signals. Weak bands based on C-H stretching vibrations were detected from 3048-2859 cm^{-1} . In addition, two sets of C=O stretching signals appear. The first is located in the range of 1730-1704 cm^{-1} and results from C=O stretching vibrations of the ester moieties. The second set is shifted to smaller wavenumbers (1655-1625 cm^{-1}), deriving from PtOC=O stretching vibrations (cf. [47]). In the carboxylated compounds the N-H bend vibrations are often superimposed by these intensive C=O stretching vibrations. In the region from 1290-1326 cm^{-1} , absorption of OCO-R (R = C_2H_5 , CH_3) vibrations were observed (Figure 2.14).

2.2.5 Crystal structures

X-ray diffraction studies were performed for compounds **A-2b** (Figure 2.15), **B-2a** (Figure 2.16) and **C-2b** (Figure 2.17). Selected bond lengths and angles are provided in Table 2.6 and Table 2.7, respectively. Table 2.8 lists relevant crystallographic data.

A-2b

Suitable crystals of **A-2b** for X-ray diffraction studies were obtained via evaporation of a solvent mixture of ethyl acetate and diethyl ether. The measurement was performed with a clear orange block-like specimen with an approximate size of 0.044 mm x 0.062 mm x 0.064 mm.

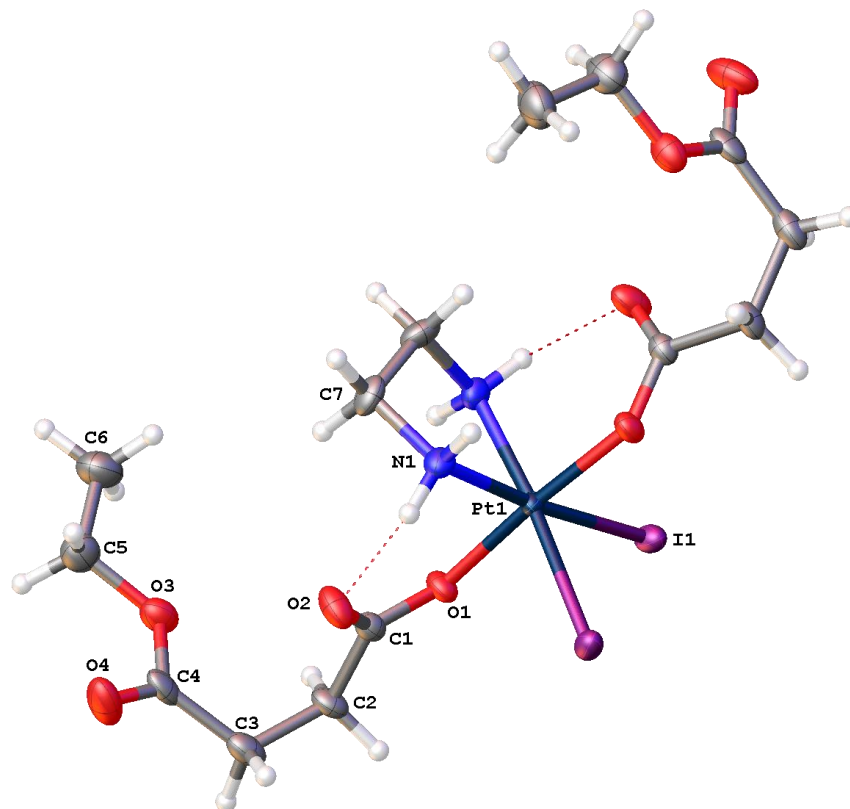


Figure 2.15. Crystal structure of compound **A-2a** with atom labeling scheme.

The platinum(IV) nucleus exhibits an octahedral coordination geometry in which two iodides (Pt-I = 2.6303 Å) and one bidentate *N,N*-ethanediamine ligand (Pt-N = 2.0723 Å) are located in the equatorial plane. Both carboxylate ligands are axially coordinated via oxygen (Pt-O = 2.0208 Å). The bond lengths are comparable to similar complexes described in the literature [48]. Complex **A-2b** crystallized in the orthorhombic space group *Iba2* featuring disorder in the ethylenediamine ring. The amines participate in intramolecular hydrogen bonds with the carboxyl group C(1)=O(2) and in intermolecular hydrogen bonds with the carboxyl group C(4)=O(4).

B-2a

Single crystals of **B-2a** were obtained after slow evaporation of a diethyl ether-methanol solution at 4°C. A clear colorless stick like-crystal with approximate dimensions of 0.010 mm x 0.030 mm x 0.140 mm was used for the X-ray diffraction studies. **B-2a** crystallized in a monoclinic cell with *C12/c1* space group. In the octahedral complex two bromides (Pt-Br = 2.4534) and two amine nitrogens of the bidentate *N,N*-ethanediamine chelate ligand (Pt-N = 2.0635) constitute the equatorial plane. The axial carboxylate ligands are coordinated via oxygen and complete the octahedral coordination geometry. Hydrogen bonds are formed between the amines, acting as donors, and the carboxyl groups C(5)=O(6) operating as hydrogen bond acceptors.

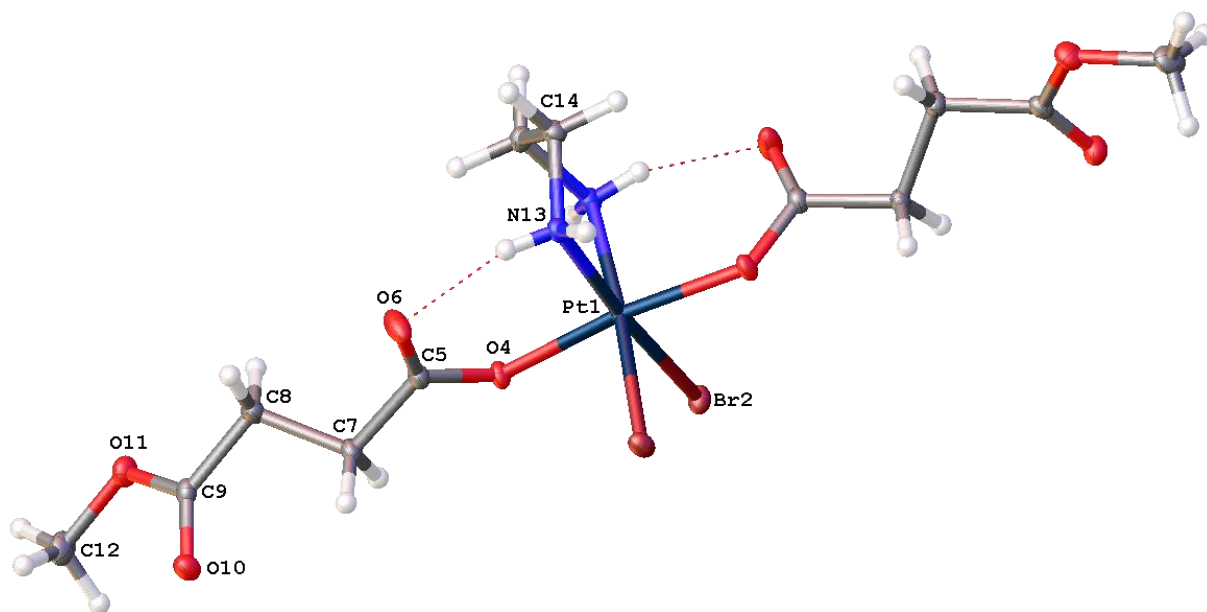


Figure 2.16. Crystal structure of compound **B-2a** with atom labeling scheme.

C-2b

Crystals of **C-2b**, suitable for X-ray crystallographic measurements, were grown in a solvent mixture of ethyl acetate and diethyl ether at 4°C. A clear colorless block-like crystal of approximate 0.030 mm x 0.070 mm x 0.070 mm was applied for the X-ray analysis. The complex crystallized in a triclinic crystal system with space group *P*1. The platinum center has octahedral coordination geometry with two acetato ligands (Pt-O = 2.0224, 2.0284 Å) and one bidentate *N,N*-ethanediamine chelate ligand (Pt-N = 2.0366, 2.0404 Å) occupying the equatorial positions. Two oxygens from the carboxylate ligands are axially coordinated (Pt-O = 2.0086, 2.0010 Å). The Pt-O bonds in the equatorial positions (avg. 2.0254 Å) are slightly longer than the axial bonds (avg. 2.0048 Å). The bond lengths are consistent with data in the literature [50]. Hydrogen bonding occurred between amines and carbonyl groups whereas N(1) forms hydrogen bonds with O(6) and O(10) (N1-O6 = 2.746 Å, N1-O10 = 2.819 Å) and N(2) with O(2) and O(12). Hydrogen bonds inclose the following angles: N(1)-H...O(6) = 129.54°; N(1)-H...O(10) = 149.24°.

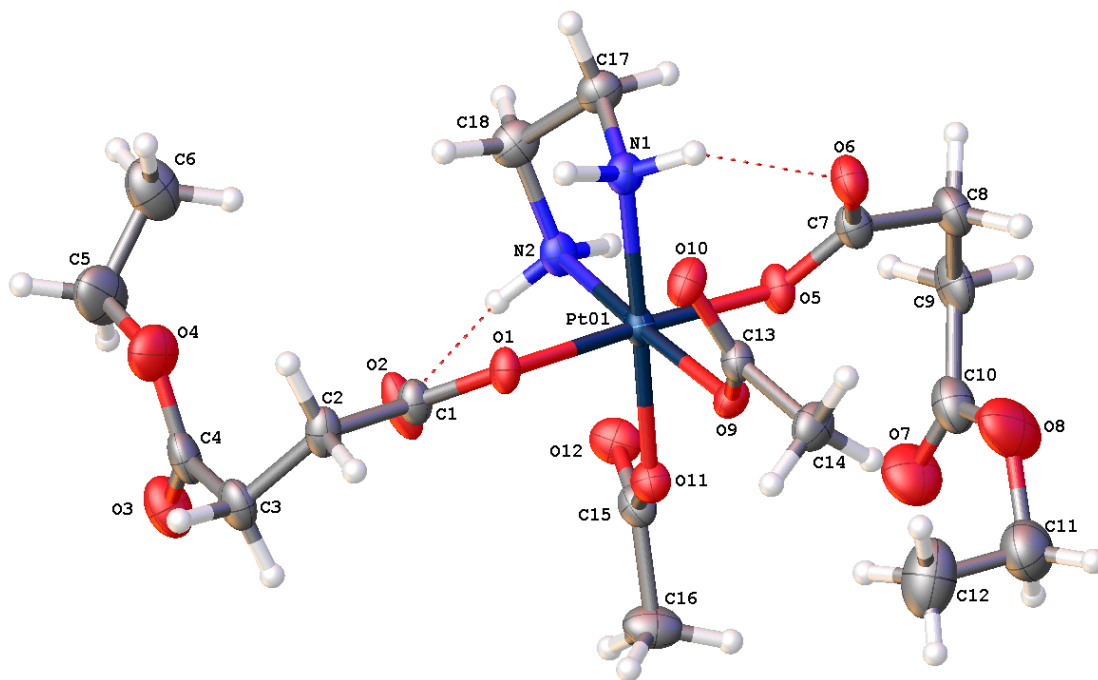


Figure 2.17. Crystal structure of compound **C-2b** with atom labeling scheme.

Selected bond lengths for all three complexes are listed in Table 2.6. It can be observed that the Pt-X distances decrease from iodide over bromide to acetate whereas the trans coordinated Pt-N bonds increase in length. This observation correlates with the trans-influence of the ligands which increases in the same order as the Pt-N bond lengths increase.

Table 2.6. Selected bond lengths in the crystal structures of complexes **A-2b**, **B-2a** and **C-2b**.

no.	ligand	Pt-X1	Pt-X2	Pt-N1	Pt-N2	Pt-O1	Pt-O2
A-2b	X=I	2.6303	2.6303	2.0723	2.0723	2.0208	2.0208
B-2a	X=Br	2.4534	2.4534	2.0635	2.0635	2.0235	2.0235
C-2b	X=O	2.0224	2.0284	2.0366	2.0404	2.0086	2.0010

Table 2.7 contains relevant angles of the crystal structures. The bidentate ethane-1,2-diamine ligand forms with the platinum center a five-membered chelate ring in half chair conformation. The torsion angle of N-C-C-N, which measures the deviation from planarity is -58.2° for the dibromido and -51.48° for the diacetato complex (cf.[51]). The O-Pt-O axis is nearly linear in the diacetato **C-2b** (177.06°) and diiodido complex **A-2b** (176.36°) but is slightly bent in the dibromido complex **B-2a** (173.4°). The two nitrogens from the ethane-1,2-diamine ligand inclose a similar angle in the halide complexes (83.61° **A-2b**, 83.77° **B-2a**) but a quite different angle in the diacetato complex (82.05° **C-2b**). The trans-coordinated ligands also exhibit different angles due to their sterical hindrance. The two acetato ligands inclose the smallest angle of 79.04° , whereas the iodides and bromides form an angle of 94.00° and 92.74° , respectively.

Table 2.7. Selected angles in the crystal structures of complexes **A-2b**, **B-2a** and **C-2b**.

no.	ligand	O1-Pt-O2	N1-Pt-N2	X-Pt-X	X-Pt-O	X-Pt-O	N1-C1-C2-N2
A-2b	X=I	176.36	83.61	94.00	90.99	90.99	
B-2a	X=Br	173.40	83.77	92.74	85.44	90.00	-58.20
C-2b	X=O	177.06	82.05	79.04	88.40	89.26	-51.48

Table 2.8. Relevant crystallographic data for the crystal structures of **A-2b**, **B-2a** and **C-2b**.

	A-2b	B-2a	C-2b
Empirical formula	C ₁₄ H ₂₆ I ₂ N ₂ O ₈ Pt	C ₁₂ H ₂₂ Br ₂ N ₂ O ₈ Pt	C ₁₈ H ₃₂ N ₂ O ₁₂ Pt
Fw	799.26	677.22	663.55
T [K]	100(2) K	100(0) K	100(2)
λ [Å]	0.71073	0.71073	0.71073
Crystal size [mm]	0.044 x 0.062 x 0.064	0.010 x 0.030 x 0.140	0.07 x 0.07 x 0.03
Crystal habit	clear orange block	clear colourless stick	clear colorless block
Crystal system	orthorhombic	monoclinic	triclinic
Space group	Iba2	C 1 2/c 1	P-1
a [Å]	9.4170(4)	18.7915(8)	9.4659(4)
b [Å]	14.9602(7)	8.8942(4)	11.8051(5)
c [Å]	16.2678(7)	11.0391(5)	12.2600(5)
α [°]	90°	90°	82.5890(10)
β [°]	90°	100.6108(14)°	71.0930(10)
γ [°]	90°	90°	69.0020(10)
V [Å ³]	2291.81(18)	1813.48(14)	1209.89(9)
Z	4	4	2
ρ_c [g/cm ³]	2.316	2.480	1.821
Reflections collected/unique	33028 / 2098	42318/2679	15954/4215
R _(int)	0.0325	0.0304	0.0378
R ₁ ¹ [I > 2 σ (I)]	0.0128	0.0109	0.0253
wR ₂ ² (all data)	0.0316	0.0256	0.0575
GOF ³	1.092	1.092	1.053

¹ $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$ ² $wR_2 = \{\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]\}^{1/2}$ ³ $GOF = \{\sum [w(F_o^2 - F_c^2)^2] / (n - p)\}^{1/2}$, n is the number of reflections and p is the total number of parameters refined.

3 Experimental

3.1 General remarks

Platinum(II) compounds disproportionate to metallic platinum(0) and platinum(IV) in the presence of light, other metals and metal ions. This side reaction was impeded due to the application of selected working techniques. All reactions were performed in absence of light which was generally realized with aluminum foil. Osmosis water was distilled two times to remove all metal ions and glass coated magnetic stirring bars were applied to avoid disproportionation based on diffusion processes. Sintered glass funnels as well as magnetic stirring bars were cleaned in hot *aqua regia* and subsequently in tridistilled water. Glass funnels that were used for the filtration of silver iodide were heated in nitric acid.

The laboratory glassware was dried at 110°C after cleaning. Moisture sensitive reactions were performed with anhydrous solvents and under argon atmosphere which was ensured by flushing the reaction vessel three times with argon after evacuation. All synthesized compounds were dried *in vacuo* and stored under argon atmosphere in the dark.

Since all synthesized platinum complexes were supposed to be cytotoxic, they were treated carefully. Caution! Although no such behavior was observed during the present work, mixtures of hydrogen peroxide and acetone are potentially explosive and should therefore be handled with utmost care.

3.2 Chemicals

All chemicals were purchased from the following commercial sources: Fluka, Acros, Riedel-de H  en, Loba, Sigma Adrich, Adrich and Donauchemie; and were used without further purification. K_2PtCl_4 was supplied from Johnson Matthey. Drying of methanol was performed by distillation over Mg and anhydrous ethanol was freshly prepared by sequent distillation over CaO and Mg. Dry dimethylformamide was used as delivered by Acros in 99.8% purity and over molecular sieve. Distilled water was prepared by double distillation of osmosis water. Thin layer chromatography was made with TLC plated of silica gel on PET-foils from Fluka. For column chromatography, silica gel 60 from Macherey-Nagel (particle size 0.04-0.063 mm) was used. MN-GF 3 ($\varnothing$ 110 mm) filter paper was also purchased from Macherey-Nagel.

3.3 Instrumental analysis

3.3.1 NMR spectroscopy

NMR measurements were recorded at 298 K on a *Bruker FT-NMR Avance III 500 MHz* spectrometer at 500.32 (^1H), 125.81 (^{13}C), 107.55 (^{195}Pt) MHz. The residual solvent resonances were used as internal reference for the chemical shifts [ppm] of ^1H and ^{13}C signals. K_2PtCl_4 and NH_4Cl served as external references for ^{195}Pt and ^{15}N chemical shifts, respectively. According to the solubility, DMF-d_7 , D_2O and CDCl_3 were applied as solvents. The spin multiplicity in ^1H NMR spectra is abbreviated as follows: s for singlet, d for doublet, t for triplet, q for quartet and m for multiplet. The letter b in front of these abbreviations represents a broad signal.

3.3.2 Elemental analysis

Elemental analyses were performed at the Microanalytical Laboratory of the University of Vienna. CHN measurements were carried out with a *2400 CHN Series II* elemental analyzer from *Perkin Elmer*. For CHNS analysis a *Eurovector EA3000 Elemental Analyzer* was used.

3.3.3 Mass spectrometry

Electrospray ionization mass spectra were measured with a *Bruker Esquire3000 ion trap* spectrometer in the positive and negative mode. In general, methanol and in few cases water was used as solvent.

3.3.4 Infrared spectroscopy

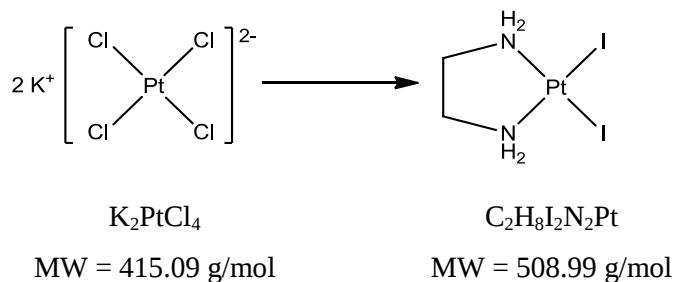
For ATR (*attenuated total reflection*) infrared spectroscopic measurements a *Bruker Vertex 70 FT-IR*-spectrometer with an ATR-unit was used. All spectra were recorded in the range of 4000-400 cm^{-1} . Strong signals are indicated with the letter s, further abbreviations are: b for broad signal, m for medium and w for weak signal.

3.3.5 X-ray crystallographic measurements

X-ray intensity data were collected with a *Bruker D8 VENTURE* system equipped with a multilayer monochromator and a Mo K α INCOATEC microfocus sealed tube ($\lambda = 0.71073 \text{ \AA}$). The structures were solved by direct methods using SHELXS-1997 [52]. Refinements were carried out with Shelx [52], Olex 2 [53] and Shelxle [54].

3.4 Platinum(II) complexes

3.4.1 (SP-4-2)-(Ethane-1,2-diamine)diiodidoplatinum(II)



Potassium tetrachloroplatinate (2.011 g, 4.84 mmol) was dissolved in distilled water (20 mL) and the clear red solution was filtrated through cotton. Potassium iodide (4.073 g, 24.54 mmol, 5 eq) dissolved in distilled water (14 mL) was added to the platinum solution and the dark red mixture was allowed to react for 30 min. Ethane-1,2-diamine (225 μL , 3.37 mmol, 1.4 eq) was added and the reaction was stirred for 3 h at room temperature. The resulting yellow precipitate was collected by filtration after cooling to 4°C for 1 h. The product was washed with cold distilled water, ethanol and diethyl ether and was dried *in vacuo* overnight.

Yield: 2.405 g (98%), orange powder

Elemental analysis: $\text{C}_2\text{H}_8\text{I}_2\text{N}_2\text{Pt}$

Element	w-% C	w-% H	w-% N
Found	4.69	1.40	5.44
Calculated	4.72	1.58	5.50

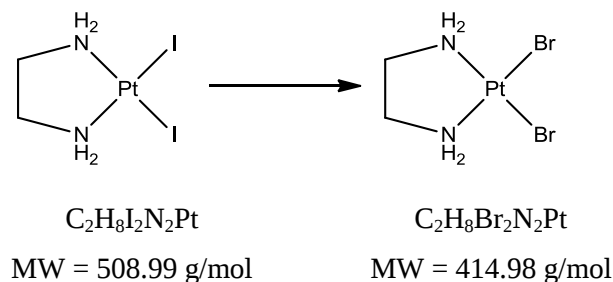
IR [cm^{-1}] – selected bands

3243 b, 3187 b ($\nu_{\text{N-H}}$)

1552 s ($\delta_{\text{N-H}}$)

1164 s, 1112 s, 1046 s, 741s

3.4.2 (SP-4-2)-Dibromido(ethane-1,2-diamine)platinum(II)



(SP-4-2)-(Ethane-1,2-diamine)diiodidoplatinum(II) (501 mg, 0.98 mmol) was suspended in distilled water (7 mL). Silver nitrate (324 mg, 1.9 mmol, 1.94 eq) was added and the mixture was allowed to react overnight at room temperature. Precipitated silver iodide was removed by filtration through a sintered glass funnel with a filter paper disk (MN-GF 3). Potassium bromide (469 mg, 3.94 mmol, 4 eq) was dissolved in a small amount of distilled water and added to the clear yellow platinum solution. The yellow product started to precipitate after several seconds and the reaction mixture was stirred for further 4 h at room temperature. The suspension was cooled to 4°C for 2 h and the final product was filtered, washed with distilled water and diethyl ether and dried *in vacuo* overnight.

Yield: 363 mg (92%), yellow powder

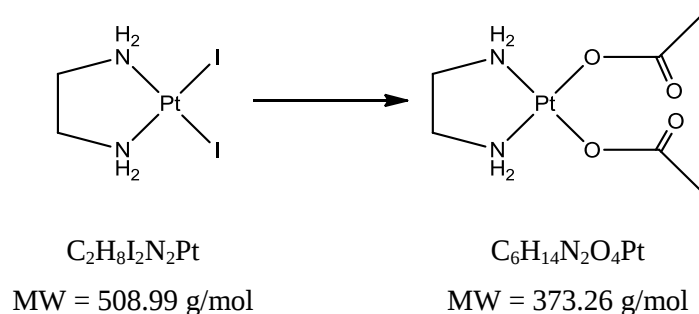
Elemental analysis: $\text{C}_2\text{H}_8\text{Br}_2\text{N}_2\text{Pt}$

Element	w-% C	w-% H	w-% N
Found	5.75	1.76	6.46
Calculated	5.79	1.94	6.75

IR [cm⁻¹] – selected bands

3261 b, 3198 b ($\nu_{\text{N-H}}$)
 1559 s ($\delta_{\text{N-H}}$)
 1180 s, 1123 s, 1050 s, 756 s

3.4.3 (SP-4-2)-Diacetato(ethane-1,2-diamine)platinum(II)



(SP-4-2)-(Ethane-1,2-diamine)diiodidoplatinum(II) (800 mg, 1.57 mmol) was suspended thoroughly in an aqueous solution (70 mL) of silver sulfate (466 mg, 1.49 mmol, 0.95 eq). The mixture was left stirring overnight at room temperature in the dark. In order to remove precipitated silver iodide, the suspension was filtrated through a sintered glass funnel with a filter paper disk (MN GF-3). Barium acetate was prepared in situ by suspending barium hydroxide octahydrate (471 mg, 1.49 mmol, 0.95 eq) in distilled water (11 mL) and acetic acid (256 μL , 4.48 mmol, 2.85 eq). The solution was stirred for 20 min and added slowly to the clear platinum solution. The reaction mixture was stirred for 2.5 h and the suspension was filtrated through a sintered glass funnel with a filter paper disk (MN GF-3) to remove precipitated barium sulfate. The clear filtrate was evaporated to dryness and a small amount of methanol was added to dissolve free ligands. The obtained suspension was cooled to 4°C for 3 h, filtered and the precipitate was washed with diethyl ether and dried *in vacuo* to yield a pale yellow powder.

Yield 412 mg (73 %), pale yellow powder

Elemental analysis: $\text{C}_6\text{H}_{14}\text{N}_2\text{O}_4\text{Pt} \cdot 0.5\text{H}_2\text{O}$

Element	w-% C	w-% H	w-% N
Found	18.48	3.67	7.30
Calculated	18.85	3.96	7.33

^1H NMR (D_2O): δ 5.24 (bs, 4H, NH_2), 2.41 (s, 4H, CH_2), 1.90 (s, 6H, CH_3) ppm.

^{13}C NMR (D_2O): δ 182.1 ($\text{C}=\text{O}$), 48.1 ($\text{C}-\text{H}_2$), 21.9 (CH_3) ppm.

^{195}Pt NMR (D_2O): δ -286 ppm.

ESI-MS^+ in H_2O

Ion	$[\text{m/z}]^+$	Molecular formula
$[\text{M}_2+\text{Na}^+]^+$	769.1	$\text{C}_{12}\text{H}_{28}\text{N}_4\text{O}_8\text{Pt}_2\text{Na}$
$[\text{M}+\text{Na}^+]^+$	395.1	$\text{C}_6\text{H}_{14}\text{N}_2\text{O}_4\text{PtNa}$
$[\text{M}-\text{CH}_3\text{COOH}+\text{Na}^+]^+$	335.1	$\text{C}_4\text{H}_{10}\text{N}_2\text{O}_2\text{PtNa}$
$[\text{M}-\text{CH}_3\text{COO}]^+$	313.2	$\text{C}_4\text{H}_{11}\text{N}_2\text{O}_2\text{Pt}$

ESI-MS^- in H_2O

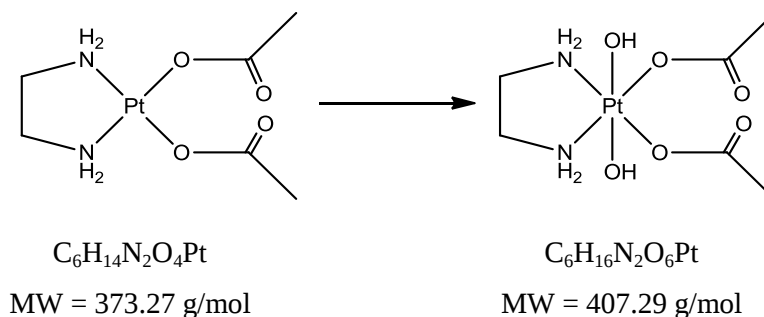
Ion	$[\text{m/z}]^-$	Molecular formula
$[\text{M}-\text{H}^+]^-$	372.4	$\text{C}_6\text{H}_{13}\text{N}_2\text{O}_4\text{Pt}$

$\text{IR} [\text{cm}^-]$ – selected bands

3215 b, 3113 b ($\nu_{\text{N-H}}$)
 1636 m, 1583 s ($\nu_{\text{as C=O}}$); ($\delta_{\text{N-H}}$)
 1390 m, 1367 m ($\nu_{-\text{OCOCH}_3}$), ($\nu_{-\text{COCH}_3}$)
 1318 s, 1151, 1121, 688

3.5 Oxidation

3.5.1 (OC-6-33)-Diacetato(ethane-1,2-diamine)dihydroxidoplatinum(IV)



(SP-4-2)-Diacetato(ethane-1,2-diamine)platinum(II) (352 mg, 0.94 mmol) was suspended in distilled water (3 mL) and 3 mL of H_2O_2 (30%). The reaction mixture was heated to 40°C for 10-15 min and stirred at room temperature for further 45 min. The volume of the resulting clear yellow solution was concentrated under reduced pressure and acetone was added while cooling to 0°C to precipitate the product. The resulting suspension was cooled to 4°C for 1.5 h. The white product was filtered, washed with cold methanol and diethyl ether and dried *in vacuo* overnight.

Yield: 133 mg (35 %), white powder

Elemental analysis: $\text{C}_6\text{H}_{14}\text{N}_2\text{O}_6\text{Pt} \cdot 0.5\text{H}_2\text{O}$

Element	w-% C	w-% H	w-% N
Found	17.15	3.94	6.58
Calculated	17.31	4.12	6.73

^1H NMR (D_2O): δ 2.64 (s+d, 4H, CH_2 , $^3J_{\text{Pt,H}} = 32.5$ Hz), 2.06 (s, 6H, CH_3) ppm.

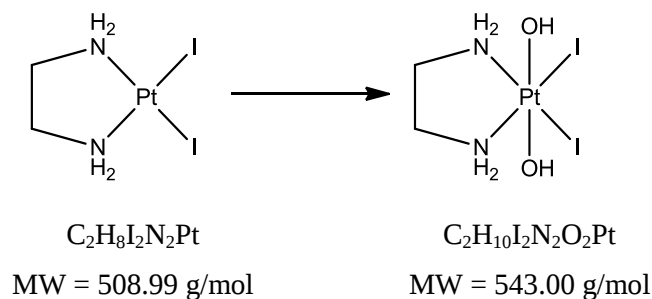
^{13}C NMR (D_2O): δ 181.2 (C=O), 47.0 (CH_2), 22.1 (CH_3) ppm.

^{195}Pt NMR (D_2O): δ 3185 ppm.

IR [cm⁻¹]- selected bands

3412 b	($\nu_{\text{Pt-OH}}$)
1594 s	($\nu_{\text{as C=O}}$); ($\delta_{\text{N-H}}$)
1366 s, 1326 s	($\nu_{\text{-O-CO-CH}_3}$), ($\nu_{\text{-CO-CH}_3}$)
1156, 1064	

3.5.2 (OC-6-33)-(Ethane-1,2-diamine)dihydroxidodiiodidoplatinum(IV)



(SP-4-2)-(Ethane-1,2-diamine)diiodidoplatinum(II) (210 mg, 0.41 mmol) was suspended in distilled water (10 mL) and a 30% hydrogen peroxide solution (10 mL) was added. The suspension was stirred for 10 min at room temperature and for further 20 min at 50°C. The resulting brown precipitate was collected by filtration and subsequently stirred for 1h in pyridine at 70° to remove unreacted starting material. The insoluble platinum(IV) complex was filtered, washed with acetone and diethyl ether and dried *in vacuo* overnight.

Yield: 150 mg (67%), orange powder

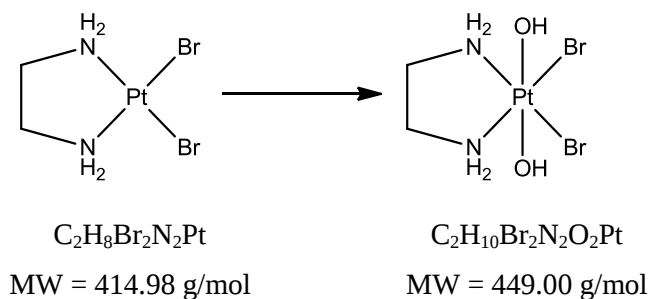
Elemental analysis: $\text{C}_2\text{H}_{10}\text{I}_2\text{N}_2\text{O}_2\text{Pt}$

Element	w-% C	w-% H	w-% N
Found	4.40	1.72	5.02
Calculated	4.42	1.86	5.16

IR [cm^{-1}] – selected bands

3475 m	($\nu_{\text{Pt-OH}}$)
3213 b, 3152 b	($\nu_{\text{N-H}}$)
1570 m	($\delta_{\text{N-H}}$)
1222 m, 1179 m, 1020 s, 982 s, 875	

3.5.3 (OC-6-33)-Dibromido(ethane-1,2-diamine)dihydroxidoplatinum(IV)



(SP-4-2)-Dibromido(ethane-1,2-diamine)platinum(II) (353 mg, 0.85 mmol) was suspended in distilled water (8 mL) and a 30% hydrogen peroxide solution (8 mL) was added. The suspension was stirred for 30 min at room temperature and the resulting green-grey precipitate was filtered. To remove remaining starting material the precipitate was stirred for 1h in pyridine at 70°C. The insoluble pale yellow product was filtered, washed with acetone and diethyl ether and dried *in vacuo* overnight.

Yield: 288 mg (76%), pale yellow powder

Elemental analysis: $\text{C}_2\text{H}_{10}\text{I}_2\text{N}_2\text{O}_2\text{Pt} \cdot 0.8\text{C}_5\text{H}_5\text{N}$ (pyridine)

Element	w-% C	w-% H	w-% N
Found	13.88	2.83	7.45
Calculated	14.07	2.75	7.66

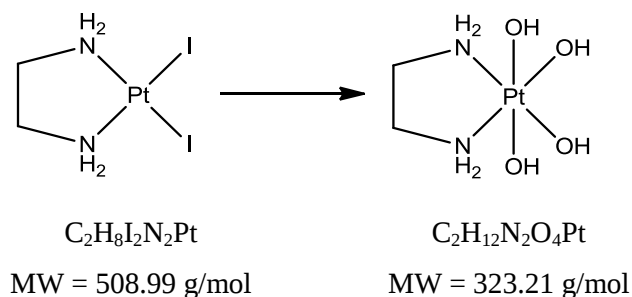
IR [cm^{-1}] – selected bands

3470 m ($\nu_{\text{Pt-OH}}$)

1579 m ($\delta_{\text{N-H}}$)

1445 m, 1049 s, 1010 s

3.5.4 (OC-6-22)-(Ethane-1,2-diamine)tetrahydroxidoplatinum(IV)



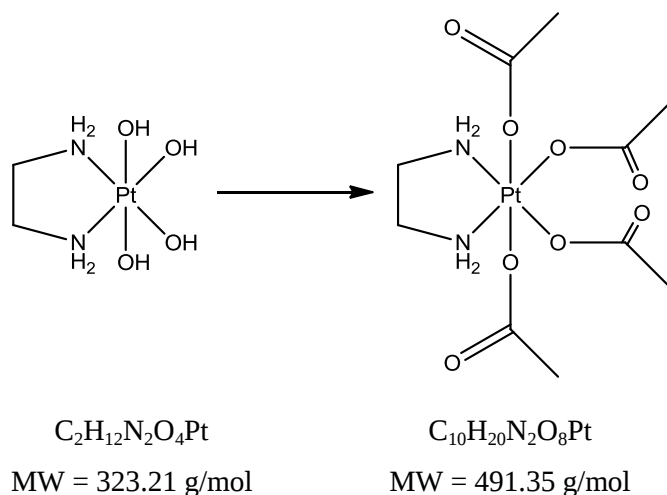
(SP-4-2)-(Ethane-1,2-diamine)diiodidoplatinum(II) (501 mg, 0.98 mmol) was suspended in distilled water (10 mL). Silver nitrate (317 mg, 1.87 mmol, 1.9 eq) was also dissolved in distilled water (2 mL) and added to the suspension of the complex. The reaction mixture was stirred for 24 h in the dark. Silver iodide was removed by filtration through a sintered glass funnel with a filter paper disk (MN GF-3). Subsequently the aqua complex was transformed into the dihydroxido complex by ion exchange chromatography. Therefore amberlite.HCl (20 g) was suspended in distilled water and filled into a column. The ion exchanger was washed with 0.5M HCl (200 mL) and with distilled water (500 mL) until pH was adjusted to 6. The ion exchanger was conditioned with 0.5M NaOH (200 mL). The column was washed again with distilled water (200 mL) until pH = 6 was reached. The solution of the complex (pH = 5) was passed through the column and all basic fractions were collected (pH = 11). The volume of the combined fractions was reduced to approximately 6 mL under reduced pressure and a 30% hydrogen peroxide solution (6 mL) was added. The reaction was left stirring overnight. The reaction volume was concentrated under reduced pressure and the yellow solution was cooled to 4°C for 1 h. Acetone was added slowly to precipitate the product. The suspension was cooled and the product was collected by filtration and dried *in vacuo* overnight.

Yield: 276 mg (90 %), pale yellow powder

¹H NMR (D₂O): δ 2.83 (s+d, 4H, CH₂, ³J_{Pt,H} = 25.0 Hz) ppm.

3.6 Carboxylation

3.6.1 (OC-6-22)-Tetraacetato(ethane-1,2-diamine)platinum(IV)



(OC-6-22)-(Ethane-1,2-diamine)tetrahydroxidoplatinum(IV) (64 mg, 0.20 mmol) was suspended in pure acetic anhydride (18 mL) and the reaction mixture was left stirring for 10 days in the dark. The suspension was filtrated through a sintered glass funnel (1st fraction) and the clear filtrate was evaporated to dryness. The residue was suspended in acetone and the product was collected by filtration (2nd fraction). The two fractions were combined and recrystallized in a solvent pair of water and acetone to yield the product as a white solid.

Yield: 52 mg (53 %), white powder

Elemental analysis: $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_8\text{Pt}$

	w-% C	w-% H	w-% N
Found	24.33	4.14	5.61
Calculated	24.44	4.10	5.70

^1H NMR (DMF- d_7): δ 8.52 (bs, 4H, NH_2), 2.80 (bs, 4H, CH_2), 1.97 (s, 6H, CH_3), 1.91 (s, 6H, CH_3) ppm.

^{13}C NMR (DMF- d_7): δ 178.9 (C=O), 176.2 (C=O), 48.0 (CH_2), 22.0 (CH_3), 21.7 (CH_3) ppm.

^{195}Pt NMR (DMF- d_7): δ 3496 ppm.

^{15}N NMR (DMF- d_7): δ -21.7 (NH_2) ppm.

ESI-MS⁺ in MeOH

Ion	[m/z] ⁺	Molecular formula
$[\text{M}+\text{Na}^+]^+$	513.1	$\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_8\text{PtNa}$
$[\text{M}-\text{CH}_3\text{COOH}+\text{Na}^+]^+$	453.1	$\text{C}_8\text{H}_{16}\text{N}_2\text{O}_6\text{PtNa}$
$[\text{M}-2\text{CH}_3\text{COOH}+\text{CH}_3\text{OH}+\text{H}^+]^+$	394.1	$\text{C}_6\text{H}_{12}\text{N}_2\text{O}_4\text{PtNa}$

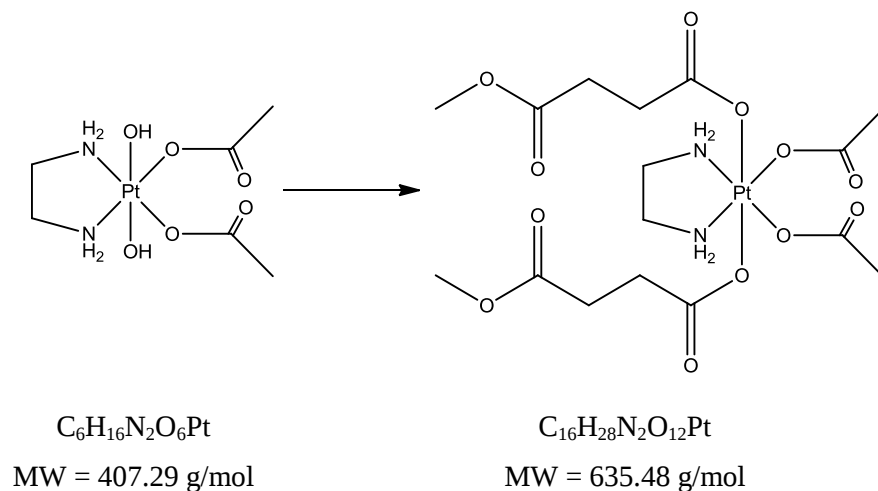
ESI-MS⁻ in MeOH

Ion	[m/z] ⁻	Molecular formula
$[\text{M}-\text{H}]^-$	489.0	$\text{C}_{10}\text{H}_{19}\text{N}_2\text{O}_8\text{Pt}$
$[\text{M}-2\text{CH}_3\text{COOH}-\text{H}]^-$	370.0	$\text{C}_6\text{H}_{11}\text{N}_2\text{O}_4\text{Pt}$
$[\text{M}-3\text{CH}_3\text{COOH}-\text{H}]^-$	310.4	$\text{C}_4\text{H}_7\text{N}_2\text{O}_2\text{Pt}$

IR [cm⁻¹] – selected bands

3214 b	($\nu_{\text{N-H}}$)
3019 w, 2930 w	($\nu_{\text{C-H}}$)
1645 s, 1621 s	($\nu_{\text{as C=O}}$); ($\delta_{\text{N-H}}$)
1356 m	($\nu_{\text{-CO-CH}_3}$)
1276 s, 1179	

3.6.2 (OC-6-13)-Diacetato(ethane-1,2-diamine)bis((4-methoxy)-4-oxobutanoato)platinum(IV)

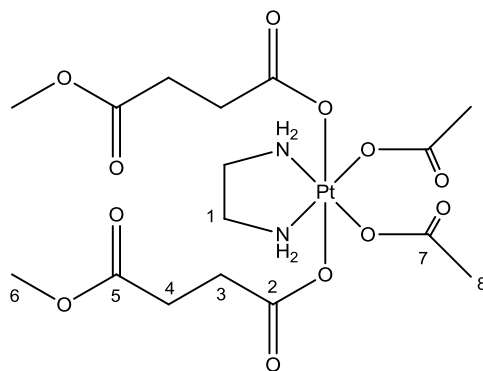


3-(Methoxycarbonyl)propanoic anhydride (344 mg, 1.40 mmol, 3 eq) in absolute DMF (6 mL) was added to the starting material (OC-6-33)-diacetato(ethane-1,2-diamine)dihydroxidoplatinum(IV) (186 mg, 0.47 mmol) under argon atmosphere. The suspension was stirred at 45°C for 5 h in a closed Schlenk flask. The resulting clear yellow solution was allowed to cool down to room temperature and after stirring the reaction for further 3 h, DMF was removed *in vacuo* overnight. The crude product was purified by column chromatography on silica using a gradient elution of ethyl acetate:methanol (6:1-2:1). The solvent was removed under reduced pressure and the residue was suspended in ethyl acetate and diethyl ether. The white product was collected by filtration and dried *in vacuo*.

Yield: 165 mg (57 %), white powder

Elemental analysis: $\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_{12}\text{Pt} \cdot 0.5\text{H}_2\text{O}$

	w-% C	w-% H	w-% N
Found	29.87	4.40	4.38
Calculated	29.82	4.54	4.35



^1H NMR (DMF- d_7): δ 8.48 (bs, 4H, NH_2), 3.65 (s, 6H, 6- H), 2.80 (bs, 4H, 1- H), 2.58-2.55 (m, 4H, 3- H), 2.53-2.50 (m, 4H, 4- H), 1.97 (s, 6H, 8- H) ppm.

^{13}C NMR (DMF- d_7): δ 180.0 (2-C), 176.3 (7-C), 173.0 (5-C), 51.1 (6-C), 47.9 (1-C), 30.5 (3-C, $^3J_{\text{Pt,C}}=39.1$ Hz), 29.6 (4-C), 21.7 (8-C, $^3J_{\text{Pt,C}}=32.0$ Hz) ppm.

^{195}Pt NMR (DMF- d_7): δ 3494 ppm.

^{15}N NMR (DMF- d_7): δ -21.6 (NH_2) ppm.

ESI-MS $^+$ in MeOH

Ion	[m/z] $^+$	Molecular formula
$[\text{M}+\text{Na}^+]^+$	656.5	$\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_{12}\text{PtNa}$
$[\text{M}-\text{CH}_3\text{COOH}+\text{Na}^+]^+$	596.5	$\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_{10}\text{PtNa}$

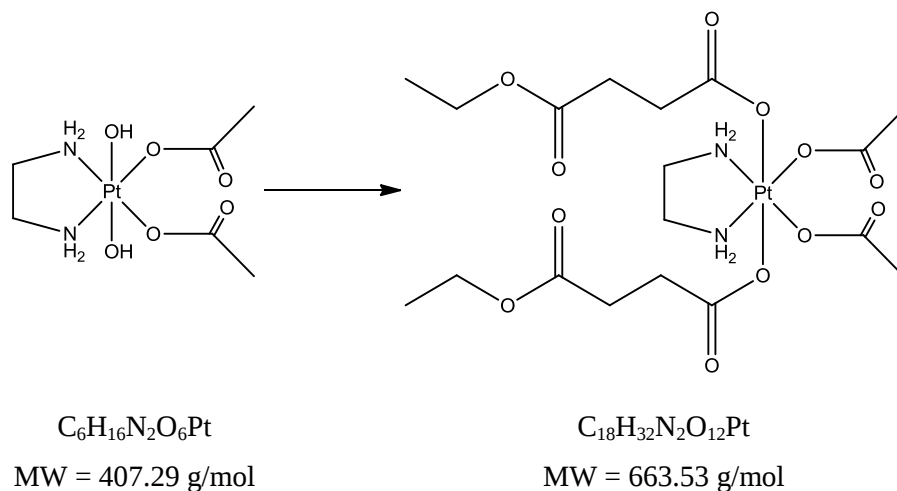
ESI-MS $^-$ in MeOH

Ion	[m/z] $^-$	Molecular formula
$[\text{M}-\text{H}^+]^-$	632.2	$\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_{12}\text{Pt}$
$[\text{M}+\text{Cl}]^-$	668.4	$\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_{12}\text{PtCl}$

IR [cm $^{-1}$] – selected bands

3230 b,	($\nu_{\text{N-H}}$)
3048 w	($\nu_{\text{C-H}}$)
1728 s, 1640 s	($\nu_{\text{as C=O}}$); ($\delta_{\text{N-H}}$)
1358 s	($\nu_{\text{-CO-CH}_3}$)
1291 s, 1172 m	

3.6.3 (OC-6-13)-Diacetato(ethane-1,2-diamine)bis((4-ethoxy)-4-oxobutanoato)platinum(IV)

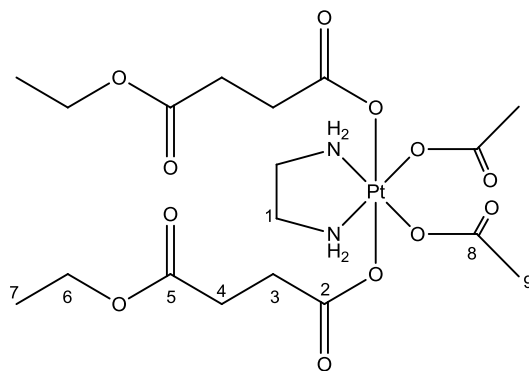


3-(Ethoxycarbonyl)propanoic anhydride (334 mg, 1.22 mmol, 3 eq) in absolute DMF (5.5 mL) was added to the starting material (OC-6-33)-diacetato(ethane-1,2-diamine)dihydroxidoplatinum(IV) (165 mg, 0.41 mmol) under argon atmosphere. The suspension was heated to 45°C for 4 h in a closed Schlenk flask. The resulting clear yellow solution was allowed to cool down to room temperature and after stirring the reaction for further 4 h, DMF was removed *in vacuo* overnight. The crude product was purified by column chromatography on silica using a gradient elution of ethyl acetate:methanol (6:1-4:1). The solvent was removed under reduced pressure and the residue was suspended in ethyl acetate and diethylether. The white product was filtered and dried *in vacuo*.

Yield 165 g (61 %), white powder

Elemental analysis: $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_{12}\text{Pt} \cdot 0.5\text{H}_2\text{O}$

Sample	w-% C	w-% H	w-% N
Found	32.15	4.95	4.16
Calculated	32.15	4.95	4.17



^1H NMR (DMF- d_7): 8.49 (bs, 4H, NH_2), 4.11 (q, 4H, 6- H , $^3J_{\text{H,H}} = 7.1$ Hz), 2.80 (bs, 4H, 1- H), 2.57-2.54 (m, 4H, 3- H), 2.52-2.49 (m, 4H, 4- H), 1.97 (s, 6H, 9- H), 1.23 (t, 6H, 7- H , $^3J_{\text{H,H}} = 7.1$ Hz) ppm.

^{13}C NMR (DMF- d_7): 180.1 (2- C), 176.3 (8- C), 172.5 (5- C), 60.1 (6- C), 47.9 (1- C), 30.5 (3- C , $^3J_{\text{Pt,C}} = 39.9$ Hz), 29.9 (4- C), 21.7 (9- C), 13.8 (7- C) ppm.

^{195}Pt NMR (DMF- d_7): δ 3494 ppm.

^{15}N NMR (DMF- d_7): -21.5 (NH_2) ppm.

ESI-MS $^+$ in MeOH

Ion	$[\text{m/z}]^+$	Molecular formula
$[\text{M}+\text{Na}^+]^+$	685.2	$\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_{12}\text{PtNa}$
$[\text{M}_2+\text{Na}^+]^+$	1347.8	$\text{C}_{36}\text{H}_{64}\text{N}_4\text{O}_{24}\text{Pt}_2\text{Na}$
$[\text{M}-\text{CH}_3\text{COOH}+\text{Na}^+]^+$	625.0	$\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_{10}\text{PtNa}$

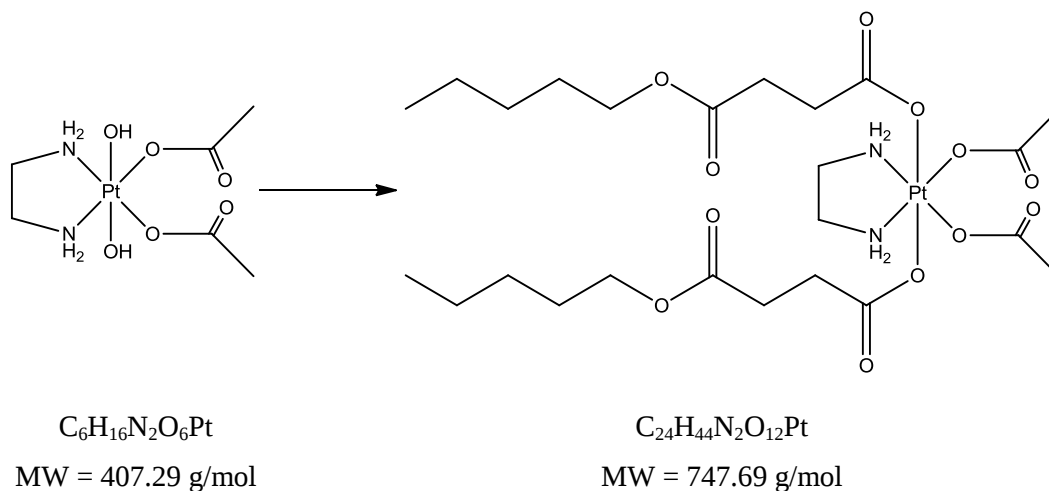
ESI-MS $^-$ in MeOH

Ion	$[\text{m/z}]^-$	Molecular formula
$[\text{M}-\text{H}]^-$	663.2	$\text{C}_{18}\text{H}_{31}\text{N}_2\text{O}_{12}\text{Pt}$
$[\text{M}+\text{Cl}]^-$	699.4	$\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_{12}\text{PtCl}$

IR [cm^{-1}] – selected bands

3226 b, 3136 b	($\nu_{\text{N-H}}$)
2985 w, 2924 w	($\nu_{\text{C-H}}$)
1724 m, 1649 s, 1626 s	($\nu_{\text{as C=O}}$); ($\delta_{\text{N-H}}$)
1359 m	($\nu_{\text{-CO-CH}_3}$)

3.6.4 (OC-6-13)-Diacetato(ethane-1,2-diamine)bis((4-pentoxo)-4-oxobutanoato)platinum(IV)

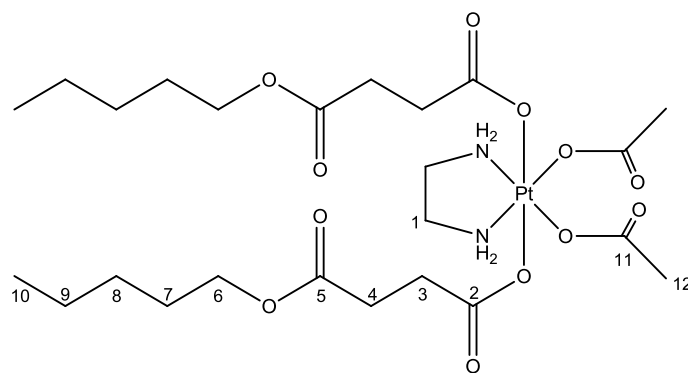


3-(Pentoxycarbonyl)propanoic anhydride (505 mg, 1.41 mmol, 3 eq) in absolute DMF (7 mL) was added to the starting material (OC-6-33)-diacetato(ethane-1,2-diamine)dihydroxidoplatinum(IV) (182 mg, 0.45 mmol) under argon atmosphere. The suspension was heated to 35°C for 8 h in a closed Schlenk flask. The resulting clear yellow solution was allowed to cool down to room temperature and DMF was removed *in vacuo* overnight while heating to 30°C. The crude product was purified by column chromatography on silica using a gradient elution of ethyl acetate:methanol (1:0-10:1). The solvent was removed under reduced pressure and the residue was suspended in diethyl ether, frozen with liquid nitrogen and stored in the freezer for two days. The white product was filtered and dried *in vacuo*.

Yield 157 mg (47 %), white powder

Elemental analysis: $\text{C}_{24}\text{H}_{44}\text{N}_2\text{O}_{12}\text{Pt}$

Sample	w-% C	w-% H	w-% N
Found	38.66	6.26	3.96
Calculated	38.55	5.93	3.75



^1H NMR (DMF- d_7): δ 8.49 (bs, 4H, NH_2), 4.06 (t, 4H, 6- H , $^3J_{\text{H,H}} = 6.7$ Hz), 2.80 (bs, 4H, 1- H), 2.58-2.55 (m, 4H, 3- H /4- H), 2.54-2.51 (m, 4H, 3- H /4- H), 1.97 (s, 6H, 12- H), 1.65-1.59 (m, 4H, 7- H), 1.36-1.30 (m, 8H, 8- H , 9- H), 0.91 (t, 6H, 10- H , $^3J_{\text{H,H}} = 6.7$ Hz) ppm.

^{13}C NMR (DMF- d_7): δ 180.1 (2- C), 176.3 (11- C), 172.6 (5- C), 64.2 (6- C), 47.9 (1- C), 30.5 (3- C /4- C), 29.9 (3- C /4- C), 28.2 (7- C), 27.9 (8- C), 22.2 (9- C), 21.7 (12- C), 13.5 (10- C) ppm.

^{195}Pt NMR (DMF- d_7): δ 3495 ppm.

^{15}N NMR (DMF- d_7): δ -21.5 (NH_2) ppm.

ESI-MS $^+$ in MeOH

Ion	[m/z] $^+$	Molecular formula
$[\text{M}+\text{Na}^+]^+$	769.3	$\text{C}_{24}\text{H}_{44}\text{N}_2\text{O}_{12}\text{PtNa}$
$[\text{M}-\text{CH}_3\text{COOH}+\text{Na}^+]^+$	710.2	$\text{C}_{22}\text{H}_{40}\text{N}_2\text{O}_{10}\text{PtNa}$
$[\text{M}-2\text{CH}_3\text{COOH}+\text{Na}^+]^+$	651.2	$\text{C}_{20}\text{H}_{36}\text{N}_2\text{O}_8\text{PtNa}$
$[\text{M}-\text{CH}_3\text{COOH}-]$	522.1	$\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_6\text{PtNa}$

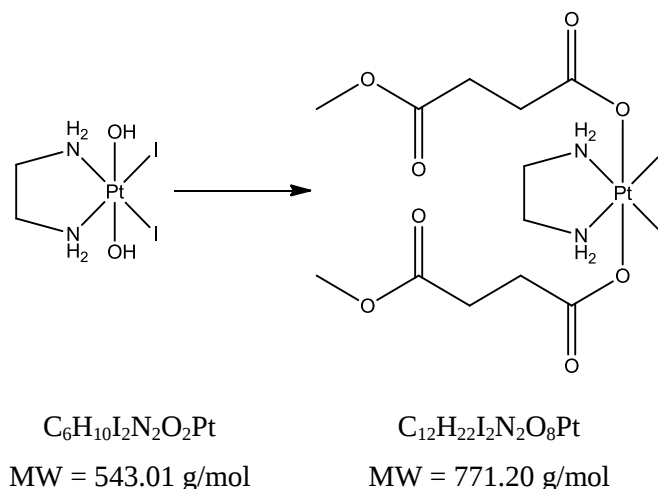
ESI-MS $^-$ in MeOH

Ion	[m/z] $^-$	Molecular formula
$[\text{M}-\text{H}^+]^-$	745.3	$\text{C}_{24}\text{H}_{43}\text{N}_2\text{O}_{12}\text{Pt}$
$[\text{M}+\text{Cl}]^-$	782.3	$\text{C}_{24}\text{H}_{44}\text{N}_2\text{O}_{12}\text{PtCl}$

IR [cm $^{-1}$] – selected bands

3190 b	($\nu_{\text{N-H}}$)
2958 m, 2930 m, 2859 w	($\nu_{\text{C-H}}$)
1730 s, 1625 s	($\nu_{\text{as C=O}}$); ($\delta_{\text{N-H}}$)
1357 s	($\nu_{\text{-CO-CH}_3}$)
1303 s, 1204 s, 1157 s	

3.6.5 (OC-6-33)-(Ethane-1,2-diamine)diiodidobis((4-methoxy)-4-oxobutanoato)platinum(IV)

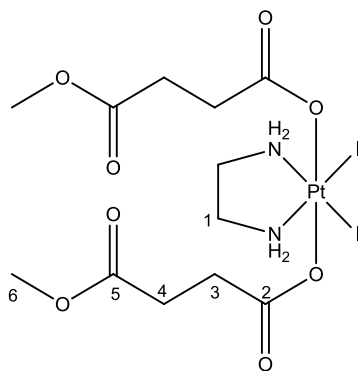


3-(Methoxycarbonyl)propanoic anhydride (304 mg, 1.23 mmol, 3 eq) in absolute DMF (6 mL) was added to the starting material (OC-6-33)-(ethane-1,2-diamine)dihydroxidodiiodidoplatinum(IV) (205 mg, 0.38 mmol) under argon atmosphere. The suspension was stirred for 3 h at 70°C and for 2 h at 35°C in a closed Schlenk flask. The resulting clear red solution was allowed to cool down to room temperature and after stirring the reaction mixture for further 12 h, DMF was removed *in vacuo* overnight. The crude product was purified by column chromatography on silica (ethyl acetate:methanol 10:1). The solvent was removed under reduced pressure and the residue was suspended in diethylether and cooled to 4°C for 2 h. The red crystalline solid was filtered, washed with cold methanol and diethyl ether and dried *in vacuo*.

Yield: 178 mg (61%), red crystalline solid

Elemental analysis: $\text{C}_{12}\text{H}_{22}\text{I}_2\text{N}_2\text{O}_8\text{Pt}$

	w-% C	w-% H	w-% N
Found	18.60	2.87	3.64
Calculated	18.69	2.88	3.63



^1H NMR (DMF- d_7): δ 8.47 (bs, 4H, NH_2), 3.64 (s, 6H, 6- H), 2.76 (bs, 4H, 1- H), 2.51 (s, 8H, 3- H , 4- H) ppm.

^{13}C NMR (DMF- d_7): δ 181.8 (2-C), 172.9 (5-C), 51.1 (6-C), 50.4 (1-C), 30.8 (3-C/4-C), 29.6 (3-C/4-C) ppm.

^{195}Pt NMR (DMF- d_7): δ 1372 ppm.

^{15}N NMR (DMF- d_7): δ -0.6 (NH_2) ppm.

ESI-MS⁺ in MeOH

Ion	[m/z] ⁺	Molecular formula
$[\text{M}+\text{Na}]^+$	793.4	$\text{C}_{12}\text{H}_{22}\text{I}_2\text{N}_2\text{O}_8\text{PtNa}$
$[\text{M}+\text{K}]^+$	809.9	$\text{C}_{12}\text{H}_{22}\text{I}_2\text{N}_2\text{O}_8\text{PtK}$

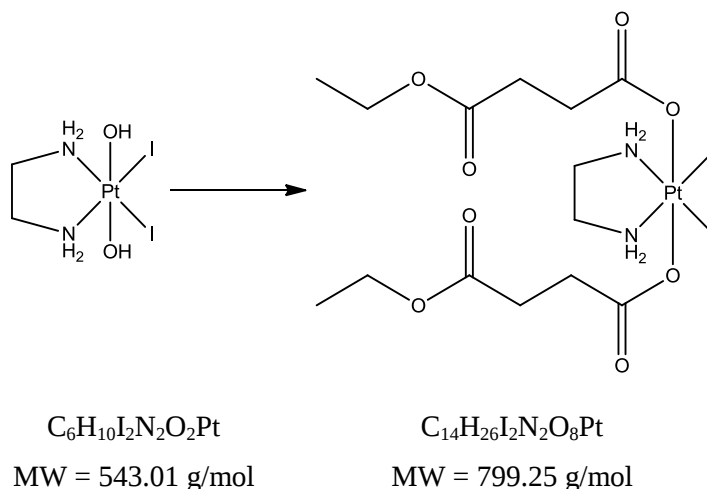
ESI-MS⁻ in MeOH

Ion	[m/z] ⁻	Molecular formula
$[\text{M}-\text{H}]^-$	769.9	$\text{C}_{12}\text{H}_{21}\text{I}_2\text{N}_2\text{O}_8\text{Pt}$

IR [cm⁻¹] – selected bands

3233 b	($\nu_{\text{N-H}}$)
2997 w, 2949 w	($\nu_{\text{C-H}}$)
1716 s, 1649 s	($\nu_{\text{as C=O}}$); ($\delta_{\text{N-H}}$)
1334 s	($\nu_{\text{-CO-CH}_3}$)
1436 m, 1246 m, 1172 s, 1055 m	

3.6.6 (OC-6-33)-(Ethane-1,2-diamine)bis((4-ethoxy)-4-oxobutanoato)diiodidoplatinum(IV)

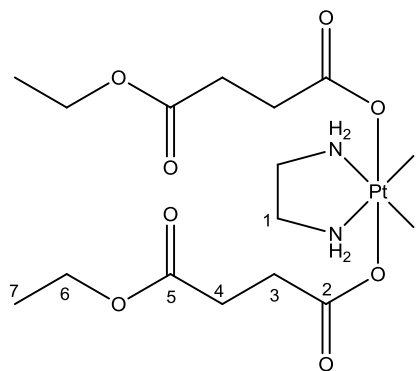


3-(Ethoxycarbonyl)propanoic anhydride (311 mg, 1.13 mmol, 3 eq) in absolute DMF (6 mL) was added to the starting material (OC-6-33)-(ethane-1,2-diamine)dihydroxidiodidoplatinum(IV) (202 mg, 0.37 mmol) under argon atmosphere. The suspension was stirred for 3 h at 70°C and for 2 h at 35°C in a closed Schlenk flask. The resulting clear red solution was allowed to cool down to room temperature and after stirring the reaction mixture for further 12 h, DMF was removed *in vacuo* overnight. The crude product was purified by column chromatography on silica (ethyl acetate:methanol 10:1). The solvent was removed under reduced pressure and the residue was suspended in diethylether and cooled to 4°C for 2 h. The red crystalline solid was filtered, washed with cold methanol and diethyl ether and dried *in vacuo*.

Yield: 177 mg (60%), red crystalline solid

Elemental analysis: $\text{C}_{14}\text{H}_{26}\text{I}_2\text{N}_2\text{O}_8\text{Pt}$

	w-% C	w-% H	w-% N
Found	21.02	3.32	3.46
Calculated	21.04	3.28	3.50



^1H NMR (DMF- d_7): δ 8.48 (bs, 4H, NH_2), 4.10 (q, 4H, 6- H , $^3J_{\text{H,H}} = 7.1$ Hz), 2.76 (bs, 4H, 1- H), 2.50 (m, 8H, 3- H /4- H), 1.22 (t, 6H, 7- H , $^3J_{\text{H,H}} = 7.1$ Hz) ppm.

^{13}C NMR (DMF- d_7): δ 181.8 (2- C), 172.4 (5- C), 60.1 (6- C), 50.4 (1- C), 30.9 (3- C /4- C), 29.9 (3- C /4- C), 13.8 (7- C) ppm.

^{195}Pt NMR (DMF- d_7): δ 1372 ppm.

^{15}N NMR (DMF- d_7): δ -0.6 (NH_2) ppm.

ESI-MS $^+$ in MeOH

Ion	[m/z] $^+$	Molecular formula
$[\text{M}+\text{Na}^+]^+$	821.4	$\text{C}_{14}\text{H}_{26}\text{I}_2\text{N}_2\text{O}_8\text{PtNa}$

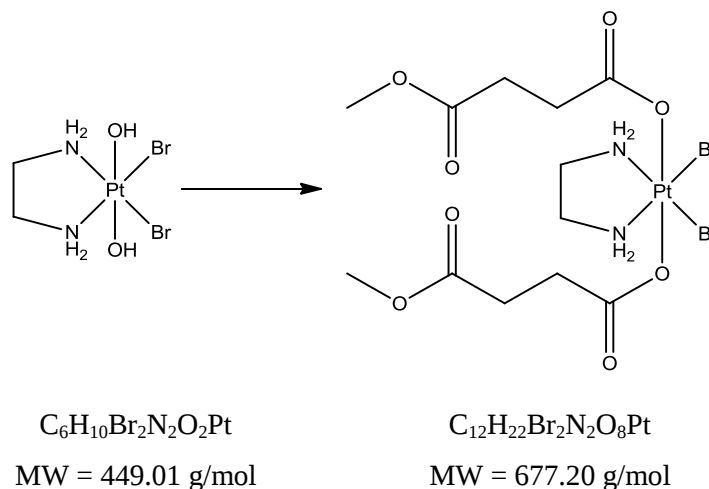
ESI-MS $^-$ in MeOH

Ion	[m/z] $^-$	Molecular formula
$[\text{M}-\text{H}^+]^-$	798	$\text{C}_{14}\text{H}_{25}\text{I}_2\text{N}_2\text{O}_8\text{Pt}$

IR [cm^{-1}] – selected bands

3181 b	($\nu_{\text{N-H}}$)
2978 w, 2904 w	($\nu_{\text{C-H}}$)
1704 s, 1645 m	($\nu_{\text{as C=O}}$); ($\delta_{\text{N-H}}$)
1369 s	($\nu_{\text{-CO-CH}_3}$)
1412 m, 1287 s, 1244 s, 1180 s, 1027 m	

3.6.7 (OC-6-33)-Dibromido(ethane-1,2-diamine)bis((4-methoxy)-4-oxobutanoato)platinum(IV)

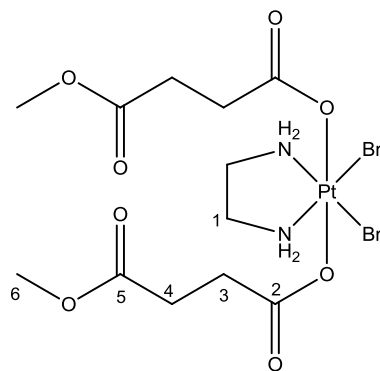


3-(Methoxycarbonyl)propanoic anhydride (466 mg, 1.89 mmol, 3 eq) in absolute DMF (6 mL) was added to the starting material (OC-6-33)-dibromido(ethane-1,2-diamine)dihydroxidoplatinum(IV) (261 mg, 0.58 mmol) under argon atmosphere. The suspension was heated to 60°C for 26 h in a closed Schlenk flask. The resulting clear orange solution was allowed to cool down to room temperature and DMF was removed *in vacuo* overnight. The crude product was purified by column chromatography on silica (ethyl acetate:methanol 10:1). The product containing fractions were combined and the solvent was removed under reduced pressure. The residue suspended in diethyl ether, filtered, washed with methanol and diethyl ether and dried *in vacuo*.

Yield: 85 mg (22%), pale yellow powder

Elemental analysis: $\text{C}_{14}\text{H}_{26}\text{Br}_2\text{N}_2\text{O}_8\text{Pt}$

	w-% C	w-% H	w-% N
Found	21.47	3.30	4.04
Calculated	21.28	3.27	4.14



^1H NMR (DMF- d_7): δ 8.73 (bs, 4H, NH_2), 3.64 (s, 6H, 6- H), 2.93 (bs, 4H, 1- H), 2.56-2.53 (m, 8H, 3- H /4- H) ppm.

^{13}C NMR (DMF- d_7): δ 181.5 (2- C), 172.9 (5- C), 51.1 (6- C), 49.8 (1- C), 31.1 (3- C /4- C), 29.6 (3- C /4- C) ppm.

^{195}Pt NMR (DMF- d_7): δ 2230 ppm.

^{15}N NMR (DMF- d_7): δ -2.45 (NH_2) ppm.

ESI-MS $^+$ in MeOH

Ion	[m/z] $^+$	Molecular formula
$[\text{M}+\text{Na}^+]^+$	699.3	$\text{C}_{12}\text{H}_{22}\text{Br}_2\text{N}_2\text{O}_8\text{PtNa}$

ESI-MS $^-$ in MeOH

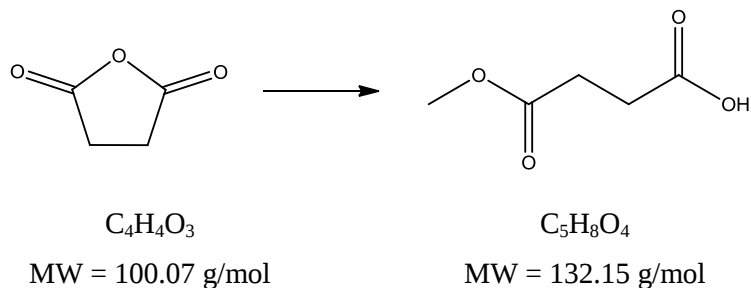
Ion	[m/z] $^-$	Molecular formula
$[\text{M}-\text{H}]^-$	676.0	$\text{C}_{12}\text{H}_{21}\text{Br}_2\text{N}_2\text{O}_8\text{Pt}$

IR [cm^{-1}] – selected bands

3222 b	($\nu_{\text{N-H}}$)
3002 w, 2954w	($\nu_{\text{C-H}}$)
1719 s, 1655 s	($\nu_{\text{as C=O}}$); ($\delta_{\text{N-H}}$)
1440 m	
1339 s	($\nu_{\text{-CO-CH}_3}$)
1237 m, 1181 s, 1149 m, 673 m	

3.7 Synthesis of the anhydrides

3.7.1 3-(Methoxycarbonyl)propanoic acid

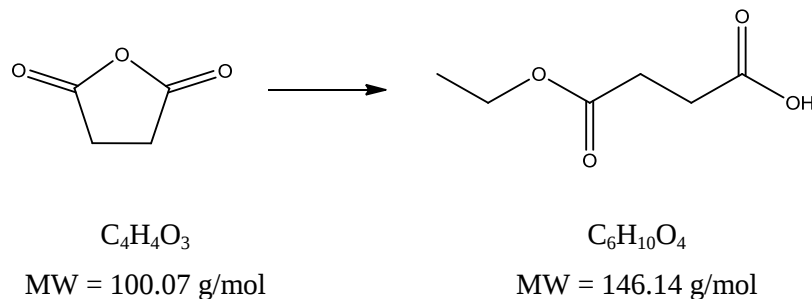


Dry methanol (20 mL) was added to succinic anhydride (5.007 g, 50 mmol) and the white suspension was refluxed under argon atmosphere for 2 h at 70°C to obtain a clear colorless liquid. The solution was allowed to cool to room temperature and the solvent was removed under reduced pressure. The colorless highly viscous liquid was cooled in the freezer for 15 min to give a white crystalline solid which was dried *in vacuo* overnight.

Yield: 6.371 g (96 %), white crystalline solid

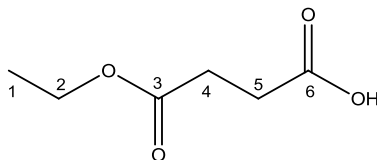
^1H NMR (CDCl_3): δ 3.74 (s, 3H, CH_3), 2.74-2.71 (m, 2H, CH_2), 2.68-2.65 (m, 2H, CH_2) ppm.

3.7.2 3-(Ethoxycarbonyl)propanoic acid

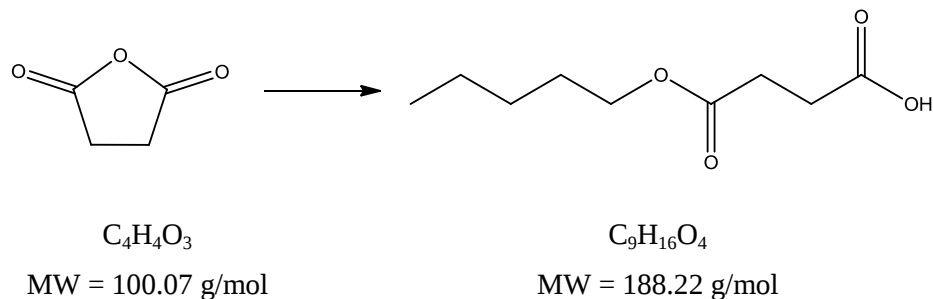


Dry ethanol (8 mL) was added to succinic anhydride (5.027 g, 50 mmol) and the white suspension was refluxed under argon atmosphere for 1 h at 100°C to obtain a clear colorless liquid. The solution was allowed to cool to room temperature and the solvent was removed under reduced pressure. Chloroform was added and precipitated succinic acid was removed by filtration. The product was dried *in vacuo* overnight.

Yield: 4.945 g (67 %), colorless liquid

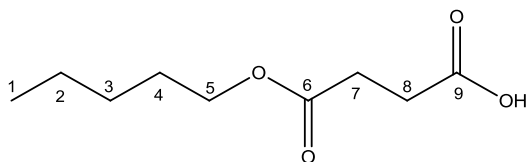


$^1\text{H NMR}$ (CDCl_3): δ 4.19 (q, 2H, 2-H, $^3J_{\text{H,H}} = 7.1$ Hz), 2.72-2.70 (m, 2H, 4-H/5-H,), 2.66-2.63 (m, 2H, 4-H/5-H), 1.28 (t, 3H, 1-H, $^3J_{\text{H,H}} = 7.1$ Hz) ppm.

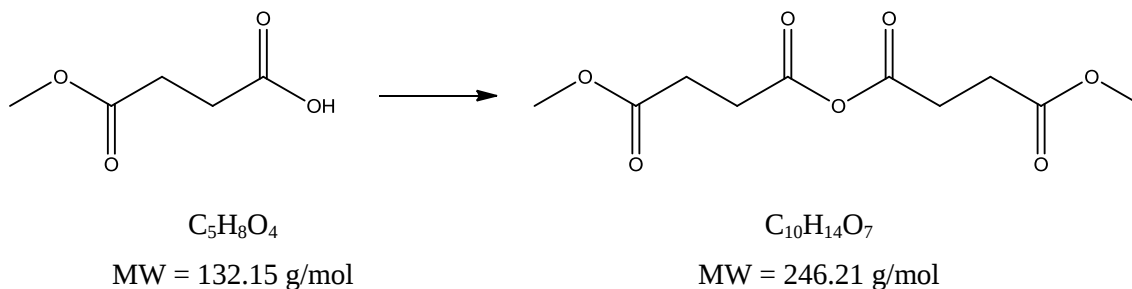
3.7.3 3-(Pentoxycarbonyl)propanoic acid

1-Pentanol (5 mL, 46 mmol, 1.5 eq) was added to succinic anhydride (3.122 g, 31 mmol) and the white suspension was refluxed under argon atmosphere for 14 h at 73°C. The resulting clear colorless liquid was stirred at room temperature for further 10 h and unreacted pentanol was *in vacuo* overnight while heating to 30°C. Remaining succinic acid was precipitated with chloroform and separated by filtration. The product was dried *in vacuo* overnight while heating to 50°C and used without further purification.

Yield: 5.824 g (99 %), colorless liquid



$^1\text{H NMR}$ (CDCl_3): δ 4.12 (t, 2H, 5-H, $^3J_{\text{H,H}} = 6.7$ Hz), 2.73-2.70 (m, 2H, 7-H/8-H), 2.67-2.64 (m, 2H, 7-H/8-H), 1.69-1.63 (m, 2H, 4-H), 1.41-1.40 (m, 4H, 3-H, 2-H), 0.93 (t, 3H, 1-H, $^3J_{\text{H,H}} = 7$ Hz) ppm.

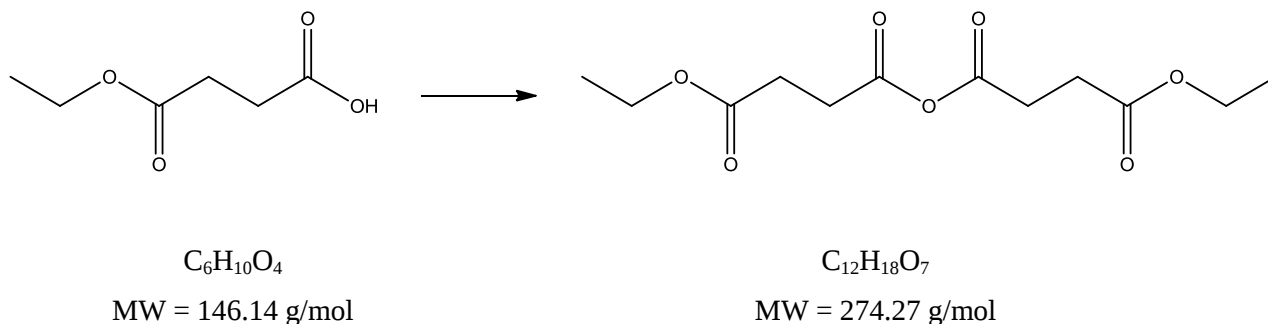
3.7.4 3-(Methoxycarbonyl)propanoic anhydride

Acetic anhydride (2.9 mL, 3.9 mmol, 4 eq) was added to 3-(methoxycarbonyl)propanoic acid (1.003 g, 7.6 mmol) under argon atmosphere and the suspension was heated to 110°C for 1.5 h. The clear solution was allowed to cool down to room temperature (2 h) and acetic acid and acetic anhydride were removed *in vacuo*. The colorless liquid was transferred into another flask with the help of diethyl ether which was removed under reduced pressure. The colorless liquid was dried *in vacuo* while heating to 30°C.

Yield: 0.896 g (96 %), colorless liquid

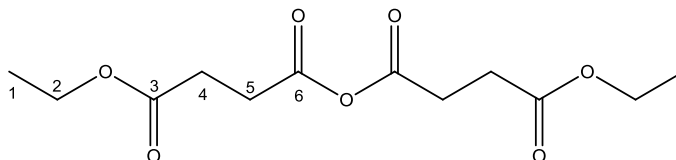
^1H NMR (CDCl_3): δ 3.74 (s, 6H, CH_3), 2.83 (t, 4H, CH_2 , $^3J_{\text{H,H}} = 6.6$ Hz), 2.70 (t, 4H, CH_2 , $^3J_{\text{H,H}} = 6.6$ Hz) ppm.

3.7.5 3-(Ethoxycarbonyl)propanoic anhydride



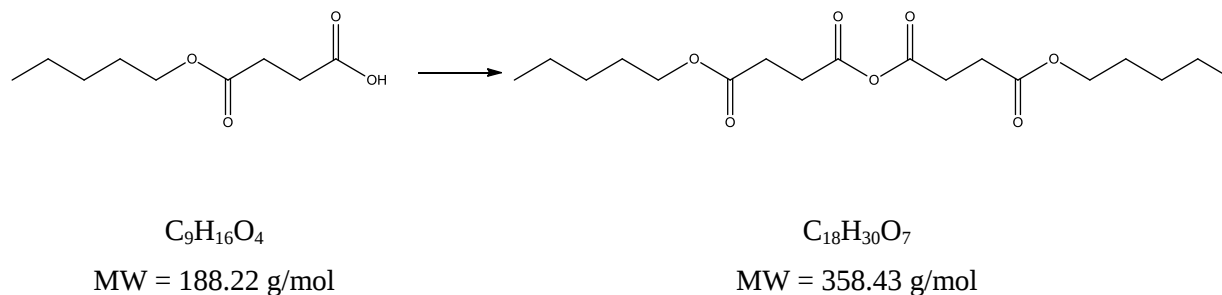
Acetic anhydride (12.5 mL, 132.8 mmol, 4 eq) was added to 3-(ethoxycarbonyl)propanoic acid (4.848 g, 33.2 mmol) under argon atmosphere and the suspension was heated to 110°C for 1.5 h. The clear solution was allowed to cool down to room temperature (1.5 h) and acetic acid as well as acetic anhydride were removed *in vacuo* while heating to 50°C. The colorless liquid was transferred into another flask with the help of diethyl ether which was removed under reduced pressure. The colorless liquid was dried *in vacuo* and used without further purification.

Yield: 4.440 g (98 %), colorless liquid



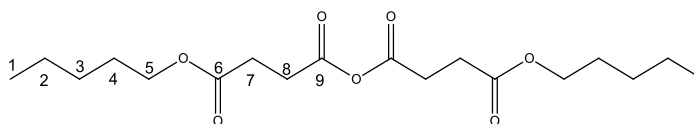
^1H NMR (CDCl_3): δ 4.19 (q, 4H, 2-H, $^3J_{\text{H,H}} = 7.1$ Hz), 2.82 (t, 4H, 4-H/5-H, $^3J_{\text{H,H}} = 6.6$ Hz), 2.69 (t, 4H, 4-H/5-H, $^3J_{\text{H,H}} = 6.5$ Hz), 1.29 (t, 6H, 1-H, $^3J_{\text{H,H}} = 7.1$ Hz) ppm.

3.7.6 3-(Pentoxycarbonyl)propanoic anhydride



Acetic anhydride (9 mL, 95.8 mmol, 6 eq) was added to 3-(pentoxycarbonyl)propanoic acid (3.004 g, 16.0 mmol) and the suspension was heated to 110°C for 1.5 h under argon atmosphere. The resulting clear solution was allowed to cool down to room temperature and acetic acid as well as acetic anhydride were removed *in vacuo* while heating to 40°C. The colorless liquid was transferred into another flask with the help of diethyl ether which was removed under reduced pressure. The product was dried *in vacuo* overnight while heating to 40°C and used without further purification.

Yield: 2.853 g (99.7 %) colorless liquid



$^1\text{H NMR}$ (CDCl_3): δ 4.12 (t, 4H, 5-H, $^3J_{\text{H,H}} = 6.8$ Hz), 2.82 (t, 4H, 7-H/8-H, $^3J_{\text{H,H}} = 6.5$ Hz), 2.69 (t, 4H, 7-H/8-H, $^3J_{\text{H,H}} = 6.5$ Hz), 1.69-1.63 (m, 4H, 4-H), 1.41-1.31 (m, 8H, 3-H, 2-H), 0.93 (t, 6H, 1-H, $^3J_{\text{H,H}} = 6.9$ Hz) ppm.

List of Abbreviations

A.....	adenine
Å.....	angstrom (10^{-10} m)
ATR.....	attenuated total reflection
b.....	broad (NMR)
CDI.....	1,1'-carbonyldiimidazole
COSY	correlation spectroscopy
CTR.....	copper transport protein
d.....	doublet (NMR)
δ.....	chemical shift (NMR)
DACH	cyclohexane-1,2-diamine
DNA	deoxyribonucleic acid
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
en.....	ethane-1,2-diamine
EPR	enhanced permeability and retention
eq.....	equivalent
et al.....	et alii (and others)
FDA.....	food and drug administration
ESI MS	electrospray ionization mass spectrometry
G.....	guanine
HMBC	heteronuclear multiple bond correlation
HPMA	hydroxypropylmethacrylamide
HSAB	hard and soft acids and bases
HSQC	heteronuclear single quantum correlation
IR	infrared
J	coupling constant
m.....	multiplet (NMR), medium (IR)
MMR.....	mismatch repair
NER.....	nucleotide excision repair
NMR.....	nuclear magnetic resonance

OAc acetate ligand
s singlet (NMR)
SWNT..... single-walled carbon nanotubes
TCM traditional Chinese medicine
TLC thin layer chromatography
w weak (IR)

Shortcuts Platinum Complexes

No.	Abbreviation	Name
A	enPtI ₂	(SP-4-2)-(Ethane-1,2-diamine)diiodidoplatinum(II)
B	enPtBr ₂	(SP-4-2)-Dibromido(ethane-1,2-diamine)platinum(II)
C	enPt(OAc) ₂	(SP-4-2)-Diacetato(ethane-1,2-diamine)platinum(II)
D	enPt(OH) ₂	(SP-4-2)-(Ethane-1,2-diamine)dihydroxidoplatinum(II)
A-1	enPt(OH) ₂ I ₂	(OC-6-33)-(Ethane-1,2-diamine)dihydroxidodiiodido-platinum(IV)
B-1	enPt(OH) ₂ Br ₂	(OC-6-33)-Dibromido(ethane-1,2-diamine)dihydroxido-platinum(IV)
C-1	enPt(OH) ₂ (OAc) ₂	(OC-6-33)-Diacetato(ethane-1,2-diamine)dihydroxido-platinum(IV)
D-1	enPt(OH) ₄	(OC-6-22)-(Ethane-1,2-diamine)tetrahydroxidoplatinum(IV)
A-2a	enPtI ₂ (C ₅ H ₇ O ₄) ₂	(OC-6-33)-(Ethane-1,2-diamine)diiodidobis((4-methoxy)-4-oxobutanoato)platinum(IV)
A-2b	enPtI ₂ (C ₆ H ₉ O ₄) ₂	(OC-6-33)-(Ethane-1,2-diamine)bis((4-ethoxy)-4-oxobutanoato)-diiodidoplatinum(IV)
B-2a	enPtBr ₂ (C ₅ H ₇ O ₄) ₂	(OC-6-33)-Dibromido(ethane-1,2-diamine)bis((4-methoxy)-4-oxobutanoato)platinum(IV)
C-2a	enPt(OAc) ₂ (C ₅ H ₇ O ₄) ₂	(OC-6-13)-Diacetato(ethane-1,2-diamine)bis((4-methoxy)-4-oxobutanoato)platinum(IV)
C-2b	enPt(OAc) ₂ (C ₆ H ₉ O ₄) ₂	(OC-6-13)-Diacetato(ethane-1,2-diamine)bis((4-ethoxy)-4-oxobutanoato)platinum(IV)
C-2c	enPt(OAc) ₂ (C ₉ H ₁₁ O ₄) ₂	(OC-6-13)-Diacetato(ethane-1,2-diamine)bis((4-pentoxy)-4-oxobutanoato)platinum(IV)
D-2d	enPt(OAc) ₄	(OC-6-22)-Tetraacetato(ethane-1,2-diamine)platinum(IV)

Bibliography

- [1] Rosenberg, B.; Camp, L.V.; Krigas, T. Inhibition of Cell Division in *Eschericia coli* by Electrolysis Products from a Platinum Electrode. *Nature*, **1965**, 205, 698-99.
- [2] Rosenberg, B. Platinum Complexes for the Treatment of Cancer. *Interdiscipl. Sci. Rev.*, **1978**, 3(2), 134-47.
- [3] Kelland, L. The resurgence of platinum-based cancer chemotherapy. *Nat. Rev. Cancer*, **2007**, 7(8), 573-84.
- [4] Bekradda, M.; Cvitkovic, E. New possibilities in chemotherapy for colorectal cancer. *Anal. Oncol.*, **1999**, 10(6), 105-11.
- [5] Wheate, N.J.; Walker, S.; Craig, G.E.; Oun, R. The status of platinum anticancer drugs in the clinic and in clinical trials. *Dalton Trans.*, **2010**, 39(35), 8113-27.
- [6] Galanski, M.; Jakupec, M.A.; Keppler, B.K. Update of the Preclinical Situation of Anticancer Platinum Complexes: Novel Design Strategies and Innovative Analytical Approaches. *Curr. Med. Chem.*, **2005**, 12(8).
- [7] O'Dwyer, P.J.; Stevenson, J.P.; Johnson, S.W. Clinical Pharmacokinetics and Administration of Established Platinum Drugs. *Drugs*, **2000**, 59(4), 19-27.
- [8] Galanski, M.; Keppler, B.K. Searching for the Magic Bullet: Anticancer Platinum Drugs Which Can Be Accumulated or Activated in the Tumor Tissue. *Anticancer Agents Med. Chem.*, **2007**, 7, 55-73.
- [9] Gately, D.P.; Howell, S.B. Cellular accumulation of the anticancer agent cisplatin: A review. *Br. J. Cancer*, **1993**, 67, 1171-76.
- [10] Wang, D.; Lippard, S.J. Cellular processing of platinum anticancer drugs. *Nat. Rev. Drug Discov.*, **2005**, 4(4), 307-20.
- [11] Andersson, A.; Hedenmalm, H.; Elfsson, B.; Ehrsson, H. Determination of the Acid Dissociation Constant for cis-Diammineaquachloroplatinum(II) Ion. A Hydrolysis Product of Cisplatin. *J. Pharm. Sci.*, **1994**, 83(6), 859-62.
- [12] Lilley, D.M.J. Cisplatin adducts in DNA: distortion and recognition. *JBIC*, **1996**, 1, 189-91.
- [13] Jamieson, E.R.; Lippard, S.J. Structure, Recognition, and Processing of Cisplatin-DNA Adducts. *Chem. Rev.*, **1999**, 99, 2467-98.
- [14] Stewart, D.J. Mechanisms of resistance to cisplatin and carboplatin. *Crit. Rev. Oncol. Hematol.*, **2007**, 63(1), 12-31.
- [15] Takahara, P.M.; Rosenzweig, A.C.; Frederick, C.A.; Lippard, S.J. Crystal structure of double-stranded DNA containing the major adduct of the anticancer drug cisplatin. *Nature* **1995**, 377(6550), 649-52.
- [16] Wexselblatt, E.; Yavin, E.; Gibson, D. Cellular interactions of platinum drugs. *Inorg. Chim. Acta*, **2012**, 393, 75-83.
- [17] Heffeter, P.; Jungwirth, U.; Jakupec, M.; Hartinger, C.; Galanski, M.; Elbling, L.; Micksche, M.; Keppler, B.; Berger, W. Resistance against novel anticancer metal compounds: differences and similarities. *Drug Resist. Update*, **2008**, 11(1-2), 1-16.
- [18] Cleare, M.J.; Hoeschele, J.D. Antitumor platinum compounds. Relation between structure and activity. *Platinum. Metals. Rev.*, **1973**, 17(1), 2-13.
- [19] Zutphen, S.v.; Reedijk, J. Targeting platinum anti-tumour drugs: Overview of strategies employed to reduce systemic toxicity. *Coord. Chem. Rev.*, **2005**, 249(24), 2845-53.

- [20] Kasparkova, J.; Vojtiskova, M.; Natile, G.; Brabec, V. Unique properties of DNA interstrand cross-links of antitumor oxaliplatin and the effect of chirality of the carrier ligand. *Chem. Eur. J.*, **2008**, 14(4), 1330-41.
- [21] Roberts, J.D.; Peroutka, J.; Beggiolin, G.; Manzotti, C.; Piazzoni, L.; Farrell, N. Comparison of cytotoxicity and cellular accumulation of polynuclear platinum complexes in L1210 murine leukemia cell lines. *J. Inorg. Biochem.*, **1999**, 77(1-2), 47-50.
- [22] Holford, J.; Sharp, S.Y.; Murrer, B.A.; Abrams, M.; Kelland, L.R. In vitro circumvention of cisplatin resistance by the novel sterically hindered platinum complex AMD473. *Br. J. Cancer*, **1998**, 77(3), 366-73.
- [23] Sood, P.; Thurmond, B.K.; Jacob, J.E.; Wallner, L.K.; Silvia, G.O.; Stewart, D.J.; Nowotnik, D.P. Synthesis and Characterization of AP5346, a Novel Polymer-Linked Diaminocyclohexyl Platinum Chemotherapeutic Agent. *Bioconjugate Chem.*, **2006**, 17, 1270-79.
- [24] Aronov, O.; Horowitz, A.T.; Gabizon, A.; Gibson, D. Folate-Targeted PEG as a Potential Carrier for Carboplatin Analogs. Synthesis and in Vitro Studies. *Bioconjugate Chem.*, **2003**, 14(3), 563-74.
- [25] Galanski, M.; Slaby, S.; Jakupec, M.A.; Keppler, B.K. Synthesis, Characterization, and in Vitro Antitumor Activity of Osteotropic Diam(m)ineplatinum(II) Complexes Bearing a N,N-Bis(phosphonomethyl)glycine Ligand. *J. Med. Chem.*, **2003**, 46(23), 4946-51.
- [26] Wexselblatt, E.; Gibson, D. What do we know about the reduction of Pt(IV) pro-drugs? *J. Inorg. Biochem.*, **2012**, 117, 220-9.
- [27] Hall, M.D.; Hambley, T.W. Platinum(IV) antitumour compounds: their bioinorganic chemistry. *Coord. Chem. Rev.*, **2002**, 232, 49-67.
- [28] Choi, S.; Filotto, C.; Bisanzo, M.; Delaney, S.; Lagasee, D.; Whitworth, J.L.; Jusko, A.; Li, C.; Wood, N.A.; Willingham, J.; Schwenker, A.; Spauding, K. Reduction and Anticancer Activity of Platinum(IV) Complexes. *Inorg. Chem.*, **1997**, 37(10), 2500-04.
- [29] Reithofer, M.R.; Bytcek, A.K.; Valiahdi, S.M.; Kowol, C.R.; Groessl, M.; Hartinger, C.G.; Jakupec, M.A.; Galanski, M.; Keppler, B.K. Tuning of lipophilicity and cytotoxic potency by structural variation of anticancer platinum(IV) complexes. *J. Inorg. Biochem.*, **2011**, 105(1), 46-51.
- [30] Kim, K.M.; Lee, Y.-A.; Lee, S.S.; Sohn, Y.S. Facile synthesis and structural properties of (diamine)tetracarboxylatoplatinum(IV) complexes. *Inorg. Chim. Acta*, **1999**, 292(1), 52-56.
- [31] Lee, Y.-A.; Lee, S.S.; Kim, K.M.; Lee, C.O.; Sohn, Y.S. Synthesis and Oral Antitumor Activity of Tetrakis(carboxylato)platinum(IV) Complexes. *J. Med. Chem.*, **2000**, 43(7), 1409-12.
- [32] Barnes, K.R.; Kutikov, A.; Lippard, S.J. Synthesis, characterization, and cytotoxicity of a series of estrogen-tethered platinum(IV) complexes. *Chem. Biol.*, **2004**, 11(4), 557-64.
- [33] Reithofer, M.R.; Valiahdi, S.M.; Galanski, M.; Jakupec, M.A.; Arion, V.B.; Keppler, B.K. Novel endothall-containing platinum(IV) complexes: synthesis, characterization, and cytotoxic activity. *Chem. Biodiv.*, **2008**, 5(10), 2160-70.
- [34] Ho, Y.P.; Au-Yeung, S.C.; To, K.K. Platinum-based anticancer agents: innovative design strategies and biological perspectives. *Med. Res. Rev.*, **2003**, 23(5), 633-55.
- [35] Feazell, R.P.; Nakayama-Ratchford, N.; Dai, H.; Lippard, S.J. Soluble Single-Walled Carbon Nanotubes as Longboat Delivery Systems for Platinum(IV) Anticancer Drug Design. *J. Am. Chem. Soc.*, **2007**, 129(27), 8438-39.
- [36] Huheey, J.; Keiter, E.; Keiter, R. *Anorganische Chemie - Prinzipien von Struktur und Reaktivität*. 3rd ed, **2003**, Berlin: de Gruyter.
- [37] Quagliano, J.V.; Schubert, L. The trans effect in complex inorganic compounds. *Chem. Rev.*, **1952**, 50, 201-60.
- [38] Dhara, S.C. A Rapid Method for the Synthesis of cis-[Pt(NH₃)₂Cl₂]. *Indian J. Chem.*, **1970**, 8, 193-94.

- [39] Rochon, F.D.; Gruia, L.M. Synthesis and characterization of Pt(II) complexes with amine and carboxylato ligands. Crystal structure of (1,1-cyclobutanedicarboxylato)di(ethylamine)-platinum(II).H₂O. *Inorg. Chim. Acta*, **2000**, 36, 193-204.
- [40] Sun, Y.; Hu, T.; Gou, S.; Cao, Z. Novel hydrophilic cis-bis(cyclopentylamine)platinum(II) complexes: Synthesis, characterization, antitumor activity and interaction with DNA. *Inorg. Chim. Acta*, **2012**, 391, 158-61.
- [41] Cui, K.; Wang, L.; Zhu, H.; Gou, S.; Liu, Y. Novel cisplatin-type platinum complexes and their cytotoxic activity. *Bioorg. Med. Chem. Lett.*, **2006**, 16(11), 2937-42.
- [42] Vollano, J.F.; Al-Baker, S.; Dabrowiak, J.C.; Schurig, J.E. Comparative antitumor studies on platinum(II) and platinum(IV) complexes containing 1,2-diaminocyclohexane. *J. Med. Chem.*, **1987**, 30(4), 716-9.
- [43] Giandomenico, C.M.; Abrams, M.J.; Murrer, B.A.; Vollano, J.F.; Rheinheimer, M.I.; Wyer, S.B.; Bossard, G.E.; Higgins, J.D. Carboxylation of Kinetically Inert Platinum(IV) Hydroxy Complexes. An Entry into Orally Active Platinum(IV) Antitumor Agents. *Inorg. Chem.*, **1995**, 34(5), 1015-21.
- [44] Galanski, M.; Keppler, B.K. Carboxylation of Dihydroxoplatinum(IV) Complexes via a New Synthetic Pathway. *Inorg. Chem.*, **1996**, 35(6), 1709-11.
- [45] Ang, W.H.; Pilet, S.; Scopelliti, R.; Bussy, F.; Juillerat-Jeanneret, L.; Dyson, P.J. Synthesis and characterization of platinum(IV) anticancer drugs with functionalized aromatic carboxylate ligands: influence of the ligands on drug efficacies and uptake. *J. Med. Chem.*, **2005**, 48(25), 8060-9.
- [46] Alvarez-Valdes, A.; Perez Jose, M.; Lopez-Solera, I.; Lannegrand, R.; Continente Jose, M.; Amo-Ochoa, P.; Camazon Maria, J.; Solans, X.; Font-Bardia, M.; Navarro-Ranninger, C. Preparation and characterization of platinum(II) and (IV) complexes of 1,3-diaminepropane and 1,4-diaminebutane: circumvention of cisplatin resistance and DNA interstrand cross-link formation in CH1cisR ovarian tumor cells. *J. Med. Chem.*, **2002**, 45(9), 1835-44.
- [47] Reithofer, M.; Galanski, M.; Roller, A.; Keppler, B.K. An Entry to Novel Platinum Complexes: Carboxylation of Dihydroxoplatinum(IV) Complexes with Succinic Anhydride and Subsequent Derivatization. *Eur. J. Inorg. Chem.*, **2006**, 2612-17.
- [48] Kratochwil, N.A.; Zabel, M.; Range, K.-J.; Bednarski, P.J. Synthesis and X-ray Crystal Structure of trans,cis-[Pt(OAc)₂I₂(en)]: A Novel Type of Cisplatin Analog That Can Be Photolyzed by Visible Light to DNA-Binding and Cytotoxic Species in Vitro. *J. Med. Chem.*, **1996**, 39, 2499-507.
- [49] Ewa, B.; Maciej, W.; Marcin, S.; Grzegorz, D.; Michal, Z.; Jan, P.; Jozef, O. The development of first Staphylococcus aureus SplB protease inhibitors: phosphonic analogues of glutamine. *Bioorg. Med. Chem. Lett.*, **2012**, 22(17), 5574-78.
- [50] Song, R.; Kim, K.M.; Lee, S.S.; Sohn, Y.S. Electrophilic Substitution of (Diamine)tetrahydroxoplatinum(IV) with Carboxylic Anhydrides. Synthesis and Characterization of (Diamine)platinum(IV) Complexes of Mixed Carboxylates. *Inorg. Chem.*, **2000**, 39, 3567-71.
- [51] Pichler, V.; Valiahdi, S.M.; Jakupec, M.A.; Arion, V.B.; Galanski, M.; Keppler, B.K. Mono-carboxylated diaminedichloridoplatinum(IV) complexes--selective synthesis, characterization, and cytotoxicity. *Dalton Trans.*, **2011**, 40(32), 8187-92.
- [52] Sheldrick, G.M. A short history of SHELX. *Acta Crystallogr. A*, **2008**, 64(1), 112-22.
- [53] Dolomanov, O.V.; Blake, A.J.; Champness, N.R.; Schroeder, M. OLEX: new software for visualization and analysis of extended crystal structures. *J. Appl. Crystallogr.*, **2003**, 36(5), 1283-84.
- [54] Hubschle, C.B.; Sheldrick, G.M.; Dittrich, B. ShelXle: a Qt graphical user interface for SHELXL. *J. Appl. Crystallogr.*, **2011**, 44(6), 1281-84.

Curriculum Vitae

Personal Data	Acad. degree	BSc.
	First Name	Doris
	Last Name	Höfer
	Date of birth	November 12, 1987
	Nationality	Austria
Education	since 2011	Master Studies of Chemistry at the University of Vienna
	2008 – 2011	Bachelor Studies of Chemistry at the University of Vienna
	2002 – 2007	HBLA Lentia (High School)
	1998-2002	Hauptschule Bad Leonfelden (Secondary School)
	1994 – 1998	Volksschule Zwettl/Rodl (Elementary School)
Experience	March-Dec. 2013	Student staff at the University of Vienna; Institute of Inorganic Chemistry
	2007-2008	Voluntary Year of Social Service in Tijuana, Mexico
Languages	German	native language
	English	fluent
	Spanish	conversant
	French	basic knowledge
Scholarship	2010	Performance Scholarship awarded by the University of Vienna according to the Studienförderungsgesetz