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# An Entry to Novel Platinum Complexes: Carboxylation of Dihydroxoplatinum(IV) Complexes with Succinic Anhydride and Subsequent Derivatization

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An improved carboxylation method of (*OC*-6-33)-dichloro-(ethane-1,2-diamine)dihydroxyplatinum(IV) based on succinic anhydride is reported. Reaction of the uncoordinated carboxylic acid with simple amines and alcohols leads to the corresponding amides and esters in the presence of 1,1′-carbonyldiimidazole. The resulting new complexes are characterized by IR, $^{1}H$, $^{13}C$, $^{15}N$, and $^{195}Pt$ NMR spectroscopy, mass spectrometry, and elemental analysis. This reaction provides an entry to a new class of kinetically inert platinum(IV) complexes.


## Introduction

Cisplatin, *cis*-diamminedichloroplatinum(II) (Figure 1),[1,2] is a highly effective platinum-based anticancer agent that is used in nearly 50% of all tumor therapies all over the world. Cisplatin alone, or in combination with other antineoplastic drugs, is used against a series of solid tumors, including ovarian cancer, non-small cell lung cancer, and head and neck cancer. Cure rates above 90% have been reported in the case of testicular germ-cell cancer, depending on the point of diagnosis; it is thus one of the few anticancer drugs with real curative potential. Nevertheless, severe adverse effects such as a dose-limiting nephrotoxicity, peripheral neuropathy, tinnitus, and hearing loss in the high frequency range are known.[3] Additionally, acquired or intrinsic resistance of tumors to cisplatin therapy narrows the use of this drug.[4] After evaluation of thousands of platinum compounds in preclinical settings during the last 40 years, the second- and third-generation platinum complexes carboplatin [*cis*-diammine(1,1-cyclobutanedicarboxylato)-platinum(II)] and oxaliplatin [(*trans*-*R*,*R*-cyclohexane-1,2-diamine)platinum(II)] were successfully introduced into clinical practice.[5,6]

Besides platinum(II) complexes, which have to be administered intravenously due to their instability in the gastrointestinal tract, platinum(IV) complexes have also been investigated, thereby opening up the possibility of an oral absorption. In this context it has to be mentioned that, in principle, an orally administrable drug offers some advantages in the clinical routine, such as a reduction of the hospitalization costs and a better acceptance of chemotherapy by the patient. From the chemical point of view, octahedrally coordinated platinum(IV) complexes exhibit a higher coordination number than their square-planar platinum(II) counterparts, and therefore variation in the ligand sphere is more easily accessible. This is of great significance in order to fine-tune important properties such as lipophilicity, stability, reduction behavior, and biological activity.[7] Platinum(IV) complexes are kinetically inert and therefore show a significantly decreased reactivity. It is generally accepted that platinum(IV) complexes act as prodrugs by extra- or intracellular reduction to the more reactive platinum(II) complexes upon release of the axial ligands (activation by reduction).[8,9] The first platinum(IV) complexes, tetraplatin and iproplatin (Figure 1), which were investigated in phase-I clinical trials both showed an unfavorable pharmacokinetic behavior in vivo. Tetraplatin (two axial chloro ligands; reduction potential: –90 mV)[10] displays a high systemic

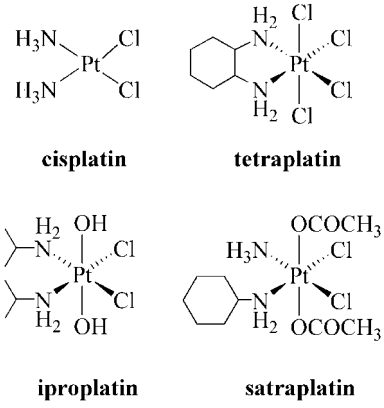


Figure 1. Chemical structures of the anticancer drug cisplatin and of tumor inhibiting platinum(IV) complexes in clinical evaluation. Tetraplatin and iproplatin were abandoned.

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toxicity due to a very fast reduction of the platinum(IV) complex in the blood stream, whereas iproplatin (two axial hydroxy ligands; reduction potential: –730 mV) was found to be inactive because it is not reduced fast enough to the more (re)active platinum(II) species in the body. A breakthrough was reached with the synthesis of satraplatin (Figure 1), which contains two carboxylate ligands in the axial positions. Satraplatin is currently being investigated in phase-III clinical trials in hormone refractory prostate cancer.[11] The reduction potential (which is most influenced by the axial ligands) of satraplatin adopts an average value with –250 mV, but the lipophilicity of this complex also seems to be in an appropriate range. Very recently, a close analogue to satraplatin, namely LA-12, a platinum(IV) complex with a bulky and hydrophobic 1-adamantylamine ligand instead of cyclohexylamine, entered clinical phase I trials.[12,13] LA-12 shows high cytotoxic potential in leukemia, melanoma, and colorectal cancer cells and has been found to overcome acquired resistance to cisplatin in human ovarian A2780cisR cells.[14]

The success of satraplatin is a direct consequence of progress in the synthesis and derivatization of platinum(IV) complexes. Some years ago, the design of platinum(IV) coordination compounds was limited to oxidation of the corresponding platinum(II) species with hydrogen peroxide or chlorine gas:[15,16] selective ligand substitution was difficult to perform since platinum(IV) complexes are kinetically inert (substitution of chloride for hydroxide, for example works under comparatively drastic conditions in the presence of hydrochloric acid at high temperature). With the knowledge that hydroxide coordinated to platinum(IV) has nucleophilic properties and therefore can be carboxylated with classical agents known from synthetic organic chemistry, a new class of platinum(IV) complexes was accessible, which resulted in the development of satraplatin. Carboxylation of *trans*-dihydroxoplatinum(IV) by anhydrides, pyrocarbonates, isocyanates, and even by carboxylic acid chlorides in the presence of pyridine has recently been described in the literature,[17–21] leading to numerous new and interesting platinum(IV) derivatives. Very recently, the carboxylation with cyclic anhydrides (succinic, maleic, glutaric, and phthalic anhydride) under different reaction conditions was reported. Carboxylation in $CH_2Cl_2$ over 1–2 days,[22] reaction in DMSO at 70 °C with a considerably large amount (3.3 g) of the dihydroxoplatinum(IV) starting complex,[23] and the unsuccessful use of molten phthalic anhydride[24] have been reported. The yields were reported to be in the range of 40 to 70%. The use of cyclic anhydrides offers a further advantage, besides the fact that novel platinum(IV) compounds are prepared: it provides an uncoordinated carboxylic acid moiety for subsequent derivatization, although in only one case has derivatization to the amide been described; amine-modified estrogens were coupled to the uncoordinated carboxylic acid by the use of a common peptide coupling reagent, namely diisopropylcarbodiimide/4-(dimethylamino)pyridine.

Here we report an improved carboxylation method based on succinic anhydride. Additionally, reaction of the uncoordinated carboxylic acid with simple amines and alcohols, leading to the corresponding amides and esters in the presence of 1,1′-carbonyldiimidazole, is described. The platinum(IV) complexes have been synthesized for the first time and were characterized in detail by multinuclear NMR spectroscopy.

## Results and Discussion

Derivatization of kinetically inert platinum(IV) complexes is an attractive entry to novel platinum compounds. Besides the well-established carboxylation of hydroxide coordinated to the $Pt^{IV}$ center, derivatization of peripheral hydroxo groups in diaminetetrachloroplatinum(IV) complexes has also been reported.[25] With the use of cyclic anhydrides, a further functional group is now accessible in the axial position. In order to set up a general reaction procedure, synthesis of the bis(carboxylato)platinum(IV) complex **2** was improved and subsequent derivatization of the uncoordinated carboxylic acid group was evaluated (Figure 2).

The starting (*OC*-6-33)-dichloro(ethane-1,2-diamine)dihydroxoplatinum(IV) complex **1** was prepared by reaction of $K_2PtCl_4$ with ethane-1,2-diamine; the dichloroplatinum(II) compound was then oxidized with hydrogen peroxide. The carboxylation reaction with succinic anhydride was performed in DMF at 70 °C, affording **2** in a good yield of 85%. This is in clear contrast to the synthetic procedures described recently. The use of DMSO at higher temperatures seems to be especially problematic since it often leads to decomposition of the platinum complexes. The subsequent derivatization of **2** was carried out in DMF by activation of the carboxylic acid with 1,1′-carbonyldiimidazole (CDI). The formed imidazolide was used directly without isolation for the next reaction step. Contrary to our synthetic procedure, Lippard and co-workers have used another typical peptide coupling reagent, namely diisopropylcarbodiimide/4-(dimethylamino)pyridine, which could cause problems in the workup of the reaction mixture and may lead to unfavorable side-reactions. Reaction of the imidazolide with amines afforded the corresponding amides, whereas the use of alcohols, which were converted in part to the alkoxides by catalytic amounts of sodium, produced the esters. In the case of ethanolamine (in the absence of a strong base), only the amide was produced, thus demonstrating the selectivity of the reaction.

The new complexes **2**, **3a**–**c**, **4a**, and **4b** were characterized in detail by elemental analysis, IR, $^1H$, $^{13}C$, $^{15}N$, and $^{195}Pt$ NMR spectroscopy, mass spectrometry, and also by X-ray diffractometry in the case of **2**. The carboxylation of **1** and its subsequent derivatization to the amide or ester can be followed by significant changes in the infrared spectra. The *trans*-dihydroxoplatinum(IV) starting complex exhibits a characteristic very sharp and intense O–H stretch at 3483 $cm^{-1}$, which disappears after carboxylation with succinic anhydride. As a result, two C=O stretches, at 1654 $cm^{-1}$ for the coordinated carboxylato moiety and at 1719 $cm^{-1}$ for the uncoordinated carboxylic acid group, are

  

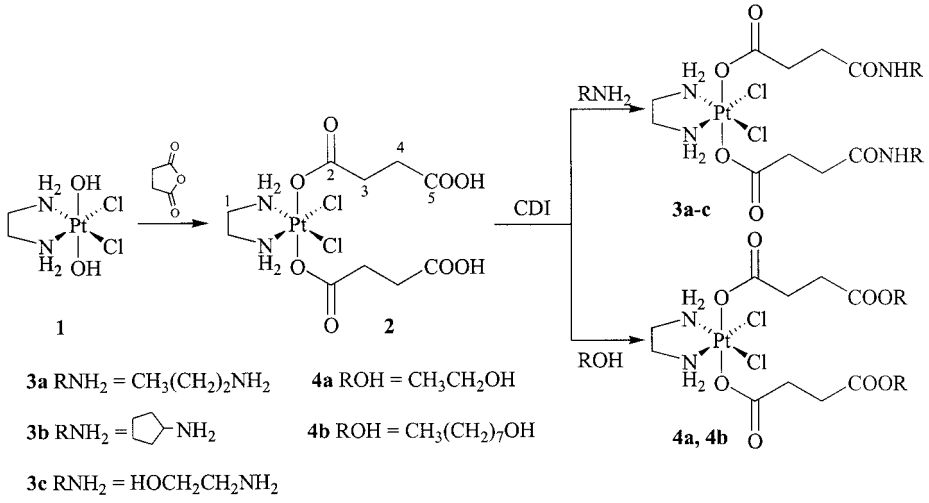


Figure 2. Synthesis of novel bis(carboxylato)platinum(IV) complexes and NMR numbering scheme.

detectable. The shift of the C=O band of the coordinated carboxylate to smaller wavenumbers is in good agreement with previously published data for analogous complexes (1633–1669 $cm^{-1}$).[19] Derivatization with amines, leading to complexes **3a**–**c**, is reflected by two characteristic absorptions (1633–1640 and 1664–1675 $cm^{-1}$) for the coordinated carboxylate and the amide C=O stretch, respectively, whereas the ester formation is accompanied by C=O absorption bands in the range of 1650 and 1658 $cm^{-1}$ for the PtOC=O stretch and between 1739 and 1745 $cm^{-1}$ for the C=O stretch of the ester moiety. Remarkably, in the case of ethanolamine the amide formation (vs. ester formation) could be confirmed by infrared spectroscopy.

$^{1}H$, and $^{195}Pt$ as well as gradient-enhanced two-dimensional $^{1}H$,$^{13}C$- and $^{1}H$,$^{15}N$-COSY NMR spectra of complexes **2**, **3a**–**c**, **4a**, and **4b** were acquired in [$D_7$]DMF. The ligand sphere around the platinum center can best be judged by the chemical shift of the $^{195}Pt$ nucleus, which spans a wide range of several thousand ppm, depending on the coordinated atoms, the geometry, and the oxidation state of the metal center. The $^{195}Pt$ resonances of the novel platinum(IV) complexes were found between $\delta$ = 2621 and 2630 ppm, which is indicative of a *cis*,*cis*,*trans*-$Pt^{IV}N_2Cl_2O_2$ ligand sphere (Table 1). These values are in good agreement with literature data {$\delta$ = 2658 ppm for [$PtCl_2$(en)-($OCOCH_3$)$_2$]}.[26] As expected, the $^{195}Pt$ chemical shifts as well as the $^{1}H$ ($\delta$ = 8.88–8.92 ppm) and $^{15}N$ resonances ($\delta$ = –3.3 to –4.2 ppm) of the coordinated amine moiety are not significantly influenced by derivatization at the uncoordinated carboxylic acid group. Nevertheless, a trend in the $^{195}Pt$ and $^{1}H$ (of the $NH_2$ group) chemical shifts seems to be obvious. In the $^{13}C$ NMR spectra, two resonances for the quaternary carbon atoms of the coordinated carboxylate (C-2 at around $\delta$ = 180 ppm and C-5 in the region between $\delta$ = 169.9 and 172.3 ppm) are detected, with an apparent upfield shift of C-5 upon derivatization of the uncoordinated carboxylic acid. Amide formation, especially in the case of the bifunctional ethanolamine, was verified by significant $^{1}H$ and $^{15}N$ shift differences. In complexes **3a**–**c** the proton resonances of the amide protons are found at around $\delta$ = 7.96 ppm, with $^{15}N$ chemical shifts in the region between $\delta$ = 90 and 109 ppm (typical region for amide nitrogens: $\delta$ = 63–113 ppm). Values between $\delta$ = 1 and 3 ppm ($^{1}H$) and –15 to +15 ppm ($^{15}N$) are found in the free amines, thus demonstrating the success of amide formation. In both **3a**–**c** and **4a**/**4b**, long-range shift correlation signals between the derivatized C=O quaternary carbon atom and the amine- or alcohol-derived residue could also be detected, additionally proving the amide or ester formation. Furthermore, these cross peaks in the two-dimensional shift correlated spectra allowed us unequivocally to distinguish between the two $^{13}C$=O resonances.

Table 1. $^{1}H$, $^{13}C$, $^{15}N$, and $^{195}Pt$ NMR spectroscopic data for the new complexes **2**, **3a**–**c**, **4a**, and **4b**.

| | $^{1}H$ | | $^{13}C$ | | $^{15}N$ | | $^{195}Pt$ |
|---|---|---|---|---|---|---|---|
| | N$H_2$ | N*H* | C-2 | C-5 | *N*$H_2$ | *N*H | |
| **2** | 8.93 | – | 180.0 | 172.3 | –3.8 | – | 2630 |
| **3a** | 8.89 | 7.95 | 180.3 | 170.0 | –3.3 | 94.6 | 2622 |
| **3b** | 8.88 | 7.94 | 180.3 | 169.9 | –3.7 | 108.5 | 2622 |
| **3c** | 8.88 | 7.98 | 180.2 | 170.3 | –4.2 | 90.1 | 2621 |
| **4a** | 8.92 | – | 179.7 | 170.8 | –3.6 | – | 2629 |
| **4b** | 8.92 | – | 179.7 | 170.9 | –3.5 | – | 2628 |

Crystals suitable for X-ray diffraction analysis were grown by vapor diffusion of diethyl ether into a solution of **2** in acetone. The result of the X-ray diffraction study of complex **2**·2($CH_3$)$_2$CO is shown in Figure 3. Crystal data, data collection parameters and structure-refinement details are given in the Experimental Section. The compound crystallizes in the monoclinic space group *P*2/*c*, with the platinum atom lying on a twofold rotation axis that also goes through the center of the C–C bond of the ethane-1,2-diamine ring. The platinum(IV) atom has an octahedral coordination geometry with ethane-1,2-diamine and two chloro ligands bound in the equatorial plane and two succinic acids coordinated in a monodentate fashion in the axial positions. The Pt–N1, Pt–Cl1, and Pt–O1 bond lengths

  

[2.0541(10), 2.3175(5), and 2.0113(12) Å, respectively] are well comparable with those in *cis,trans*-[Pt(en)$Cl_2$-($OCOCH_3$)$_2$] [2.040(5), 2.315(1), and 2.017(5) Å, respectively].[27] A five-membered chelate ring, with a bite angle of 83.66(6)°, is formed upon coordination of ethane-1,2-diamine to $Pt^{IV}$. A zigzag arrangement of the ligand atoms alternately above and below the mean least-squares plane through $PtCl_2N_2$ is observed. The dihedral angle $\Theta_{N1-C1-C1^i-N1^i}$ (superscript i denotes $-x + 1$, $y$, $1/2 - z$), which serves as a measure of the deviation of the corresponding chelate ring from planarity, is –55.8°.

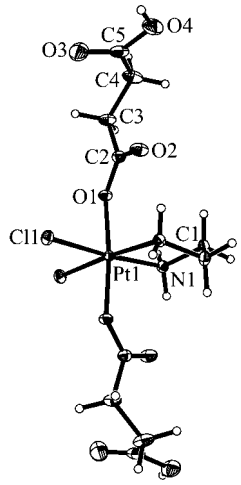


Figure 3. ORTEP diagram of **2** displaying thermal ellipsoids at 50% probability (the solvent molecule has been omitted). Selected bond lengths [Å] and angles [°]: Pt–N1 2.0541(10), Pt–Cl1 2.3175(5), Pt–O1 2.0113(12), O1–C2 1.3095(16), C2–O2 1.2235(16), C2–C3 1.5122(19), C3–C4 1.519(2), C4–C5 1.497(2), C5–O3 1.234(2), C5–O4 1.3070(18); O1–C2–O2 126.42(13), O3–C5–O4 123.13(15).

## Conclusions

It has been demonstrated that carboxylation of (*OC*-6-33)-dichloro(ethane-1,2-diamine)dihydroxoplatinum(IV) with succinic anhydride results in a platinum complex with coordinated carboxylato ligands, which contains further uncoordinated carboxylic acid groups for subsequent derivatization. Improved reaction conditions have allowed synthesis of this new complex in a pleasingly high yield of 85%. Reaction of the uncoordinated carboxylic acid with simple amines and alcohols, which leads to the corresponding amides and esters in the presence of 1,1′-carbonyldiimidazole, has been shown to be generally applicable to this kind of platinum complex, and provides entry to a new class of kinetically inert platinum(IV) complexes with potentially useful anticancer properties.

## Experimental Section

All chemicals were obtained from commercial suppliers and were used as received. The $^1$H, $^{195}$Pt and two-dimensional $^1$H,$^{13}$C- and $^1$H,$^{15}$N-COSY NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (Ultrashield™ Magnet) at 400.13, 86.11, 100.62, and 40.55 MHz, respectively, in [$D_7$]DMF at 25 °C, using standard pulse programs; two-dimensional spectra were measured in a gradient-enhanced mode. $^{15}$N and $^{195}$Pt chemical shifts are referenced relative to external $NH_4Cl$ and $K_2PtCl_4$, respectively. Half-height line widths of $^{195}$Pt resonances are given in parentheses. IR spectra were measured in a KBr matrix (4000–400 $cm^{-1}$) with a Perkin–Elmer Spectrum 2000 FT-IR spectrometer. Mass spectra (ESI-MS) were recorded with a Bruker $ESQUIRE_{3000}$ ion-trap mass spectrometer in the negative- as well as in the positive-ion mode. The elemental analyses were performed with a Perkin–Elmer 2400 CHN elemental analyzer by the microlaboratory of the Institute of Physical Chemistry, University of Vienna. Silica gel 60 (Fluka) was used for column chromatography. (*OC*-6-33)-Dichloro-(ethane-1,2-diamine)dihydroxoplatinum(IV) (**1**) was synthesized according to standard literature procedures by mixing equivalent amounts of ethane-1,2-diamine and $K_2PtCl_4$ in aqueous solution and subsequent oxidation with $H_2O_2$.[16]

**(*OC*-6-33)-Bis(3-carboxypropanoato)dichloro(ethane-1,2-diamine)-platinum(IV) (2):** Succinic anhydride (114 mg, 1.139 mmol) was added to a suspension of **1** (100 mg, 0.278 mmol) in DMF (2 mL) and the reaction mixture was stirred at 70 °C for 24 h. During this time the solid material dissolved to form a yellow-brown solution. DMF was then removed under reduced pressure. The residue was dissolved in acetone and filtered to give a clear, yellow solution. This solution was concentrated under reduced pressure, and subsequent addition of diethyl ether led to precipitation of a pale-yellow solid. The product was dried in vacuo. Yield: 131.5 mg (85%). $C_{10}H_{18}Cl_2N_2O_8Pt$ (560.24): calcd. C 21.44, H 3.24, N 5.00; found C 21.72, H 3.18, N 4.89. ESI-MS: *m*/*z* 561.1 [M + $H^+$]$^+$, 583.1 [M + $Na^+$]$^+$, 598.1 [M + $K^+$]$^+$, 559.1 [M – $H^+$]$^-$. IR: $\tilde{\nu}$ = 3445 ($\nu_{COO-H}$), 3202 ($\nu_{N-H}$), 3039–2927 ($\nu_{C-H}$), 1719, 1654 ($\nu_{as\ C=O}$) $cm^{-1}$. $^1$H NMR: $\delta$ = 12.52 (s, 2 H, COO*H*), 8.93 (s, $^2J_{H,Pt}$ = 52.7 Hz, 4 H, N$H_2$), 3.15 (s, 4 H, 1-H), 2.70 (m, 4 H, 3-H/4-H), 2.67 (m, 4 H, 3-H/4-H) ppm. $^{13}$C NMR: $\delta$ = 180.0 (C-2), 172.3 (C-5), 47.6 (C-1), 28.1, 29.5 (C-3/C-4) ppm. $^{15}$N NMR: $\delta$ = –3.8 ppm. $^{195}$Pt NMR: $\delta$ = 2630 (420 Hz) ppm. Crystals suitable for X-ray data collection were grown by vapor diffusion of diethyl ether into a solution of **2** in acetone.

**(*OC*-6-33)-Dichloro(ethane-1,2-diamine)bis{(4-propylamino)-4-oxobutanoato}platinum(IV) (3a):** 1,1′-Carbonyldiimidazole (CDI; 237.3 mg, 1.464 mmol) in DMF (16 mL) was added to a solution of **2** (400 mg, 0.714 mmol) in DMF (8 mL) and the mixture heated to 60 °C. After 10 min stirring, the solution was cooled down to room temperature and $CO_2$ was removed by flushing with argon. Propylamine (120.8 μL, 1.464 mmol) in DMF (24 mL) was added to the solution and stirred for 24 h at room temperature. DMF was then removed under reduced pressure to form a yellow-brown oil. The crude product was purified by column chromatography (EtOAc/MeOH, 4:1) to yield a white powder. Yield: 253.1 mg (55%). $C_{16}H_{32}Cl_2N_4O_6Pt$ (642.43): calcd. C 29.91, H 5.02, N 8.72; found C 30.12, H 4.89, N 8.67. ESI-MS: *m*/*z* 643.1 [M + $H^+$]$^+$, 665.1 [M + $Na^+$]$^+$, 681.0 [M + $K^+$]$^+$, 641.1 [M – $H^+$]$^-$, 677 [M + $Cl^-$]$^-$. IR: $\tilde{\nu}$ = 3300, 3206 ($\nu_{N-H}$), 2963, 2929–2873 ($\nu_{C-H}$), 1664, 1640 ($\nu_{as\ C=O}$) $cm^{-1}$. $^1$H NMR: $\delta$ = 8.89 (br. s, 4 H, N$H_2$), 7.95 (br. s, 2 H, N*H*), 3.25 [q, $^3J_{H,H}$ = 6.3 Hz, 4 H, 6-H], 3.16 (br. s, 4 H, 1-H), 2.66 (t, $^3J_{H,H}$ = 7.0 Hz, 4 H, 3-H/4-H), 2.55 (t, $^3J_{H,H}$ = 7.0 Hz, 4 H, 3-H/4-H), 1.62 (m, 4 H, 7-H), 1.03 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H, 8-H) ppm. $^{13}$C NMR: $\delta$ = 180.3 (C-2), 170.0 (C-5), 47.5 (C-1), 39.1 (C-6), 30.0, 30.5 (C-3/C-4), 21.0 (C-7), 9.4 (C-8) ppm. $^{15}$N NMR: $\delta$ = 94.6 (*N*H), –3.3 (*N*$H_2$) ppm. $^{195}$Pt NMR: $\delta$ = 2622 (440 Hz) ppm.

  

**(*OC*-6-33)-Dichlorobis{(4-cyclopentylamino)-4-oxobutanoato}-(ethane-1,2-diamine)platinum(IV) (3b):** The synthesis was carried out as described for **3a**. The crude product was purified by column chromatography (EtOAc/MeOH, 4:1) and recrystallized from MeOH to yield a white powder. Yield: 102.3 mg (21%). $C_{20}H_{36}Cl_2N_4O_6Pt$ (694.51): calcd. C 34.59, H 5.22, N 8.07; found C 34.56, H 5.02, N 7.89. ESI-MS: *m/z* 717.1 $[M + Na^+]^+$, 733.0 $[M + K^+]^+$, 693.1 $[M - H^+]^-$. IR: $\tilde{\nu}$ = 3251, 3199 ($\nu_{N-H}$), 2947–2865 ($\nu_{C-H}$), 1664, 1638 ($\nu_{as\ C=O}$) $cm^{-1}$. $^1H$ NMR: $\delta$ = 8.88 (br. s, 4 H, N*H*$_2$), 7.94 (d, $^3J_{H,H}$ = 6.8 Hz, 2 H, N*H*), 4.23 (m, 2 H, 6-H), 3.17 (br. s, 4 H, 1-H), 2.65 (t, $^3J_{H,H}$ = 7.1 Hz, 4 H, 3-H/4-H), 2.52 (t, $^3J_{H,H}$ = 7.1 Hz, 4 H, 3-H/4-H), 1.99 (m, 4 H, 7-H), 1.82 (m, 4 H, 8-H), 1.68 (m, 4 H, 8-H), 1.60 (m, 4 H, 7-H) ppm. $^{13}C$ NMR: $\delta$ = 180.3 (C-2), 169.6 (C-5), 49.1 (C-6), 47.6 (C-1), 30.9 (C-7), 30.0, 30.5 (C-3/C-4), 21.9 (C-8) ppm. $^{15}N$ NMR: $\delta$ = 108.5 (*N*H), –3.7 (*N*H$_2$) ppm. $^{195}Pt$ NMR: $\delta$ = 2622 (433 Hz) ppm.

**(*OC*-6-33)-Dichloro(ethane-1,2-diamine)bis{[4-(2-hydroxyethyl)-amino]-4-oxobutanoato}platinum(IV) (3c):** The synthesis was carried out as described for **3a**. The crude product was purified by column chromatography (MeOH) to yield a pale-yellow powder. Yield: 87.7 mg (38%). $C_{14}H_{28}Cl_2N_4O_8Pt$ (646.38): calcd. C 26.01, H 4.37, N 8.67; found C 25.81, H 4.07, N 8.43. ESI-MS: *m/z* 669.3 $[M + Na^+]^+$, 645.2 $[M - H^+]^-$. IR: $\tilde{\nu}$ = 3592, 3530 ($\nu_{O-H}$), 3309, 3213 ($\nu_{N-H}$), 1675, 1633 ($\nu_{as\ C=O}$) $cm^{-1}$. $^1H$ NMR: $\delta$ = 8.88 (br. s, N*H*$_2$), 7.98 (br. s, 2 H, N*H*), 4.88 (br. s, 2 H, O*H*), 3.70 (m, 4 H, 7-H), 3.42 (m, 4 H, 6-H), 3.16 (br. s, 4 H, 1-H), 2.67 (t, $^3J_{H,H}$ = 6.8 Hz, 4 H, 3-H/4-H), 2.57 (t, $^3J_{H,H}$ = 6.8 Hz, 4 H, 3-H/4-H) ppm. $^{13}C$ NMR: $\delta$ = 180.2 (C-2), 170.3 (C-5), 59.1 (C-7), 47.6 (C-1), 40.3 (C-6), 30.4, 29.9 (C-3/C-4) ppm. $^{15}N$ NMR: $\delta$ = 90.1 (*N*H), –4.2 (*N*H$_2$) ppm. $^{195}Pt$ NMR: $\delta$ = 2621 (440 Hz) ppm.

**(*OC*-6-33)-Dichloro(ethane-1,2-diamine)bis{(4-ethoxy)-4-oxobutanoato}platinum(IV) (4a):** CDI (59.3 mg, 0.365 mmol) in abs. DMF (4 mL) was added to a solution of **2** (100 mg, 0.178 mmol) in abs. DMF (2 mL) and heated to 60 °C. After 10 min stirring, the solution was cooled down to room temperature and $CO_2$ was removed by flushing with argon. Sodium ethanolate (4 mg of Na in 10 mL of abs. ethanol) in abs. ethanol was added to the solution and stirred for 24 h at room temperature. Ethanol and DMF were removed under reduced pressure to form a yellow-brown oil. The crude product was purified by column chromatography (EtOAc/MeOH, 7:1) to yield a white powder. Yield: 41.5 mg (38%). $C_{14}H_{26}Cl_2N_2O_8Pt$ (616.35): calcd. C 27.28, H 4.25, N 4.55; found C 27.58, H 4.09, N 4.50. ESI-MS: *m/z* 616.1 $[M + H^+]^+$, 639.1 $[M + Na^+]^+$, 655.0 $[M + K^+]^+$, 615.2$[M - H^+]^-$. IR: $\tilde{\nu}$ = 3203 ($\nu_{N-H}$); 2985, 2929 ($\nu_{C-H}$); 1739, 1654 ($\nu_{as\ C=O}$) $cm^{-1}$. $^1H$ NMR: $\delta$ = 8.92 (t, $^2J_{H,Pt}$ = 53.6 Hz, 4 H, N*H*$_2$), 4.25 (q, $^3J_{H,H}$ = 7.1 Hz, 4 H, 6-H), 3.16 (br. s, 4 H, 1-H), 2.73 (m, 4 H, 3-H/4-H), 2.68 (m, 4 H, 3-H/4-H), 1.37 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H, 7-H) ppm. $^{13}C$ NMR: $\delta$ = 179.7 (C-2), 170.8 (C-5), 58.4 (C-6), 47.6 (C-1), 28.2, 29.3 (C-3/C-4), 12.1 (C-7) ppm. $^{15}N$ NMR: $\delta$ = –3.6 ppm. $^{195}Pt$ NMR: $\delta$ = 2629.1 (460 Hz) ppm.

**(*OC*-6-33)-Dichloro(ethane-1,2-diamine)bis{(4-octyloxy)-4-oxobutanoato}platinum(IV) (4b):** The synthesis was carried out as described for **4a**. The crude product was purified by column chromatography (EtOAc) to yield a white powder. Yield: 143.9 mg (34%). $C_{26}H_{50}Cl_2N_2O_8Pt$ (784.67): calcd. C 39.80, H 6.42, N 3.57; found C 39.69, H 6.26, N 3.49. ESI-MS: *m/z* 807.3 $[M + Na^+]^+$, 823.2 $[M + K^+]^+$, 783.3 $[M - H^+]^-$. IR: $\tilde{\nu}$ = 3210 ($\nu_{N-H}$), 2958, 2927, 2856 ($\nu_{C-H}$), 1745, 1650 ($\nu_{as\ C=O}$) $cm^{-1}$. $^1H$ NMR: $\delta$ = 8.92 (br. s, 4 H, N*H*$_2$), 4.21 (t, $^3J_{H,H}$ = 6.7 Hz, 4 H, 6-H), 3.16 (br. s, 4 H, 1-H), 2.74 (m, 4 H, 3-H/4-H), 2.69 (m, 4 H, 3-H/4-H), 1.77 (m, 4 H, 7-H), 1.46 (br. s, 20 H, 8-H to 12-H), 1.04 (t, $^3J_{H,H}$ = 6.6 Hz, 6 H, 13-H) ppm. $^{13}C$ NMR: $\delta$ = 179.7 (C-2), 170.9 (C-5), 62.6 (C-6), 47.7 (C-1), 29.5, 28.1 (C-3/C-4), 26.9 (C-7), 30.1, 27.5$_2$, 27.4$_8$, 24.1, 20.8 (C-8 to C-12), 12.0 (C-13) ppm. $^{15}N$ NMR: $\delta$ = –3.5 ppm. $^{195}Pt$ NMR: $\delta$ = 2628 (420 Hz) ppm.

X-ray diffraction measurements were performed on a Bruker X8APEX II CCD diffractometer at 100 K. Single crystals were positioned 37.5 mm from the detector and 813 frames were measured, each for 80 s over a 1° scan. The data were processed using the Denzo-SMN software package.[28] Crystal data, data collection parameters, and structure-refinement details for **2**·2$CH_3COCH_3$ are given in Table 2. The structures were solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. H atoms were calculated and allowed to ride. Computer programs: structure solution: SHELXS-97;[29] refinement: SHELXL-97;[30] molecular diagrams: ORTEP.[31] Computer: PC, Pentium II; scattering factors taken from the literature.[32]

Table 2. Crystallographic data for **2**·2$CH_3COCH_3$.

| | |
|---|---|
| Empirical formula | $C_{16}H_{30}Cl_2N_2O_{10}Pt$ |
| Fw | 676.41 |
| Space group | *P*2/*c* |
| *a* [Å] | 15.128(3) |
| *b* [Å] | 7.9108(16) |
| *c* [Å] | 10.745(2) |
| $\beta$ [°] | 110.72(3) |
| *V* [Å$^3$] | 1202.8(4) |
| *Z* | 2 |
| $\lambda$ [Å] | 0.71073 |
| $\rho_{calcd.}$ [g cm$^{-3}$] | 1.868 |
| Crystal size [mm] | 0.18 × 0.10 × 0.04 |
| *T* [K] | 100 |
| $\mu$ [cm$^{-1}$] | 61.06 |
| $R_1$[a] | 0.0108 |
| $wR_2$[b] | 0.0259 |
| GOF[c] | 1.061 |

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

CCDC-297226 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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