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Bis(2-amino alcohol-κ*N*)dicarboxylatoplatinum(II) Complexes – Elegant Synthesis via Ring-Opening of Bis(2-amino alcoholato-κ^2*N*,*O*)platinum(II) Species with Dicarboxylic Acids

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Synthesis and purification of bis(2-amino alcohol-κ*N*)dicarboxylatoplatinum(II) complexes is problematic because of the use of light-sensitive silver(I) salts and the competing ring-closing side-reactions, especially after release of the chloro- or iodo ligands of the dihalogeno starting platinum(II) species. A novel synthetic procedure, namely selective synthesis of doubly ring-closed bis(2-amino alcoholato-κ^2*N*,*O*)platinum(II) compounds as the purification step and subsequent coordination of dicarboxylates in the absence of silver(I) via a ring-opening reaction, yielded a series of new complexes, which were characterized by elemental analysis, NMR spectroscopy, and X-ray crystallography. Exemplarily, the ring-opening of bis(2-aminoethanolato-κ^2*N*,*O*)platinum(II) was performed in the NMR tube by means of oxalic acid and investigated by ^{1}H and ^{195}Pt NMR spectroscopy. The reaction was found to be highly efficient: within 3 h complete transformation to the dicarboxylatoplatinum(II) complex was observed. Contrary, when sodium oxalate was used, no reaction could be detected at all during a period of one day.

Introduction

Cisplatin, carboplatin, and oxaliplatin are the only metal-based chemotherapeutic drugs routinely used in the clinics in the fight against cancer (Figure 1).[1–4] In nearly 50% of all tumor therapies, platinum complexes are involved; in the case of testicular cancer, cisplatin demonstrates extraordinary tumor-inhibiting properties with real cure rates beyond 90%. Nevertheless, severe toxic side-effects and success of platinum complexes in only a limited number of solid tumors led to extensive attempts in the synthesis of a plethora of new platinum compounds.[5–7] In this context, hydrolysis of the administered drug was decreased by the use of dicarboxylato ligands (e.g., 1,1-cyclobutanedicarboxylate in carboplatin) resulting in significantly reduced systemic toxicity. Research has also focused on improving the solubility of the drugs for example by using oxalate (e.g., oxaliplatin) instead of chloro ligands (Figure 1).

Additionally, monodentate 2-amino alcohol or hydroxyethyl-substituted bidentate diamine ligands have been introduced in the drug development process in order (i) to increase the solubility, (ii) to further use the functional group for subsequent derivatization,[8,9] or (iii) to take advantage of the OH groups as donor or acceptor for hydrogen bonds with the DNA, the primary target of anticancer platinum complexes.[10,11]

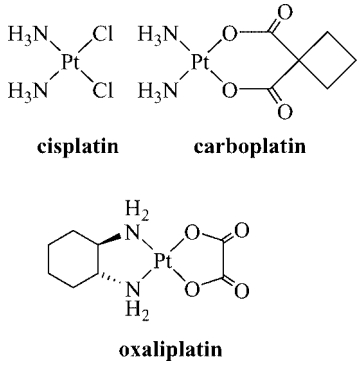

Figure 1. Chemical structures of established platinum-based anticancer drugs in world-wide clinical use.

Synthesis of bis(2-amino alcohol-κ*N*)platinum(II) complexes with dicarboxylato ligands, which would combine both structural features, is a logical consequence of the aforementioned considerations and seems to be straightforward from the chemical point of view. But only one publication by Khokhar et al. deals with this type of complex.[12] This is explainable by a set of problems arising during the synthetic procedure. Here we present an elegant and novel strategy in the preparation of bis(2-amino alcohol-κ*N*)dicarboxylatoplatinum(II) complexes as well as their characterization by elemental analysis, NMR spectroscopy, and X-ray crystallography. As the purification step, doubly ring-closed bis(2-amino alcoholato-κ^2*N*,*O*)platinum(II) com-

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plexes were prepared, now allowing us to omit silver(I) salts in the very last reaction step.

Results and Discussion

In almost every case, dicarboxylatoplatinum(II) compounds have been synthesized starting from dichloro- or diiodoplatinum(II) complexes (Figure 2) followed by release and precipitation of the halide through addition of silver(I) salts (predominantly $AgNO_3$ or Ag_2SO_4). After filtration, the activated platinum species is brought to reaction with the respective sodium dicarboxylate (commercially available or synthesized in situ via addition of NaOH). A second variant is based directly on the use of silver dicarboxylates, offering the advantage that separation from $NaNO_3$ or Na_2SO_4 in the case of highly soluble dicarboxylatoplatinum(II) compounds is not required. However, in both instances reactions including light-sensitive silver salts are inherently problematic especially in the last reaction step.[13] In the case of a slight excess of Ag^+, difficulties in the purification of the reaction product can be expected. Furthermore, Ag^+ itself is biologically active, leading to false positive or false negative results during the evaluation of the anticancer properties.

Consequently, one strategy is to take substoichiometric amounts of the silver salt,[14,15] which then could lead to a contamination with monochloro- or monoiodoplatinum(II) species, depending on the solubility of the target platinum compounds. Additionally, and this is a characteristic feature of bis(2-amino alcohol-κ*N*)platinum(II) complexes, intramolecular ligand exchange reactions leading to singly and doubly ring-closed analogues must be taken into consideration. This facet has been studied in detail by NMR spectroscopy and was published recently in the case of (*SP*-4–2)-bis(2-aminoethanol-κ*N*)dichloroplatinum(II) and (*OC*-6–22)-bis(2-aminoethanol-κ*N*)tetrachloroplatinum(IV).[16] For activated platinum complexes (no halogeno ligand), an effective ring-closing side reaction should logically be expected.

In order to circumvent these synthetic difficulties, namely to avoid the use of silver salts in the very last reaction step

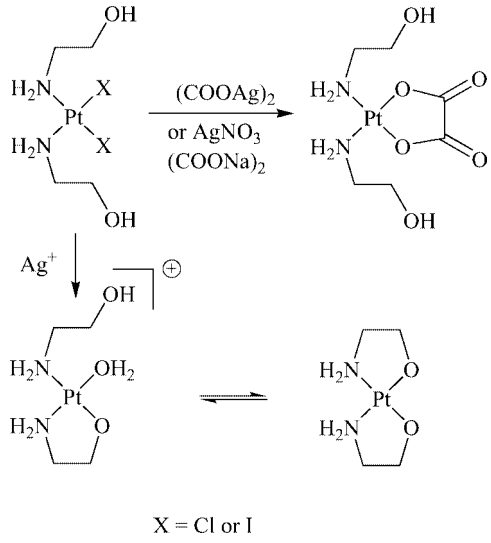

Figure 2. General synthesis of dicarboxylatoplatinum(II) complexes [e.g., (*SP*-4–2)-bis(2-aminoethanol-κ*N*)oxalatoplatinum(II)]; in the case of amino alcohol ligands, undesired side reactions to the singly and doubly ring-closed species are observed.

and to suppress side reactions as much as possible, a novel and elegant synthetic strategy was evaluated for its general applicability in the preparation of bis(2-amino alcohol-κ*N*)-dicarboxylatoplatinum(II) complexes. The basis of this procedure is the selective synthesis of the doubly ring-closed platinum species **2a**–**d** (which are in the above-mentioned synthetic pathway one of the unwanted side products) directly starting from the diiodoplatinum(II) compounds **1a**–**d** (Figure 3).

This is in contrast to our previously published pathway, where the dichloro analogues have been used.[17] Release of the iodo ligands is thereby accomplished (i) in the presence of substoichiometric amounts of $AgNO_3$ and (ii) additionally by the use of a basic anion exchanger (IRA 402), which further accelerates the ring formation process by a high pH value. The doubly ring-closed platinum(II) complexes **2a**–**d** were isolated and characterized by elemental analysis, NMR spectroscopy and in the case of **2c**(***S***) and **2d**(***S***) (*S*-enantiomers of complexes **2c** and **2d**) by X-ray diffraction

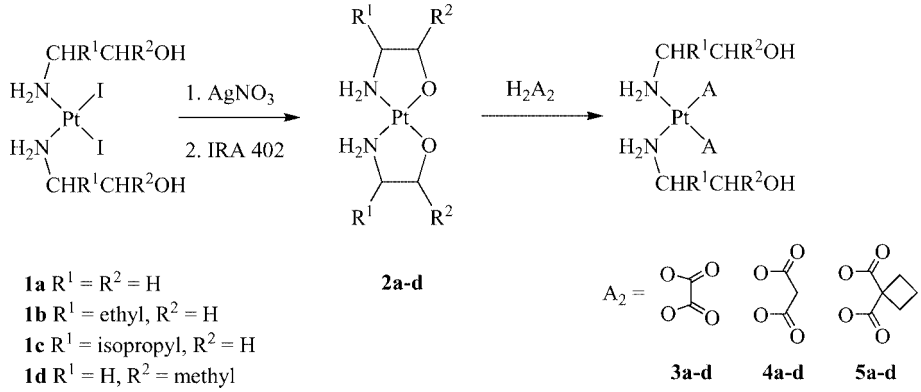

Figure 3. Synthesis of the target bis(2-amino alcohol-κ*N*)dicarboxylatoplatinum(II) complexes **3a**–**5d** via ring-opening with dicarboxylic acids (stereochemistry omitted).

analysis (Figure S1 and S2, Table S1 and S2, Supporting Information). The analytical data are in agreement with recently published results.[16] Most indicative for the success of the ring-closing reaction are the ^{1}H and ^{13}C chemical shifts of the methylene (**2a**–**c**) or methine (**2d**) group as well as the ^{195}Pt satellites of the C*H*R^{2}OPt protons. The latter, deriving from a $^{3}J(^{1}H,^{195}Pt)$ coupling are only visible in the case of the ring-closed complexes. In proton NMR spectra, the C*H*R^{2}OPt protons display an upfield shift in **2a**–**c** (e.g., **2a**, 2.97 ppm, corresponding dichloro complex, 3.76 ppm).

Typically, for the *C*HR^{2}OPt carbon atoms of **2a**–**d** resonances in the region between δ = 69.3 and 75.1 ppm can be detected. This is about 10 ppm downfield from the signals of the analogous ring-opened dichloro complexes (e.g., **2a**, 69.3 ppm, corresponding dichloro complex, 60.8 ppm). As could be shown earlier, addition of HCl or DCl results in the formation of the dichloro counterparts.[18] But addition of NaCl to the doubly ring closed species even in a 35-fold excess (without decrease of the pH value) shifts the equilibrium slightly towards the mono- but not to the dichloro complex (Figure S3). Consequently, **2a**–**d** have been used as starting complexes for the synthesis of compounds **3a**–**5d** via direct reaction with oxalic-, malonic-, and 1,1-cyclobutanedicarboxylic acid in water without addition of any other reagent. The products **3a**–**5d** were characterized by elemental analysis, NMR spectroscopy, and X-ray single crystal diffraction (**3a** and **5a**). Products **3a**–**d** were investigated by ^{1}H and ^{13}C NMR spectroscopy, whereas in the case of the analogous dicarboxylates **4a**–**5d** only ^{1}H NMR spectra have been performed for comparison.

In analogy to the reactions with HCl and NaCl, ring-opening could only be performed by means of dicarboxylic acids. When the respective sodium salt (e.g., sodium oxalate) was used, no reaction could be observed at all during a period of 24 h, as could be demonstrated by ^{1}H NMR spectroscopy (Figure S4). Formation of the bis(2-amino alcohol-κ*N*)dicarboxylatoplatinum(II) complexes **3a**–**5d** can best be judged by significant changes in ^{1}H NMR spectra. An apparent downfield shift of C*H*R^{2}OH proton resonances from 2.97–3.41 ppm in **2a**–**d** to 3.74–4.11 ppm in **3a**–**5d** was detected in conjunction with loss of the $^{3}J(^{1}H,^{195}Pt)$ coupling. Within the series of dicarboxylates (e.g., **3a**, **4a**, and **5a**, the same amine ligand, but different dicarboxylato ligand) the C*H*R^{2}OH chemical shifts showed marginal deviations within 0.04 ppm. In ^{13}C NMR spectra of the oxalato complexes **3a**–**d** noteworthy changes were observed for *C*HR^{2}OH carbon atoms (between δ = 60.5 and 66.9 ppm) in comparison to the ring-closed species **2a**–**d** (between δ = 69.3 and 75.1 ppm). Furthermore, in oxalato complexes **3a**–**d** ^{13}COO signals of the coordinated carboxylato ligands were detected in a narrow range at δ = 169.2 and 169.3 ppm (oxalic acid, 161.9 ppm; sodium oxalate, 173.8 ppm). The elemental analysis data of all new complexes were found in accordance with the expected values, proving their identity as well.

For complexes **3a** and **5a** it was possible to determine their solid-state structure by X-ray diffraction. Structural features of the square-planar platinum(II) complex **3a** are revealed in Figure 4. Selected bond lengths and angles are given in Table 1.

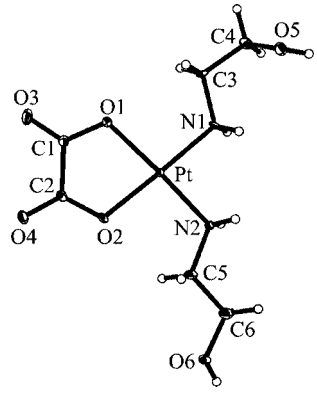

Figure 4. ORTEP diagram of **3a** displaying thermal ellipsoids at 50% probability.

Table 1. Bond lengths [Å] and angles [°] in the platinum(II) coordination polyhedron of **3a** and **5a**.

atom1–atom2	**3a**	atom1–atom2	**5a**
Pt–O1	2.032(5)	Pt–O3	2.012(2)
Pt–O2	2.033(5)	Pt–O5	2.023(2)
Pt–N1	2.050(6)	Pt–N1	2.027(2)
Pt–N2	2.038(6)	Pt–N2	2.037(2)
C1–O1	1.311(9)	C5–O3	1.305(3)
C1–O3	1.248(9)	C5–O4	1.228(3)
C2–O2	1.293(9)	C10–O5	1.296(3)
C2–O4	1.238(9)	C10–O6	1.233(3)
atom1–atom2–atom3		atom1–atom2–atom3	
O1–Pt–O2	82.0(2)	O3–Pt–O5	91.17(8)
N1–Pt–N2	86.6(3)	N1–Pt–N2	91.19(10)

A projection of the molecule of **5a** on the coordination plane through PtN1N2O3O5 is shown in Figure 5. Selected bond lengths and angles are listed in Table 1. In **5a** the Pt atom has a square-planar coordination geometry. The Pt–O bond lengths are 2.012(2) and 2.023(2) Å, while the Pt–N bonds are 2.027(2) and 2.037(2) Å. These parameters are comparable with those in Pt(EtNH$_2$)$_2$(1,1-cyclobutanedicarboxylato)·H$_2$O [Pt–O 2.000(4) and 2.015(4) Å, Pt–N 1.992(5) and 2.020(5) Å].[19] As expected the C–O bonds (involving coordinated oxygens) at 1.305(3) and 1.296(3) Å are significantly longer than the two C=O bonds [C5–O4 1.228(3) and C10–O6 1.233(3) Å]. The angles inside the cyclobutane ring vary between 87.69(19) and 89.2(2)°, in agreement with those reported for Pt{*trans*-(–)-1,2-cyclohexanediamine}(1,1-cyclobutanedicarboxylate).[20] The mean deviation of the four atoms forming the four-membered ring from the best plane through C6, C7, C8, and C9 does not exceed 0.129 Å. The dihedral angle between the cyclobutane ring and the Pt coordination plane is ca. 70.9°. The two ethanolamine ligands and the cyclobutane ring are all on the same side of the Pt coordination plane. The six-membered malonate chelate cycle has a boat conformation. The mean deviation of O3, C5, O5, and C10 from the best plane through these four atoms is 0.0041 Å, with Pt and C6

atoms on the same side of the plane with deviations of 0.6858 and 0.6290 Å. The two carbonyl oxygen atoms O4 (deviation –0.4585 Å) and O6 (deviation –0.4667 Å) are oriented towards the other side of the plane. Of note is also the intramolecular hydrogen bond O1–H1···O3 [O1–H1 0.84, H1···O3 2.457, O1···O3 3.159 Å, ∠O1H1O3 141.72°] (see Figure 5).

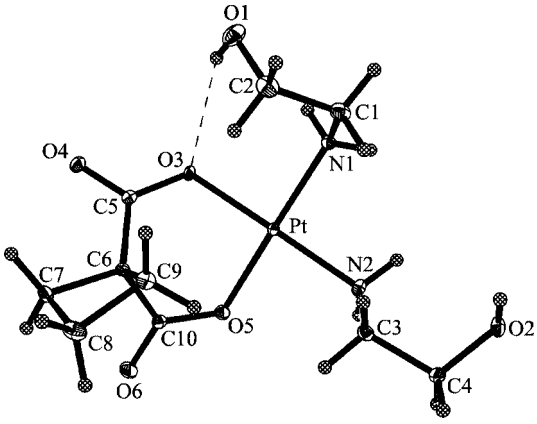

Figure 5. ORTEP diagram of **5a** displaying thermal ellipsoids at 50% probability.

Additionally, ring-opening of **2a** and formation of the dicarboxylatoplatinum(II) complex **3a** were studied directly in the NMR tube (Figure 6). As can be deduced from the ^{1}H and ^{195}Pt NMR spectra the reaction of oxalic acid with **2a** was very efficient. Three hours after mixing of **2a** (10.0 mg, 0.032 mmol) with oxalic acid (3.0 mg, 0.033 mmol) dissolved in 0.6 mL of D_2O, the dicarboxylato complex **3a** was formed and was detected as the sole species in both ^{1}H and ^{195}Pt NMR spectra (note that this is in clear contrast to the reaction with sodium oxalate, where no ring-opening could be observed at all during a period of 24 h; compare Figure S4). Ring-opening and dicarboxylate formation is reflected by significant downfield shifts of ^{1}H and ^{195}Pt resonances. In the case of CH_2N protons, chemical shift differences are consequently smaller (**2a**, 2.27 ppm; **3a**, 2.67 ppm) than for CH_2O protons (**2a**, 2.98 ppm; **3a**, 3.76 ppm) since the oxygen atom is released from the platinum(II) center (Figure 6).

Unresolved ^{195}Pt satellites deriving from a $^{3}J(^{1}H,^{195}Pt)$ coupling were detected for CH_2N and CH_2OPt protons (marked with asterisks in Figure 6) at the base of the respective resonances. In **3a** the CH_2OH signals do not display such satellites, further proving the ring-opening reaction. Moreover, a remarkable downfield shift in the ^{195}Pt NMR spectra from –621 (**2a**) to –255 ppm (**3a**) finally documents the success of the conversion from **2a** to **3a**.

Conclusions

The synthesis of bis(2-amino alcohol-κ*N*)dicarboxylatoplatinum(II) complexes was advantageously performed via a ring-opening reaction of the respective bis(2-amino alcoholato-κ^2*N*,*O*)platinum(II) species with dicarboxylic acids. This novel synthetic strategy is independent from the use of light-sensitive silver(I) salts in the last reaction step, which could cause problems during the purification and isolation of the target compounds. As could be exemplarily shown by ^{1}H and ^{195}Pt NMR spectroscopy for the reaction of bis(2-aminoethanolato-κ^2*N*,*O*)platinum(II) with oxalic acid, the transformation to the dicarboxylato complex is considerably fast and efficient. In contrast, reaction with sodium oxalate did not result in any detectable product during a period of one day.

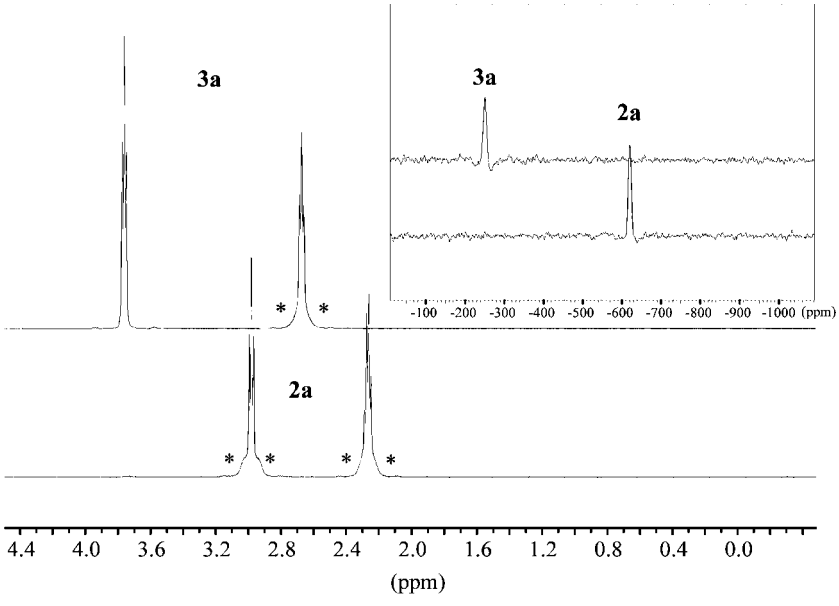

Figure 6. ^{1}H and ^{195}Pt (small insert) NMR spectra of the conversion of **2a** to **3a** through addition of an equivalent amount of oxalic acid; reaction was directly performed in the NMR tube, ^{195}Pt satellites are marked with asterisks.

Experimental Section

All chemicals were purchased from commercial suppliers; K_2PtCl_4 was obtained from Johnson Matthey. Deionized water (reverse osmosis) was doubly distilled before use. All reactions were carried out under protection from light and for stirring a glass-coated magnetic stirrer was used. The ^1H, ^{13}C, and ^{195}Pt NMR spectra were recorded with a Bruker DPX 400 (Ultrashield™ Magnet) at 400.13, 100.62, and 86.11 MHz, respectively at 25 °C, using standard pulse programs. ^{195}Pt chemical shifts were referenced relative to external K_2PtCl_4. The elemental analyses were performed using a Perkin–Elmer 2400 CHN Elemental Analyzer by the microlaboratory of the Institute of Physical Chemistry, University of Vienna.

(*SP*-4–2)-Bis(2-aminoethanol-κ*N*)diiodoplatinum(II), **1a**, (*SP*-4–2)-bis[(*S*)-2-amino-1-butanol-κ*N*]diiodoplatinum(II), **1b(*S*)**, and (*SP*-4–2)-bis[(*R*)-2-amino-1-butanol-κ*N*]diiodoplatinum(II), **1b(*R*)**, were synthesized as described elsewhere.[16]

(*SP*-4–2)-Bis[(*S*)-2-amino-3-methyl-1-butanol-κ*N*]diiodoplatinum(II) [1c(*S*)]: K_2PtCl_4 (5.997 g, 14.45 mmol) was dissolved in water (50 mL) and treated with KI (12.0 g, 72.29 mmol). After stirring for 30 min at room temperature, a solution of (*S*)-2-amino-3-methyl-1-butanol (3.428 g, 33.23 mmol) in water (10 mL) was added in small portions and the brown reaction mixture was stirred for 10 h at room temperature. Precipitation of a yellow solid was completed by cooling the mixture for 12 h at 4 °C. The product was filtered off, washed with cold water (three times, 2 mL), and dried in vacuo over P_4O_{10}. Yield: 4.408 g (47%). $C_{10}H_{26}I_2N_2O_2Pt$ (655.21): calcd. C 18.33, H 4.00, N 4.27; found C 18.37, H 3.87, N 4.15.

(*SP*-4–2)-Bis[(*R*)-2-amino-3-methyl-1-butanol-κ*N*]diiodoplatinum(II) [1c(*R*)]: The synthesis was carried out as described for **1c(*S*)**, starting from K_2PtCl_4 (1.574 g, 3.79 mmol). Yield: 1.760 g (71%). $C_{10}H_{26}I_2N_2O_2Pt$ (655.21): calcd. C 18.33, H 4.00, N 4.27; found C 18.38, H 3.80, N 4.17.

(*SP*-4–2)-Bis[(*S*)-1-amino-2-propanol-κ*N*]diiodoplatinum(II) [1d(*S*)]: K_2PtCl_4 (618 mg, 1.49 mmol) was dissolved in water (ca. 5 mL) and treated with KI (1.235 g, 7.44 mmol). After stirring for 30 min at room temperature, a solution of (*S*)-1-amino-2-propanol (224 mg, 2.98 mmol) in water (1 mL) was added dropwise. The mixture was stirred for 3 h at room temperature. Precipitation of a yellow solid could be observed, which was completed by cooling for 1 h at 4 °C. The product was filtered off, washed with ice-cold water (three times, 1 mL), and dried in vacuo over P_4O_{10}. Yield: 640 mg (72%). $C_6H_{18}I_2N_2O_2Pt$ (599.11): calcd. C 12.03, H 3.03, N 4.68; found C 12.08, H 2.86, N 4.48.

(*SP*-4–2)-Bis[(*R*)-1-amino-2-propanol-κ*N*]diiodoplatinum(II) [1d(*R*)]: The synthesis was carried out as described for **1d(*S*)**, starting from K_2PtCl_4 (2.100 g, 5.06 mmol). Yield: 2.078 g (69%).

(*SP*-4–2)-Bis(2-aminoethanolato-κ²*N*,*O*)platinum(II) (2a): 1a (5.660 g, 9.91 mmol) was suspended in water (80 mL), mixed with $AgNO_3$ (3.198 g, 18.83 mmol), and stirred for 24 h at room temperature. AgI was filtered off and the clear solution was mixed with a preconditioned basic anion exchange resign, IRA 402 (the commercially available chloride form was treated with 2 M NaOH for 30 min and washed with deionized water until a pH of 7). After stirring for 12 h at room temperature, the liquid was decanted from the resign, which was washed three times with water. The combined aqueous solutions were filtered and thereafter concentrated to ca. 1 mL under reduced pressure at 30 °C. Crystallization of the product occurred at room temperature and was completed at 4 °C. The white product was isolated by filtration, rinsed with a few drops of ice-cold water, and dried in vacuo over P_4O_{10}. Yield: 1.337 g (45%). $C_4H_{12}N_2O_2Pt$ (315.23): calcd. C 15.24, H 3.84, N 8.89; found C 15.33, H 3.68, N 8.69. ^1H NMR (D_2O): δ = 2.97 (t, $^3J_{H,H}$ = 5.4 Hz, 4 H, CH_2O), 2.25 (t, $^3J_{H,H}$ = 5.5 Hz, 4 H, CH_2N) ppm. ^{13}C NMR (D_2O): δ = 69.3 (2 C, *C*H_2O), 50.8 (2 C, *C*H_2N) ppm.

(*SP*-4–2)-Bis[(*S*)-2-amino-1-butanolato-κ²*N*,*O*]platinum(II) [2b(*S*)]: 1b(*S*) (2.860 g, 4.56 mmol) was suspended in water (60 mL), treated with $AgNO_3$ (1.405 g, 8.27 mmol), and stirred for 24 h. After filtration of AgI, the clear solution was treated with preconditioned IRA 402 as described for **2a**; the reaction was stirred for 48 h. After removal of the ion exchange resign and filtration, the solution was concentrated until a solid product appeared. Precipitation was completed first at room temperature and later at 4 °C. The white product was isolated by filtration, rinsed with a few drops of ice-cold water, and dried in vacuo over P_4O_{10}. Yield: 745 mg (48%). $C_8H_{20}N_2O_2Pt$ (371.33): calcd. C 25.88, H 5.43, N 7.54; found C 26.05, H 5.21, N 7.47. ^1H NMR (H_2O/D_2O, 9:1): δ = 3.01 (m, 2 H, CH_2O), 2.88 (m, 2 H, CH_2O), 2.48 (m, 2 H, C*H*N), 1.53 (m, 2 H, CH_3CH_2), 1.34 (m, 2 H, CH_3CH_2), 0.80 (t, $^3J_{H,H}$ = 7.3 Hz, 6 H, CH_3) ppm. ^{13}C NMR (H_2O/D_2O, 9:1): δ = 73.0 (2 C, *C*H_2O), 64.1 (2 C, *C*HN), 22.9 (2 C, CH_3CH_2), 10.8 (2 C, *C*H_3) ppm.

(*SP*-4–2)-Bis[(*R*)-2-amino-1-butanolato-κ²*N*,*O*]platinum(II) [2b(*R*)]: The synthesis was carried out as described for **2b(*S*)**, starting from **1b(*R*)** (1.260 g, 2.01 mmol). Yield: 366 mg (52%). $C_8H_{20}N_2O_2Pt$ (371.33): calcd. C 25.88, H 5.43, N 7.54; found C 25.99, H 5.14, N 7.50. ^1H NMR (H_2O/D_2O, 9:1): δ = 3.06 (m, 2 H, CH_2O), 2.94 (m, 2 H, CH_2O), 2.54 (m, 2 H, C*H*N), 1.59 (m, 2 H, CH_3CH_2), 1.42 (m, 2 H, CH_3CH_2), 0.86 (t, $^3J_{H,H}$ = 7.6 Hz, 6 H, CH_3) ppm. ^{13}C NMR (H_2O/D_2O, 9:1): δ = 72.9 (2 C, *C*H_2O), 64.1 (2 C, *C*HN), 22.9 (2 C, CH_3CH_2), 10.8 (2 C, *C*H_3) ppm.

(*SP*-4–2)-Bis[(*S*)-2-amino-3-methyl-1-butanolato-κ²*N*,*O*]platinum(II) [2c(*S*)]: 1c(*S*) (2.058 g, 3.14 mmol) was suspended in water (70 mL), treated with $AgNO_3$ (1.024 g, 6.03 mmol), and stirred for 24 h. After filtration of AgI, the clear solution was treated with preconditioned IRA 402 as described for **2a**; the reaction was stirred for 48 h. After removal of the ion exchange resign and filtration, the solution was concentrated until a solid product appeared. Precipitation was completed first at room temperature and later at 4 °C. The white product was isolated by filtration, rinsed with a few drops of ice-cold water, and dried in vacuo over P_4O_{10}. Yield: 103 mg (8%). $C_{10}H_{24}N_2O_2Pt{\cdot}H_2O$ (417.40): calcd. C 28.77, H 6.28, N 6.71; found C 28.78, H 6.02, N 6.68. ^1H NMR (D_2O): δ = 3.09 (m, 2 H, CH_2O), 2.99 (m, 2 H, CH_2O), 2.30 (m, 2 H, C*H*N), 1.62 [m, 2 H, $(CH_3)_2CH$], 0.85 (d, $^3J_{H,H}$ = 7.8 Hz, 12 H, CH_3) ppm. ^{13}C NMR (D_2O): δ = 71.9 (2 C, *C*H_2O), 68.5 (2 C, *C*HN), 28.8 [2 C, *C*$H(CH_3)_2$], 20.4 (2 C, *C*H_3), 18.9 (2 C, *C*H_3) ppm.

(*SP*-4–2)-Bis[(*R*)-2-amino-3-methyl-1-butanolato-κ²*N*,*O*]platinum(II) [2c(*R*)]: The synthesis was carried out as described for **2c(*S*)**, starting from **1c(*R*)** (1.700 g, 2.59 mmol). Yield: 112 mg (11%). $C_{10}H_{24}N_2O_2Pt{\cdot}H_2O$ (417.40): calcd. C 28.77, H 6.28, N 6.71; found C 28.78, H 6.02, N 6.68. ^1H NMR (D_2O): δ = 3.06 (m, 2 H, CH_2O), 2.97 (m, 2 H, CH_2O), 2.29 (m, 2 H, C*H*N), 1.60 [m, 2 H, $(CH_3)_2CH$], 0.84 (t, $^3J_{H,H}$ = 7.8 Hz, 12 H, CH_3) ppm. ^{13}C NMR (D_2O): δ = 71.8 (2 C, *C*H_2O), 68.4 (2 C, *C*HN), 28.6 [2 C, *C*$H(CH_3)_2$], 20.2 (2 C, *C*H_3), 18.7 (2 C, *C*H_3) ppm.

(*SP*-4–2)-Bis[(*S*)-1-amino-2-propanolato-κ²*N*,*O*]platinum(II) [2d(*S*)]: 1d(*S*) (3.026 g, 5.05 mmol) was suspended in water (80 mL), treated with $AgNO_3$ (1.647 g; 9.70 mmol), and stirred for 24 h. After filtration of AgI, the clear solution was treated with preconditioned IRA 402 as described for **2a**; the reaction was stirred for 48 h. After removal of the ion exchange resign and filtration, the solution was concentrated until a solid product appeared. Precipitation was completed first at room temperature and later at 4 °C. The white

product was isolated by filtration, rinsed with a few drops of ice-cold water, and dried in vacuo over P_4O_{10}. Yield: 186 mg (10%). $C_6H_{16}N_2O_2Pt·1.5H_2O$ (370.30): calcd. C 19.46, H 5.17, N 7.56; found C 19.60, H 4.87, N 7.33. ^{1}H NMR (D_2O): δ = 3.42 (m, 2 H, C*H*O), 2.28 (dd, $^3J_{H,H}$ = 3.5 Hz, $^3J_{H,H}$ = 11.5 Hz, 2 H, CH_2N), 2.01 (dd, $^3J_{H,H}$ = 11.4 Hz, 2 H, CH_2N), 1.03 (d, $^3J_{H,H}$ = 6.0 Hz, 6 H, CH_3) ppm. ^{13}C NMR (D_2O): δ = 75.2 (2 C, *C*HO), 55.3 (2 C, *C*H_2N), 17.7 (2 C, *C*H_3) ppm.

(*SP*-4-2)-Bis[(*R*)-1-amino-2-propanolato-κ^2*N*,*O*]platinum(II) [2d(*R*)]: The synthesis was carried out as described for **2d(*S*)**, starting from **1d(*R*)** (2.022 g, 3.37 mmol). Yield: 429 mg (39%). $C_6H_{16}N_2O_2Pt$ (343.28): calcd. C 20.99, H 4.70, N 8.16; found C 20.76, H 4.99, N 7.86. ^{1}H NMR (D_2O): δ = 3.41 (m, 2 H, C*H*O), 2.27 (dd, $^3J_{H,H}$ = 3.4 Hz, $^3J_{H,H}$ = 11.5 Hz, 2 H, CH_2N), 2.00 (dd, $^3J_{H,H}$ = 10.7 Hz, 2 H, CH_2N), 1.03 (d, $^3J_{H,H}$ = 6.3 Hz, 6 H, CH_3) ppm. ^{13}C NMR (D_2O): δ = 75.1 (2 C, *C*HO), 54.9 (2 C, *C*H_2N), 17.6 (2 C, *C*H_3) ppm.

(*SP*-4-2)-Bis(2-aminoethanol-κ*N*)oxalatoplatinum(II) (3a): 2a (122 mg, 0.39 mmol) and oxalic acid dihydrate (50 mg, 0.40 mmol) were dissolved in water (2 mL) and stirred for 20 h at room temperature. The solution was filtered and reduced in a hood air stream until crystallization of colorless needles occurred. The product was separated and dried in vacuo over P_4O_{10}. Yield: 140 mg (89%). $C_6H_{14}N_2O_6Pt$ (405.26): calcd. C 17.78, H 3.48, N 6.91; found C 17.82, H 3.28, N 6.73. ^{1}H NMR (D_2O): δ = 3.76 (t, $^3J_{H,H}$ = 5.3 Hz, 4 H, CH_2O), 2.68 (m, 4 H, CH_2N) ppm. ^{13}C NMR (D_2O): δ = 169.3 (2 C, *C*OO), 60.5 (2 C, *C*H_2O), 48.3 (2 C, *C*H_2N) ppm.

(*SP*-4-2)-Bis[(*S*)-2-amino-1-butanol-κ*N*]oxalatoplatinum(II) [3b(*S*)]: 2b(*S*) (49 mg, 0.13 mmol) and oxalic acid dihydrate (17 mg, 0.13 mmol) were dissolved in water (1 mL) and stirred for 18 h at room temperature. The solution was filtered and concentrated under reduced pressure over P_4O_{10} until a crystalline product appeared, which was washed with water (two times with 0.5 mL) and dried in vacuo over P_4O_{10}. Yield: 28 mg (46%). $C_{10}H_{22}N_2O_6Pt$ (461.37): calcd. C 26.03, H 4.81, N 6.07; found C 25.98, H 4.70, N 5.94. ^{1}H NMR (D_2O): δ = 3.92 (dd, $^3J_{H,H}$ = 3.6 Hz, $^3J_{H,H}$ = 12.0 Hz, 2 H, CH_2O), 3.63 (dd, $^3J_{H,H}$ = 5.1 Hz, $^3J_{H,H}$ = 12.0 Hz, 2 H, CH_2O), 2.59 (m, 2 H, C*H*N), 1.72 (m, 2 H, CH_3CH_2), 1.54 (m, 2 H, CH_3CH_2), 0.89 (t, $^3J_{H,H}$ = 7.5 Hz, 6 H, CH_3) ppm. ^{13}C NMR (D_2O): δ = 169.3 (2 C, *C*OO), 62.4 (2 C, *C*H_2O), 59.1 (2 C, *C*HN), 24.3 (2 C, *C*H_2CH_3), 9.9 (2 C, *C*H_3) ppm.

(*SP*-4-2)-Bis[(*R*)-2-amino-3-methyl-1-butanol-κ*N*]oxalatoplatinum(II) [3c(*R*)]: 2c(*R*) (76 mg, 0.19 mmol) and oxalic acid dihydrate (24 mg, 0.19 mmol) were dissolved in water (5 mL) and stirred for 48 h at room temperature. The solution was concentrated under reduced pressure at 35 °C to ca. 1 mL and stored at room temperature for 12 h. A white product was isolated and dried in vacuo. Yield: 75 mg (81%). $C_{12}H_{26}N_2O_6Pt$ (489.44): calcd. C 29.45, H 5.35, N 5.72; found C 29.44, H 5.13, N 5.59. ^{1}H NMR (D_2O): δ = 4.02 (dd, $^3J_{H,H}$ = 3.7 Hz, $^3J_{H,H}$ = 12.0 Hz, 2 H, CH_2O), 3.73 (dd, $^3J_{H,H}$ = 5.6 Hz, $^3J_{H,H}$ = 12.0 Hz, 2 H, CH_2O), 2.45 (m, 2 H, C*H*N), 1.99 [m, 2 H, $(CH_3)_2CH$], 0.91 (d, $^3J_{H,H}$ = 6.8 Hz, 6 H, CH_3), 0.87 (d, $^3J_{H,H}$ = 6.8 Hz, 6 H, CH_3) ppm. ^{13}C NMR (D_2O): δ = 169.3 (2 C, *C*OO), 63,2 (2 C, *C*HN), 61.5 (2 C, *C*H_2O), 29.4 [2 C, *C*$H(CH_3)_2$], 18.9 (2 C, *C*H_3), 18.1 (2 C, *C*H_3) ppm.

(*SP*-4-2)-Bis[(*R*)-1-amino-2-propanol-κ*N*]oxalatoplatinum(II) [3d(*R*)]: 2d(*R*) (157 mg, 0.46 mmol) and oxalic acid dihydrate (58 mg, 0.46 mmol) were dissolved in water (5 mL) and stirred for 48 h at room temperature. The solution was reduced to 1 mL and stored at room temperature for 12 h. A white precipitate was separated from the residual solution and dried in vacuo. Yield: 79 mg (40%). $C_8H_{18}N_2O_6Pt$ (433.32): calcd. C 22.17, H 4.19, N 6.46; found: C 22.40, H 3.97, N 6.31. ^{1}H NMR (D_2O): δ = 4.07 (m, 2 H, C*H*O), 2.65 (m, 2 H, CH_2N), 2.41 (m, 2 H, CH_2N), 1.11 (d, $^3J_{H,H}$ = 6.4 Hz, 6 H, CH_3) ppm. ^{13}C NMR (D_2O): δ = 169.2 (2 C, *C*OO), 66.9 (2 C, *C*HO), 53.2 (2 C, *C*H_2N), 20.1 (2 C, *C*H_3) ppm.

(*SP*-4-2)-Bis(2-aminoethanol-κ*N*)malonatoplatinum(II) (4a): 2a (200 mg, 0.63 mmol) and malonic acid (66 mg, 0.65 mmol) were dissolved in water (10 mL) and stirred for 24 h at room temperature. The colorless solution was filtered and the solvent was removed slowly under reduced pressure over $CaCl_2$. A white crystalline product was isolated and dried in vacuo over P_4O_{10}. Yield: 230 mg (86%). $C_7H_{16}N_2O_6Pt$ (419.30): calcd. C 20.05, H 3.85, N 6.68; found C 20.18, H 3.69, N 6.53. ^{1}H NMR (H_2O/D_2O, 9:1): δ = 3.75 (t, $^3J_{H,H}$ = 5.2 Hz, 4 H, CH_2O), 3.57 (s, 2 H, CH_2COO), 2.64 (m, 4 H, CH_2N) ppm.

(*SP*-4-2)-Bis[(*R*)-2-amino-1-butanol-κ*N*]malonatoplatinum(II) [4b(*R*)]: 2b(*R*) (200 mg, 0.54 mmol) and malonic acid (56 mg, 0.55 mmol) were dissolved in water (10 mL) and stirred for 24 h at 40 °C. The solution was filtered and the solvent was removed under reduced pressure at 40 °C. The residual yellow oil was treated with diethyl ether (15 mL) for 30 s in an ultra sonic bath, then the solvent was immediately evaporated. This procedure was repeated five times. The solid product was dried in vacuo, recrystallized from acetone/ethanol (3:1), and finally dried in vacuo. Yield: 82 mg (32%). $C_{11}H_{24}N_2O_6Pt$ (475.40): calcd. C 27.79, H 5.09, N 5.89; found C 27.58, H 4.80, N 5.65. ^{1}H NMR (H_2O/D_2O, 9:1): δ = 3.92 (m, 2 H, CH_2O), 3.60 (m, 2 H, CH_2O), 3.58 (s, 2 H, CH_2COO), 2.58 (s, 2 H, C*H*N), 1.71 (m, 2 H, CH_2CH_3), 1.53 (m, 2 H, CH_2CH_3), 0.87 (m, 6 H, CH_3) ppm. ^{13}C NMR (H_2O/D_2O, 9:1): δ = 178.4 (2 C, CH_2COO), 62.6 (2 C, *C*H_2O), 58.7 (2 C, *C*HN), 48.0 (1 C, *C*H_2COO), 24.3 (2 C, *C*H_2CH_3), 9.9 (2 C, *C*H_3) ppm.

(*SP*-4-2)-Bis[(*R*)-2-amino-3-methyl-1-butanol-κ*N*]malonatoplatinum(II) [4c(*R*)]: Malonic acid (52 mg, 0.51 mmol) was dissolved in water (10 mL). To this solution **2c(*R*)** (200 mg, 0.48 mmol) was added and the mixture was stirred for 24 h at 35 °C. The solution was filtered, the solvent was removed, and the residual yellow paste-like solid was treated with ether as described for **4b(*R*)**. A white solid product was isolated and dried in vacuo. Yield: 103 mg (43%). $C_{13}H_{28}N_2O_6Pt$ (503.45): calcd. C 31.01, H 5.61, N 5.56; found C 31.23, H 5.39, N 5.33. ^{1}H NMR (H_2O/D_2O, 9:1): δ = 4.01 (dd, $^3J_{H,H}$ = 3.8 Hz, $^3J_{H,H}$ = 11.9 Hz, 2 H, CH_2O), 3.70 (dd, $^3J_{H,H}$ = 6.0 Hz, $^3J_{H,H}$ = 12.1 Hz, 2 H, CH_2O), 3.57 (s, 2 H, CH_2COO), 2.46 (m, 2 H, C*H*N), 2.04 [m, 2 H, C$H(CH_3)_2$], 0.91 (d, $^3J_{H,H}$ = 7.1 Hz, 6 H, CH_3), 0.86 (d, $^3J_{H,H}$ = 6.8 Hz, 6 H, CH_3) ppm.

(*SP*-4-2)-Bis[(*R*)-1-amino-2-propanol-κ*N*]malonatoplatinum(II) [4d(*R*)]: 2d(*R*) (175 mg, 0.51 mmol) and malonic acid (53 mg, 0.51 mmol) were dissolved in water (10 mL) and stirred for 24 h at room temperature. The solution was filtered and lyophilized. A white product was isolated and dried in vacuo over P_4O_{10}. Yield: 216 mg (95%). $C_9H_{20}N_2O_6Pt$ (447.34): calcd. C 24.16, H 4.51, N 6.26; found C 23.86, H 4.56, N 6.05. ^{1}H NMR (H_2O/D_2O, 9:1): δ = 4.11 (m, 2 H, C*H*O), 3.56 (s, 2 H, CH_2COO), 2.63 (m, 2 H, CH_2N), 2.38 (m, 2 H, CH_2N), 1.12 (d, $^3J_{H,H}$ = 6.4 Hz, 6 H, CH_3) ppm.

(*SP*-4-2)-Bis(2-aminoethanol-κ*N*)cyclobutane-1,1-dicarboxylatoplatinum(II) (5a): 2a (200 mg, 0.63 mmol) and cyclobutane-1,1-dicarboxylic acid (91 mg, 0.63 mmol) were dissolved in water (10 mL) and stirred for 48 h at room temperature. The solution was concentrated in a hood air stream until crystallization could be observed. The colorless product was collected and dried in vacuo over P_4O_{10}. Yield: 220 mg (75%). $C_{10}H_{20}N_2O_6Pt$ (459.35): calcd. C 26.15, H 4.39 N 6.10; found C 26.22, H 4.16, N 5.98. ^{1}H NMR (D_2O): δ =

3.74 (t, $^3J_{H,H}$ = 5.3 Hz, 4 H, CH_2O), 2.78 (t, $^3J_{H,H}$ = 7.8 Hz, 4 H, CH_2CH_2CH_2), 2.66 (m, 4 H, CH_2N), 1.81 (m, 2 H, $CH_2CH_2CH_2$) ppm.

(*SP*-4–2)-Bis[(*R*)-2-amino-1-butanol-κ*N*]cyclobutane-1,1-dicarboxylatoplatinum(II) [5b(*R*)]: 2b(*R*) (205 mg, 0.55 mmol) and cyclobutane-1,1-dicarboxylic acid (86 mg, 0.60 mmol) were dissolved in water (10 mL) and stirred for 48 h at 40 °C. The solvent was evaporated in a hood air stream at 40 °C. A white solid was isolated, washed with water twice, and dried in vacuo over P_4O_{10}. Yield: 151 mg (53%). $C_{14}H_{28}N_2O_6Pt$ (515.46): calcd. C 32.62, H 5.47, N 5.43; found C 32.01, H 5.07, N 5.26. ^{1}H NMR (D_2O): δ = 3.92 (m, 2 H, CH_2O), 3.62 (m, 2 H, CH_2O), 2.76 (m, 4 H, CH_2CH$_2$CH_2), 2.58 (m, 2 H, C*H*N), 1.87–1.67 (m, 4 H, CH_2CH$_3$), 1.53 (m, 2 H, CH$_2$CH_2CH$_2$), 0.88 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H, CH_3) ppm.

(*SP*-4–2)-Bis[(*R*)-2-amino-3-methyl-1-butanol-κ*N*]cyclobutane-1,1-dicarboxylatoplatinum(II) [5c(*R*)]: 2c(*R*) (160 mg, 0.38 mmol) and cyclobutane-1,1-dicarboxylic acid (58 mg, 0.40 mmol) were dissolved in water (10 mL) and stirred for 48 h at 40 °C. The solution was reduced in a hood air stream at 40 °C to ca. 2 mL, which led to the precipitation of a white solid. The latter was filtered off, washed with water (two times with 0.5 mL), and dried in vacuo over P_4O_{10}. Yield: 109 mg (52%). $C_{16}H_{32}N_2O_6Pt$ (543.51): calcd. C 35.36, H 5.93, N 5.15; found C 35.13, H 5.65, N 5.00. ^{1}H NMR (D_2O): δ = 4.01 (dd, $^3J_{H,H}$ = 3.9 Hz, $^3J_{H,H}$ = 12.0 Hz, 2 H, CH_2O), 3.70 (dd, $^3J_{H,H}$ = 5.9 Hz, $^3J_{H,H}$ = 12.0 Hz, 2 H, CH_2O), 2.74 (m, 4 H, CH_2CH$_2$CH_2), 2.46 (m, 2 H, C*H*N), 2.06 [m, 2 H, C*H*(CH$_3$)$_2$], 1.80 (m, 2 H, CH$_2$CH_2CH$_2$), 0.92 (d, $^3J_{H,H}$ = 6.8 Hz, 6 H, CH_3), 0.86 (d, $^3J_{H,H}$ = 7.1 Hz, 6 H, CH_3) ppm.

(*SP*-4–2)-Bis[(*R*)-1-amino-2-propanol-κ*N*]cyclobutane-1,1-dicarboxylatoplatinum(II) [5d(*R*)]: 2d(*R*) (182 mg, 0.53 mmol) and cyclobutane-1,1-dicarboxylic acid (80 mg, 0.55 mmol) were dissolved in water (10 mL) and stirred for 48 h at room temperature. The solvent was removed in a hood air stream. This yielded a slightly yellow paste-like solid, which was dissolved in ethanol (4 mL). Upon addition of acetone (30 mL), a white solid precipitated. After 12 h the product was separated, washed with acetone (5 mL), and dried in vacuo over P_4O_{10}. Yield: 180 mg (70%). $C_{12}H_{24}N_2O_6Pt$ (487.41): calcd. C 29.57, H 4.96, N 5.75; found C 29.66, H 4.72, N 5.63. ^{1}H NMR (D_2O): δ = 4.09 (m, 2 H, C*H*O), 2.76 (m, 4 H, CH_2CH$_2$CH_2), 2.64 (m, 2 H, CH_2N), 2.41–2.30 (m, 2 H, CH_2N), 1.80 (m, 2 H, CH$_2$CH_2CH$_2$), 1.12 (d, $^3J_{H,H}$ = 6.6 Hz, 6 H, CH_3) ppm.

Table 2. Crystallographic data for **3a** and **5a**.

Complex	**3a**	**5a**
Empirical formula	$C_6H_{14}N_2O_6Pt$	$C_{10}H_{20}N_2O_6Pt$
Fw	405.28	459.37
Space group	*C*2/*c*	P$\bar{1}$ (No. 2)
a [Å]	17.453(4)	8.0934(16)
b [Å]	8.0475(16)	8.2393(16)
c [Å]	16.371(3)	10.253(2)
a [deg]		92.81(3)
β [deg]	119.35(3)	92.05(3)
γ [deg]		104.30(3)
V([Å]^3)	2004.3(7)	660.9(2)
Z	8	2
λ [Å]	0.71073	0.71073
ρ_{calcd} (g cm^{-3})	2.686	2.308
Crystal size ([mm^3])	0.22×0.20×0.10	0.30×0.25×0.18
T [K]	100	120
μ [cm^{-1}]	14.015	10.640
R_1[a]	0.0290	0.0187
wR_2[b]	0.0806	0.0476
GOF[c]	1.120	1.026

[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.

X-ray diffraction measurements were performed with Nonius Kappa CCD and Bruker X8APEX II CCD diffractometers for **2c(*S*)**, **2d(*S*)**, **3a**, and **5a**, respectively. Single crystals were positioned at 35, 30, 37.5, and 30 mm from the detector and 747, 371, 673, and 379 frames were measured, each for 10, 15, 40, and 8 s over 1, 2, 1, and 2° scan width [complexes **2c(*S*)**, **2d(*S*)**, **3a**, and **5a**, respectively]. The data were processed using Denzo-SMN software.[21] Crystal data, data collection parameters, and structure refinement details for **2c(*S*)** and **2d(*S*)** are given in Table S2, whereas those for **3a** and **5a** 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,[22] refinement, SHELXL-97,[23] molecular diagrams, ORTEP,[24] computer: Pentium II; scattering factors.[25]

CCDC-298141 (for **2c*S***), -298142 [for **2d(*S*)**], -298144 (for **3a**), and -298143 (for **5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): ORTEP drawings and Tables with bond lengths, angles, and crystallographic data of **2c(*S*)** and **2d(*S*)**. NMR spectra for the reaction of **2a** with NaCl and sodium oxalate.

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