Notes

Carboxylation of Dihydroxoplatinum(IV) Complexes via a New Synthetic Pathway

M. Galanski and B. K. Keppler*

Anorganisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

Received July 28, 1995

Introduction

cis-Diamminedichloroplatinum(II) (cisplatin) is widely used to treat various types of human cancer.[1] The aim of overcoming its severe side effects forms the basis of the continuing search for new platinum-based anticancer drugs with reduced toxicity, improved clinical effectiveness, and, in addition, a broader spectrum of activity.[2−4] In the 20 years after the introduction of cisplatin into the clinic, orally applicable platinum drugs played no role in cancer treatment. This is almost inexplicable because orally active platinum drugs could offer significant advantages, and the ease of administration may considerably improve patients' quality of life. Besides, treatment on an outpatient basis reduces hospitalization costs. On the other hand, it might be explained by the fact that orally absorbable platinum compounds must meet a number of criteria: They have to be neutral, lipophilic, and stable enough to survive in the acidic and alkaline media of the stomach and the intestine.

Such kinetically inert platinum compounds, which can be absorbed by the gastrointestinal tract, were synthesized by carboxylation of hydroxide coordinated to Pt(IV).[5,6] This uncommon procedure in synthetic inorganic chemistry leads to a new class of platinum-based antitumor agents.

The principal platinum(II) chemistry is based on ligand substitution reactions or oxidation of the platinum(II) species with hydrogen peroxide or chlorine to platinum(IV) compounds. Ligand substitution reactions with platinum(IV) complexes do not work because of their inertness. Only the substitution of chloride for the hydroxo ligands under drastic conditions (reaction with concentrated hydrochloric acid at 100 °C) was successful. Platinum(IV) chemistry however made considerable progress through the carboxylation of hydroxide coordinated to Pt(IV). The carboxylation by anhydrides, pyrocarbonates, and isocyanates to the corresponding Pt(IV) carboxylates, carbonates, and carbamates was recently described in the literature.[7] A series of compounds were synthesized which showed a marked antitumor activity when administered orally. One of them, (*OC*-6-43)-bis(acetato-*O*)amminedichloro(cyclohexanamine)platinum(IV), JM-216,[8] is currently in clinical trials.[9,10]

The use of the classical carboxylation agent, the acyl chlorides, was reported not to be successful even though they show a high reactivity toward platinum hydroxo complexes.[7] It was also reported that the formation of free HCl during the reaction produces complex mixtures of compounds due to the displacement of both coordinated hydroxide and carboxylate and that there was no adaquate buffer system found for the reaction.

The recent publications and the fact that the classical organic carboxylation agent has played no role in the new platinum-(IV) chemistry prompted us to focus our chemistry program on the carboxylation with acyl chlorides. The use of chlorides of fatty acids which show a moderate reactivity was the decisive step toward the fourth class of carboxylation agent. Moreover the reaction was carried out in the presence of pyridine to minimize the concentration of free HCl.

A series of compounds with dodecanoato, tetradecanoato, hexadecanoato, octadecanoato, adamantanecarboxylato, and acetylsalicylato as ligands in the axial position were synthesized and characterized by elemental analyses and infrared and NMR spectroscopic techniques. Various platinum(II) complexes $Pt^{II}A_2X_2$ with A_2 = diammine, ethanediamine (en), or *cis*-cyclohexanediamine (*cis*-chxn) and X_2 = dichloro, cyclobutane-1,1-dicarboxylato (CBDCA), or malonato (mal) were used as starting material to prove the new synthetic procedure. The yields ranged from 32% up to 94%.

Experimental Section

Cisplatin, dichloro(ethane-1,2-diamine)platinum(II), (*cis*-cyclohexane-1,2-diamine)dichloroplatinum(II), cyclobutane-1,1-dicarboxylato-(ethane-1,2- diamine)platinum(II), and (ethane-1,2-diamine)(malonato)-platinum(II) were prepared by general synthetic procedures[5,11−13] and oxidized with hydrogen peroxide. The acyl chlorides were prepared by reaction of the corresponding carboxylic acid with thionyl chloride or obtained by commercial suppliers and used as received. Potassium tetrachloroplatinate was obtained from Degussa-Frankfurt. Elemental analyses were performed in our own laboratories. IR spectra were recorded in KBr pellets on a Bruker IFS 66. NMR spectra were measured in DMSO-d_6 using a Bruker Ac 200 MHz spectrometer. Platinum(II) compounds and reactions involving silver(I) salts are light sensitive, so the reaction must be carried out shielded from room light. Reactions with platinum(IV) compounds were also carried out under light protection. Water was used bidistilled. Acetone was dried over P_2O_5. The solvents for the extraction of the carboxylic acids were used distilled. **Warning:** Cisplatin is a potent antitumor agent reported to be mutagenic and carcinogenic in animals. All of the platinum

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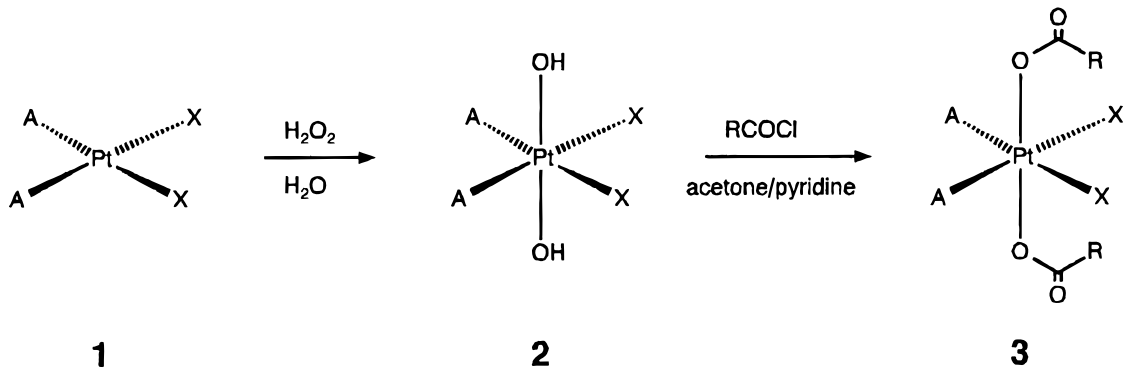
0020-1669/96/1335-1709$12.00/0

Scheme 1. Synthesis of the Bis(carboxylato)platinum(IV) Compounds



1 **2** **3**

3a A_2 = en, X = Cl, R = $(CH_2)_{10}CH_3$
3b A_2 = en, X = Cl, R = $(CH_2)_{12}CH_3$
3c A_2 = en, X = Cl, R = $(CH_2)_{14}CH_3$
3d A_2 = en, X = Cl, R = $(CH_2)_{16}CH_3$
3e A_2 = en, X = Cl, R = 1-adamantyl
3f A_2 = en, X = Cl, R = 2-acetoxyphenyl
3g A_2 = en, X_2 = CBDCA, R = $(CH_2)_{12}CH_3$
3h A_2 = en, X_2 = CBDCA, R = $(CH_2)_{14}CH_3$
3i A_2 = en, X_2 = CBDCA, R = $(CH_2)_{16}CH_3$
3j A_2 = en, X_2 = CBDCA, R = 1-adamantyl
3k A_2 = en, X_2 = mal, R = $(CH_2)_{14}CH_3$
3l A = NH_3, X = Cl, R = $(CH_2)_{12}CH_3$
3m A = NH_3, X = Cl, R = $(CH_2)_{14}CH_3$
3n A = NH_3, X = Cl, R = $(CH_2)_{16}CH_3$
3o A = NH_3, X = Cl, R = 1-adamantyl
3p A_2 = cis-chxn, X = Cl, R = $(CH_2)_{12}CH_3$
3q A_2 = cis-chxn, X = Cl, R = $(CH_2)_{14}CH_3$
3r A_2 = cis-chxn, X = Cl, R = $(CH_2)_{16}CH_3$
3s A_2 = cis-chxn, X = Cl, R = 1-adamantyl

compounds reported in this paper should be considered to have similar biological properties. Consequently, precautions should be made to avoid skin contact with these platinum compounds as well as their ingestion or inhalation.

All *trans*-(dicarboxylato)platinum(IV) compounds were prepared in the same manner. Therefore we will refrain from enumerating every single reaction and will, instead, describe a general procedure and give an example.

General Procedure. After suspension of $Pt^{IV}A_2X_2(OH)_2$ in dry acetone, excesses of both dry pyridine and acyl chloride are added. The mixture is stirred overnight at room temperature and gently refluxed for 6 h. The excess of acid chloride is hydrolyzed by the addition ofwater. The product and the carboxylic acid are filtered off, washed with water, and dried in vacuo over P_2O_5. The carboxylic acid is extracted with an organic solvent ($CHCl_3$, hexane, or diethyl ether), and the final product is dried under reduced pressure over P_2O_5. The yields, elemental analyses, and characteristic N−H and C═O stretches are listed in Tables 1 and 2 of the Supporting Information.

(*OC*-6-33)-Dichloro(ethane-1,2-diamine)bis(tetradecanoato)platinum(IV) (3b). $Pt^{IV}enCl_2(OH)_2$ (515 mg, 1.43 mmol) is suspended in 25 mL of dry acetone. Absolute pyridine (888 mg, 11.23 mmol) and tetradecanoyl chloride (2.1 g, 8.52 mmol) are added, and the mixture is stirred overnight at room temperature. Then it is gently refluxed for 6 h and slowly cooled to room temperature. A 70 mL portion of water is added, and the reaction mixture is stored overnight in a refrigerator. The (carboxylato)platinum(IV) complex and the formed tetradecanoic acid are filtered off, washed intensively with water, and dried over P_2O_5. The fatty acid is extracted with 25 mL of $CHCl_3$. After filtration, the final white product is dried in vacuo over P_2O_5. Yield: 94%.

Because of the poor solubility of the compounds in most of the common organic solvents, ^1H and ^{13}C NMR spectroscopic data could only be obtained for **3e** and **3f**.

(*OC*-6-33)-Bis(1-adamantanecarboxylato)dichloro(ethane-1,2-diamine)-platinum(IV) (3e). ^1H NMR: δ = 1.62 (s, 12H), 1.77 (s,-12H), 1.91 (6H), 2.57 (m, 4H), 8.52 (m, 4H). ^{13}C NMR: δ = 27.74, 36.27, 39.21, 42.47, 48.62, 186.47.

(*OC*-6-33)-Bis(*o*-acetylsalicylato)dichloro(ethane-1,2-diamine)-platinum(IV) (3f). ^1H NMR: δ = 2.28 (s, 6H), 2.76 (m, 4H), 7.11 (m, 2H), 7.32 (m, 2H), 7.55 (m, 2H), 7.81 (m, 2H), 8.54 (m, 4H). ^{13}C NMR: δ = 21.12, 48.96, 123.33, 125.47, 126.65, 131.35, 132.31, 148.85, 169.06, 172.97.

Results and Discussion

The carboxylation of hydroxide coordinated to Pt(IV) by reaction with acyl chlorides in the presence of pyridine is shown in Scheme 1. The compounds were characterized by elemental analysis, IR spectroscopy, and, if soluble enough, NMR spectroscopy. The theoretical values of the elemental analyses are in good agreement with the actual findings. The oxidation of Pt(II) complexes **1** to their *trans*-dihydroxoplatinum(IV) counterparts **2,** and the subsequent carboxylation can easily be seen by significant changes in the infrared spectrum.

The Pt(IV) dihydroxo products **2** of the oxidation with hydrogen peroxide can readily be identified[14,15] by their characteristic PtO−H stretches in the range 3469−3535 cm^{-1} and their Pt−O stretches in the region between 539 and 569 cm^{-1}. After carboxylation, both PtO−H and Pt−O stretches disappear. For all *trans*-(dicarboxylato)platinum(IV) complexes, a strong C═O stretch in the range 1633−1669 cm^{-1} is observed. The C═O stretch of the free carboxylic acids or their acid chlorides is not observed. In the case of coordinated fatty acids, two strong C−H bands are seen in the ranges 2919−2924 and 2849−2853 cm^{-1}, respectively. In the case of the bis(1-adamantanecarboxylato)platinum(IV) compounds, the two strong C−H bands are observed at 2905−2907 and 2850−2851 cm^{-1}, respectively. The ^{13}C═O resonances of **3e** at 186.5 and of **3f** at 173.0 cm^{-1} are shifted to lower field. The additional ^{13}C═O resonance at 169.1 cm^{-1} in the case of **3f** is assigned to the acetoxy group.

In conclusion, new representatives of bis(carboxylato)-platinum(IV) compounds which are very interesting with regard

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to the development of platinum anticancer drugs that can be orally administered have been synthesized and characterized.

A series of Pt(IV) carboxylates have been prepared by carboxylation of kinetically inert hydroxide coordinated to platinum(IV). These results demonstrate that coordinated hydroxide can be nucleophilic and that these hydroxo compounds can be used to synthesize coordination compounds containing carboxylato ligands which would otherwise be difficult to prepare by substitution reactions.

Besides the use of anhydrides, pyrocarbonates, and isocyanates, we thus add a fourth class of carboxylation agent that can be used very successfully: the acyl chlorides. The classical organic carboxylation system of acyl chloride/pyridine permits the synthesis of a wide variety of complexes. The use of different kinds of ligands in the equatorial position (NH_3, en, *cis*-chxn, Cl, CBDCA, mal) shows that this synthetic method can be transferred to a wide variety of *trans*-(dicarboxylato)-platinum(IV) complexes. At the moment, this carboxylation method is limited to acyl chlorides with moderate reactivity. The search for reaction conditions for the use of reactive acyl chlorides is in progress.

Acknowledgment. This work was supported by the Deutsche Krebshilfe, Dr. Mildred-Scheel-Stiftung für Krebsforschung, Bonn, and the Fonds der Chemischen Industrie, Frankfurt, Germany. The support of the European Community through the HCM and COST programs is gratefully acknowledged.

Supporting Information Available: Tables of yields, elemental analyses, and characteristic N−H and C═O stretches (2 pages). Ordering information is given on any current masthead page.

IC9509490