Articles

Carboxylation of Kinetically Inert Platinum(IV) Hydroxy Complexes. An Entrée into Orally Active Platinum(IV) Antitumor Agents

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Carboxylation of hydroxide coordinated to Pt(IV) by anhydrides, pyrocarbonates, and isocyanates to form the corresponding Pt(IV) carboxylates, carbonates, and carbamates is described. For example, the acylation with acetic anhydride of (*OC*-6-33)-amminedichloro(cyclohexanamine)dihydroxyplatinum(IV) leads to formation of (OC-6-43)-bis(acetato-*O*)amminedichloro(cyclohexanamine)platinum(IV) (JM-216) in 60% yield. This compound is currently in worldwide clinical trials as an *orally active* antitumor agent. Pt(IV) dicarbonates and dicarbamates are prepared similarly by reaction of a Pt(IV) hydroxide with a pyrocarbonate or isocyanate. The carboxylation reaction can be used to prepare molecules containing ligands with pendant functional groups that would be difficult to introduce by substitution reactions. Thus (*OC*-6-43)-amminedichloro(cyclohexanamine)bis((methylthio)acetato-*O*)platinum(IV) was prepared, which was oxidized to the corresponding sulfoxide (*OC*-6-43)-amminedichloro-(cyclohexanamine)bis((methylsulfinyl)acetato-*O*)platinum(IV). Finally, unsymmetrical carboxylate complexes may be obtained by reaction of a binary mixture of two electrophiles with a Pt(IV) hydroxide followed by chromatographic separation of the carboxylation products. A simplified synthesis of the $K[Pt^{II}Cl_3NH_3]$ in 55% yield from cisplatin is also reported. This improves the availability of molecules of the general formula *cis*-$Pt^{II}Cl_2AA'$ (A, A′ = ammine, amine) which are critical intermediates in the multistep synthesis of the Pt(IV) carboxylates having antitumor activity.

Twenty years after the introduction of the anticancer agent cisplatin, *cis*-$Pt^{II}Cl_2(NH_3)_2$, only one other platinum compound, *cis*-$Pt^{II}(CBDCA)(NH_3)_2$, has been approved for use in humans. Although several classes of platinum-based antitumor agents overcame resistance in animal models,[1] these results have not translated to improved efficacy in humans. A desirable alternate approach which has potential therapeutic advantages that could improve patient quality of life is to develop an orally absorbed platinum antitumor agent. Since the clinical platinum drugs are not suitable for this application, we sought to discover usable candidates. In addition to the cis arrangement of labile ligands that permits binding and intrastrand cross-linking of the putative target, DNA, compounds suitable for oral administration are typically neutral, lipophilic, water soluble, and robust enough to survive the gastric environment. Our search for a platinum antitumor agent meeting the above criteria led to a new class of platinum compounds synthesized by an uncommon reaction that takes advantage of the kinetic inertness of Pt(IV).

At the time this work was undertaken, the principal chemistry of platinum(II) antitumor compounds was ligand substitution or oxidation of the platinum(II) with hydrogen peroxide or chlorine to Pt(IV). The chemistry of the platinum(IV) antitumor compounds was limited principally to substitution of hydroxide by chloride under strongly acidic conditions. We report here the carboxylation of hydroxide coordinated to Pt(IV). This reaction, centered one atom away from the platinum center, is ideally suited for ligand transformations on kinetically inert metals yet has not been widely exploited in synthetic inorganic chemistry. We used this reaction to synthesize a series of compounds that exhibit excellent antitumor activity when administered orally. One of them, (*OC*-6-43)-bis(acetato-*O*)-amminedichloro(cyclohexanamine)platinum(IV) (JM-216), is currently in worldwide clinical trials. An additional impediment to the development of this series of compounds and other potential platinum-based antitumor agents has been limited access to the *cis*-$Pt^{II}Cl_2AA'$ (A, A′ = ammine, amine) core, caused by the difficulty of preparing the $[Pt^{II}Cl_3NH_3]^-$ anion. Recently, improved syntheses of this key intermediate were reported from our laboratory[2] and by Kraker et al.[3] We report additional improvements of the method that permit convenient laboratory preparation of gram quantities of $K[Pt^{II}Cl_3NH_3]$ and the *cis*-$Pt^{II}Cl_2AA'$ core.

Experimental Section

cis,trans,cis-Dichlorodihydroxybis(isopropylamine)platinum(IV) was prepared by the method of Barnard et al.[4] *cis*-Diamminedichloroplatinum(II), the amines, anhydrides, pyrocarbonates, isocyanates, 30% hydrogen peroxide, silver nitrate, sodium iodide, solvents, and other reagents are all commercially available. Microchemical analyses were performed in-house or by Atlantic Microlab Inc., Norcross, GA.

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(1) Kelland, L. R.; Clarke, S. J.; McKeage, M. J. *Platinum Met. Rev.* **1992**, *36*, 178.
(2) Abrams, M. J.; Giandomenico, C. M.; Vollano, J. F.; Schwartz, D. A. *Inorg. Chim. Acta* **1987**, *131*, 3−4.
(3) Kraker, A. J.; Hoeschele, J. D.; Elliott, W. L.; Showalter, H. D. H.; Sercel, A. D.; Farrell, N. P. *J. Med. Chem.* **1992**, *35*, 4526−4532.
(4) Barnard, C. F. J.; Hydes, P. C.; Griffiths, W. P.; Mills, O. S. *J. Chem. Res., Synop.* **1983**, 302.

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Nuclear magnetic resonance spectra were recorded on a Bruker NR/80AF or a Bruker AR/300, and chemical shifts are reported in ppm relative to TMS equal to 0. Infrared spectra were recorded on a Mattson Galaxy 5000 series FTIR equipped with cesium iodide optics or a Perkin-Elmer 598 infrared spectrometer. Reactions involving silver(I) salts are light sensitive and must be carried out shielded from room light. Solutions of many platinum(IV) compounds reported here are slightly light sensitive and should not be exposed to room light for extended periods. Brief manipulations such as recrystallization may be carried out in room light without noticeable degradation. All of these compounds are air and moisture stable. **Warning:** Cisplatin is a potent antitumor agent reported to be mutagenic and carcinogenic in animals.[5] All of the platinum(II) and platinum(IV) compounds reported in this paper should be considered to have similar biological properties. Additionally, the amminetrichloroplatinate anion belongs to a class of platinum anions that are reported to be allergenic.[5] Consequently, precautions should be made to avoid skin contact, ingestion, or inhalation of these platinum compounds.

Potassium (*SP*-4-2)-Amminetrichloroplatinate(1−) Hemihydrate (1). Prepare by a modification of a method described by Abrams et al.[2] Heat a stirred solution of 2.34 g (7.8 mmol) of Cisplatin and 1.66 g (9.4 mmol) of $Et_4NCl{\cdot}xH_2O$ in 200 mL of fresh reagent grade dimethylacetamide to 100 °C (±2 °C) for 6−8 h in a 250 mL beaker while purging with a slow stream of nitrogen introduced by a gas dispersion tube. (Prolonged heating above 105 °C or use of old dimethylacetamide leads to decomposition.) Add solvent as needed to maintain temperature control but allow the volume to reduce to ~50 mL by the end of the reaction. After the orange solution has cooled, pour into 450 mL of 1/1 v/v hexane/ethyl acetate and cool 12 h at −10 °C. Decant and discard the clear solution. Dissolve the orange oil in 20 mL of water, allow the mixture to stand for 1/2 h to allow complete precipitation of a small amount of unreacted *cis*-Pt(II)$(NH_3)_2Cl_2$, and filter. This solution contains $Et_4N[Pt^{II}Cl_3NH_3]$ used in subsequent reactions. Stir this solution with 50 mL of rinsed Dowex 50W-X8 H^+ cation exchange resin for 1 h. Filter off the resin and reduce the volume under vacuum to 1−2 mL. (If the product is allowed to reach dryness, the platinum dimerizes to insoluble $[Pt^{II}Cl_2NH_3]_2$ with loss of HCl. This dimer may be converted back to $H[Pt^{II}Cl_3NH_3]$ by prolonged warming in HCl.) Add 3 mL of saturated KCl and cool to 5 °C for 3 h. Collect 1.6 g (55% yield) of orange crystalline $K[Pt^{II}Cl_3NH_3]{\cdot}{}^1/_2H_2O$. Anal. Calcd for $Cl_3H_4KNO_{0.5}Pt$: H, 1.10; N, 3.82; Cl, 29.01. Found: H, 1.43; N, 3.83; Cl, 29.36. IR (KBr) ν: 3530 (s), 3476 (s), 1629 (s), 1550 (m), 1324 (s), 544 (s), 522 (s), 317 (s) cm^{-1}.

(*SP*-4-3)-Amminechloro(cyclohexanamine)iodoplatinum(II) (2). Add 1.2 g (8.0 mmol) of NaI in 2 mL of H_2O to a stirred solution of 1.5 g (4.1 mmol) of **1** in 8 mL of water followed by 0.55 mL of cyclohexylamine. Stir the solution 4 h at room temperature. Collect the yellow product, and wash with water and ethanol. Suspend the solid in ~10 mL of acetone and stir for 1/2 h. Decant the acetone and repeat the procedure three times before collecting the solid and drying in vacuo. Collect 1.21 g (62% yield). Anal. Calcd for $C_6H_{16}ClN_2IPt$: C, 15.21; H, 3.40; N, 5.91; Cl, 7.49; I, 26.79. Found: C, 15.37; H, 3.50; N, 5.93; Cl, 7.29; I, 26.52. IR (KBr) ν: 3449 (m), 3219 (s), 2931 (s), 2855 (s), 1634 (m), 1568 (s), 1448 (s), 1386 (w), 1310 (s), 1229 (s), 1152 (s), 1079 (w), 1054 (m), 1036 (w), 960 (w), 893 (w), 717 (w), 324 (s) cm^{-1}. ^1H NMR (DMF-d_7) δ: 1.10 (1H, m), 1.27 (4H, m), 1.57 (1H, m), 1.71 (2H, m), 2.40 (2H, m), 2.91 (1H, m), 4.19 (3H, b), 4.96 (2H, b).

(*SP*-4-3)-Amminedichloro(cyclohexanamine)platinum(II) (3). Add 0.95 g (5.6 mmol, 1.6 equiv) of $AgNO_3$ in the dark to a stirred suspension of 1.6 g (3.4 mmol) of **2** in 20 mL of H_2O. Stir for 4 h and then test for free silver ion.[6] Once a negative test is obtained, add a small amount of decolorizing carbon and stir 0.5 h. Filter off the AgCl and add ca. 10 mL of concentrated HCl to the clear supernatant. Let the solution stand overnight, collect the product by vacuum filtration, wash with water, ethanol, and ether, and dry in a vacuum. Collect 0.72 g (56% yield). Anal. Calcd for $C_6H_{16}N_2Cl_2Pt$: C, 18.86; H, 4.22; N, 7.33; Cl, 18.55. Found: C, 18.72; H, 4.04; N, 7.24; Cl, 18.42. IR (KBr) ν: 3299 (s), 3236 (vs), 3199 (vs), 3122 (s), 2922 (vs), 2858 (s), 1637 (m), 1575 (s), 1474 (sh), 1449 (s), 1388 (w), 1361 (w), 1337 (w), 1305 (s), 1281 (w), 1238 (m), 1200 (w), 1155 (m), 1080 (m), 1054 (m), 960 (m), 897 (m), 852 (w), 818 (m), 795 (m), 785 (m), 742 (w), 615 (w), 544 (w), 507 (w), 462 (w), 426 (w), 326 (s) cm^{-1}. ^1H NMR (DMF-d_7) δ: 1.08 (1H, m), 1.27 (4H, m), 1.57 (1H, m), 1.71 (2H, m), 2.40 (2H, m), 2.91 (1H, m), 4.20 (3H, b), 4.96 (2H, b).

(*SP*-4-3)-Amminedichloro(2-methyl-1-propanamine)platinum(II) (4). Stir a 20 mL aqueous solution of $Et_4N[Pt^{II}Cl_3NH_3]$ (prepared from 2.34 g of *cis*-$Pt^{II}Cl_2(NH_3)_2$ (7.80 mmol) according to the method described in the preparation of **1**) and 6 g of $NaClO_4$ (49.2 mmol) for 45 min. Filter off unreacted *cis*-$Pt^{II}Cl_2(NH_3)_2$ and precipitated $[Et_4N]ClO_4$. Add 1.30 g of NaI (8.67 mmol) dissolved in a minimum amount of water immediately followed by 0.85 mL (8.55 mmol) of isobutylamine. Let the resultant suspension stand for 4−6 h before collecting. Wash with 95% ethanol. When the washes are colorless, wash with ether, and then air-dry to obtain 1.59 g of crude (*SP*-4-3)-amminechloroiodo(2-methyl-1-propanamine)platinum(II) as a yellow solid. Add 0.88 g (5.2 mmol, ~1.6 equiv) of $AgNO_3$ in the dark to stirred suspension of 1.45 g (3.2 mmol) of crude (*SP*-4-3)-amminechloroiodo(2-methyl-1-propanamine)platinum(II) in 25 mL of H_2O. Stir for 4 h and then test for free silver ion.[6] Once a negative test is obtained, filter off the AgCl precipitate and add ca. 10 mL of concentrated HCl to the clear supernatant. Let stand overnight, collect a 0.77 g crop of product by vacuum filtration, wash with water, ethanol, and ether, and dry in a vacuum. Concentrate the mother liquor by rotary vacuum evaporation and collect a second crop of 0.27 g. Combine the crops for a total of 1.04 g (37% yield). Anal. Calcd for $C_4H_{14}N_2Cl_2Pt$: C, 13.49; H, 3.96; N, 7.87; Cl, 19.91. Found: C, 13.73; H, 3.88; N, 7.77; Cl, 19.72. IR (KBr) ν: 3255 (s), 3203 (m), 2961 (m), 2875 (sh), 1637 (m), 1559 (m), 1465 (m), 1393 (w), 1371 (w), 1279 (m), 1207 (m), 1122 (w), 1030 (w), 788 (w), 711 (w), 326 (m) cm^{-1}. ^1H NMR (DMF-d_7) δ: 0.91 (6H, d, J = 6.7 Hz), 1.99 (1H, sept, J = 6.7 Hz), 2.74 (2H, mult), 4.25 (3H, b), 4.78 (2H, b).

(*OC*-6-43)-Amminedichloro(cyclohexanamine)dihydroxyplatinum(IV) (5). Thoroughly wet a suspension of 1 g (2.6 mmol) of **3**[7] in 10 mL of water in a 100 mL beaker equipped with a stirrer and covered with a watch glass. Add 1.3 mL of 30% H_2O_2 (~13 mmol, 5 equiv) and heat in a water bath at 70 °C for 2 h, periodically scraping (with a plastic spatula) the foam and undissolved starting material from the sides of the beaker. Cool to room temperature and let stand overnight. Cool in an ice bath and collect the precipitate by filtration. Wash with water, ethanol, and ether and dry in vacuo. Collect 0.7 g (1.7 mmol, 64% yield) of yellow solid. Anal. Calcd for $C_6H_{18}N_2Cl_2O_2Pt$: C, 17.33; H, 4.43; N, 6.68; Cl, 17.25. Found: C, 17.30; H, 4.36; N, 6.73; Cl, 17.04. IR (KBr) ν: 3527 (s), 3329 (m), 3278 (m), 3224 (s), 3177 (m), 3035 (s), 2931 (s), 2855 (s), 2667 (m), 1620 (sh), 1587 (s), 1451 (m), 1391 (m), 1369 (m), 1353 (m), 1339 (m), 1283 (w), 1264 (w), 1248 (w), 1220 (s), 1155 (w), 1133 (w), 1078 (m), 1055 (s), 1024 (s), 960 (w), 898 (w), 866 (w), 847 (w), 549 (s), 335 (s) cm^{-1}.

(*OC*-6-43)-Amminedichlorodihydroxy(2-methyl-1-propanamine)-platinum(IV) (6). Prepare as described for **5** from 1 g (2.8 mmol) of **4**[7] in 4 mL of water in a 100 mL beaker with 1 mL of 30% H_2O_2 (~8.8 mmol, 3 equiv) heated at 55 °C for 2 h. Collect 0.75 g (1.9 mmol, 68% yield) of yellow solid. Anal. Calcd for $C_4H_{16}N_2Cl_2O_2Pt$: C, 12.31; H, 4.13; N, 7.18; Cl, 18.17. Found: C, 12.50; H, 4.01; N, 7.15; Cl, 18.34. IR (KBr) ν: 3503 (s), 3249 (s), 2957 (s), 1583 (s), 1468 (m), 1392 (w), 1368 (w), 1346 (w), 1266 (w), 1132 (m), 1019 (m), 911 (w), 761 (w), 538 (s), 336 (s) cm^{-1}. ^1H NMR (D_2O) δ: 1.00 (6H, d, J = 6.5 Hz), 2.00 (1H, sept, J = 6.5 Hz), 2.66 (2H, m).

(5) Bradford, C. W. In *Handbook on Toxicity of Inorganic Compounds*; Seiler, H. G., Sigel, H., Eds.; Marcel Dekker, Inc.: New York, 1988; p 537.

(6) One can check for complete reaction of the $AgNO_3$ by adding ca. 0.1 mL of filtered supernatant to one or two crystals of NaCl. An immediate white precipitate (positive test) indicates that the silver ion has not been completely consumed. No precipitate or a precipitate of $Pt^{II}Cl_2AA'$ that forms slowly is a negative test. In rare cases, insoluble $Pt^{II}Cl_2AA'$ forms very fast and a false positive is obtained. A positive test indicates that the reaction mixture should be stirred for several more hours.

(7) Platinum black (a possible contaminant in the starting material) is an excellent catalyst of the futile disproportionation of H_2O_2 to water and oxygen. Platinum black is most conveniently removed by efficiently filtering the $Pt^{II}Cl_x(OH_2)_{2-x}AA'$ (x = 1, 2; A, A' = ammine, amine) during the preparation of the corresponding $Pt^{II}Cl_2AA'$ starting material.

(*OC*-6-33)-Bis(acetato-*O*)dichlorobis(2-propanamine)platinum(IV) (7). Stir a suspension of 1 g (2.4 mmol) of c-t-c-$Pt^{IV}Cl_2(OH)_2(NH_2$-*i*-$C_3H_7)_2$ in 20 mL (210 mmol) of acetic anhydride in the dark at room temperature until it completely dissolves. Cool the solution until the product precipitates. Collect, wash with ether, and dry in a vacuum. An additional crop may be obtained by adding ether to the motherliquor and cooling. The combined crops are recrystallized by dissolving in hot ethyl acetate, precipitating with ether, and cooling the solution. Anal. Calcd for $C_{10}H_{24}N_2Cl_2O_4Pt$: C, 23.91; H, 4.82; N, 5.58. Found: C, 23.71; H, 4.79; N, 5.51. IR (KBr) ν: 3290 (s), 3040 (m), 2970 (m), 2863 (m), 1660 (s), 1623 (s), 1590 (s), 1562 (s), 1462 (m), 1399 (w), 1361 (s), 1312 (s), 1335 (m), 1312 (s), 1270 (s), 1250 (s), 1162 (s), 1121 (s), 1103 (m), 1021 (m), 950 (w), 929 (m), 835 (m), 705 (s), 612 (m), 455 (m), 451 (m), 335 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.33 (12H, d, J = 6.5 Hz), 2.14 (6H, s), 3.76 (2H, sept, J = 6.5 Hz).

(*OC*-6-33)-Dichlorobis(pentanoato-*O*)bis(2-propanamine)platinum(IV) (8). Stir a suspension of 1.25 g (2.9 mmol) of c-t-c-$Pt^{IV}Cl_2(OH)_2(NH_2$-*i*-$C_3H_7)_2$ and 25 mL (140 mmol) of valeric anhydride for 2 h. Precipitate with hexane and cool at 0 °C for 24 h. Collect the solid, wash with ether, and dry in a vacuum. Anal. Calcd for $C_{16}H_{36}Cl_2N_2O_4Pt$: C, 32.77; H, 6.19; N, 4.78. Found: C, 32.99; H, 6.19; N, 4.78. IR (KBr) ν: 3190 (sh), 3165 (s), 2989 (sh), 2960 (s), 2935 (s), 2875 (m), 1655 (sh), 1638 (s), 1580 (m), 1468 (m), 1415 (m), 1380 (sh), 1370 (m), 1350 (m), 1288 (s), 1268 (s), 1217 (s), 1205 (sh), 1165 (m), 1120 (m), 1105 (m), 930 (m), 830 (w), 820 (w), 717 (w), 670 (w), 610 (w), 440 (w), 335 (s) cm^{-1}.

(*OC*-6-33)-Dichlorobis(trifluoroacetato-*O*)bis(2-propanamine)platinum(IV) (9). Prepare as described for **8** above. An exothermic reaction occurs when the reactants, 10 mL of trifluoroacetic anhydride, and 1.5 g of c-t-c-$Pt^{IV}Cl_2(OH)_2(NH_2$-*i*-$C_3H_7)_2$ are mixed. Yield: 1.3 g of product (61%) after stirring 24 h at RT. Anal. Calcd for $C_{10}H_{18}Cl_2N_2O_4F_6Pt$: C, 19.7; H, 3.0; N, 4.6; Cl, 11.6. Found: C, 19.3; H, 2.8; N, 4.5; Cl, 11.5. IR (KBr) ν: 3163 (m), 3090 (m), 2989 (m), 2940 (w), 1760 (sh), 1741 (sh), 1722 (s), 1699 (s), 1687 (s), 1578 (m), 1555 (m), 1467 (m), 1417 (m), 1398 (m), 1379 (m), 1280 (m), 1210 (s), 1190 (s), 1163 (s), 1115 (m), 940 (w), 921 (w), 857 (m), 824 (w), 781 (m), 736 (m), 524 (w), 366 (sh), 345 (m).

(*OC*-6-33)-Dichlorobis(methylcarbamato-*O*)bis(2-propanamine)platinum(IV) (10). Prepare as described for **8** from 2.5 g (6.0 mmol) of c-t-c-$Pt^{IV}Cl_2(OH)_2(NH_2$-*i*-$C_3H_7)_2$ stirred 12 h in 25 mL of methyl isocyanate (420 mmol). Recrystallize by precipitation with hexane from hot ethyl acetate. IR (KBr) ν: 3380 (s), 3259 (s), 2970 (s), 2935 (s), 1587 (s), 1512 (s), 1469 (m), 1412 (s), 1380 (m), 1365 (s), 1285 (s), 1218 (w), 1160 (m), 1137 (m), 1111 (s), 1099 (s), 955 (m), 941 (s), 840 (m), 792 (s), 691 (s), 618 (m), 457 (m), 409 (w), 360 (m), 339 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.32 (12H, d, J = 6.5 Hz), 2.76 (6H, d, J = 2.3 Hz), 3.77 (2H, sept, J = 6.5 Hz), 5.1 (2H, b).

(*OC*-6-33)-Dichlorobis(ethylcarbamato-*O*)bis(2-propanamine)platinum(IV) (11). Prepare as described for **8** from 1 g (2.4 mmol) of c-t-c-$Pt^{IV}Cl_2(OH)_2(NH_2$-*i*-$C_3H_7)_2$ stirred 12 h in 25 mL of ethyl isocyanate (320 mmol). Recrystallize by precipitation with hexane from hot ethyl acetate. Anal. Calcd for $C_{12}H_{30}Cl_2N_4O_4Pt$: C, 25.72; H, 5.40; N, 10.00. Found: C, 26.31; H, 5.43; N, 10.24. IR (KBr) ν: 3378 (s), 3359 (s), 3400 (sh), 3140 (s), 2965 (s), 2925 (m), 2868 (m), 1624 (s), 1594 (s), 1505 (s), 1440 (m), 1375 (m), 1370 (m), 1325 (m), 1305 (s), 1268 (s), 1260 (s), 1155 (m), 1111 (m), 1075 (w), 982 (s), 835 (w), 785 (m), 678 (s), 595 (m), 458 (m), 339 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.89 (6H, t, J = 8 Hz), 1.32 (12H, d, J = 3.2 Hz), 3.1 (4H, q, J = 8 Hz), 3.8 (2H, sept, J = 3.2 Hz), 5.2 (2H, b).

(*OC*-6-33)-Dichlorobis(2-propanamine)bis(propylcarbamato-*O*)platinum(IV) (12). Prepare as described for **8** from 1 g of c-t-c-$Pt^{IV}Cl_2(OH)_2(NH_2$-*i*-$C_3H_7)_2$ (2.4 mmol) stirred 12 h in 10 mL of *n*-propyl isocyanate (110 mmol). Anal. Calcd for $C_{14}H_{34}Cl_2N_4O_4Pt$: C, 28.58; H, 5.82; N, 9.52. Found: C, 28.77; H, 5.75; N, 9.50. IR (KBr) ν: 3519 (s), 3390 (s), 3290 (s), 3200 (br), 2960 (s), 2928 (s), 2868 (s), 1630 (s), 1605 (s), 1510 (m), 1455 (m), 1395 (m), 1362 (w), 1352 (m), 1335 (m), 1305 (m), 1275 (m), 1245 (m), 1160 (m), 1120 (s), 1025 (m), 970 (m), 820 (w), 780 (m), 640 (w), 329 (m) cm^{-1}.

(*OC*-6-33)-Dichlorobis(methyl carbonato-*O*)bis(2-propanamine)platinum(IV) (13). Prepare as described for **8** from 1 g (2.4 mmol) of c-t-c-$Pt^{IV}Cl_2(OH)_2(NH_2$-*i*-$C_3H_7)_2$ stirred 24 h in 15 mL of dimethyl pyrocarbonate (180 mmol). Yield: 0.54 g of product (42%). Anal. Calcd for $C_{10}H_{24}Cl_2N_2O_6Pt$: C, 22.48; H, 4.53; N, 5.24. Found: C, 21.99; H, 4.36; N, 5.23. IR (KBr) ν: 3210 (s), 3160 (s), 2980 (m), 2955 (w), 1665 (s), 1572 (m), 1462 (sh), 1438 (s), 1393 (m), 1375 (m), 1340 (sh), 1305 (sh), 1290 (sh), 1258 (s), 1188 (m), 1153 (m), 1128 (sh), 1095 (s), 932 (s), 840 (sh), 798 (m), 718 (m), 695 (m), 605 (w), 435 (w), 410 (w), 343 (s) cm^{-1}.

(*OC*-6-43)-Bis(acetato-*O*)amminedichloro(cyclohexanamine)platinum(IV) (14). Prepare as described for **8** from 0.83 g of **5** stirred in 20 mL of acetic anhydride (200 mmol). Yield: 0.6 g product (60% yield). Anal. Calcd for $C_{10}H_{22}Cl_2N_2O_4Pt$: C, 24.01; H, 4.43; N, 5.60. Found: C, 24.44; H, 4.45; N, 5.50. IR (KBr) ν: 3220 (s), 3055 (s), 2925 (s), 2850 (s), 1605 (s), 1425 (m), 1380 (sh), 1358 (s), 1280 (s), 1188 (w), 1168 (w), 1113 (w), 1080 (m), 1020 (m), 1038 (m), 895 (w), 705 (m), 610 (m), 460 (w), 340 (m) cm^{-1}.

(*OC*-6-43)-Amminedichloro(cyclohexanamine)bis(2,2-dimethylpropanoato-*O*)platinum(IV) (15). Stir a suspension of 3.0 g (7.2 mmol) of **5** and 3.2 mL (16 mmol) of pivalic anhydride in 10 mL of acetone for 2 days at RT. Filter off undissolved starting material and remove the solvent from the filtrate. Collect the resulting solid, wash with ethanol and ether, and dry in vacuo to obtain 1.6 g of product (38% yield). Anal. Calcd for $C_{16}H_{34}Cl_2N_2O_4Pt$: C, 32.9; H, 5.8; N, 4.8; Cl, 12.2. Found: C, 32.8; H, 5.8; N, 4.5; Cl, 12.5. IR (KBr) ν: 3182 (m), 3066 (m), 2954 (s), 2929 (s), 2859 (m), 1672 (s), 1631 (s), 1569 (m), 1544 (m), 1479 (m), 1454 (m), 1394 (m), 1363 (m), 1291 (s), 1193 (s), 1044 (w), 1030 (w), 938 (w), 896 (w), 850 (w), 800 (w), 773 (w), 662 (m), 576 (w), 441 (w), 382 (w), 334 (m) cm^{-1}.

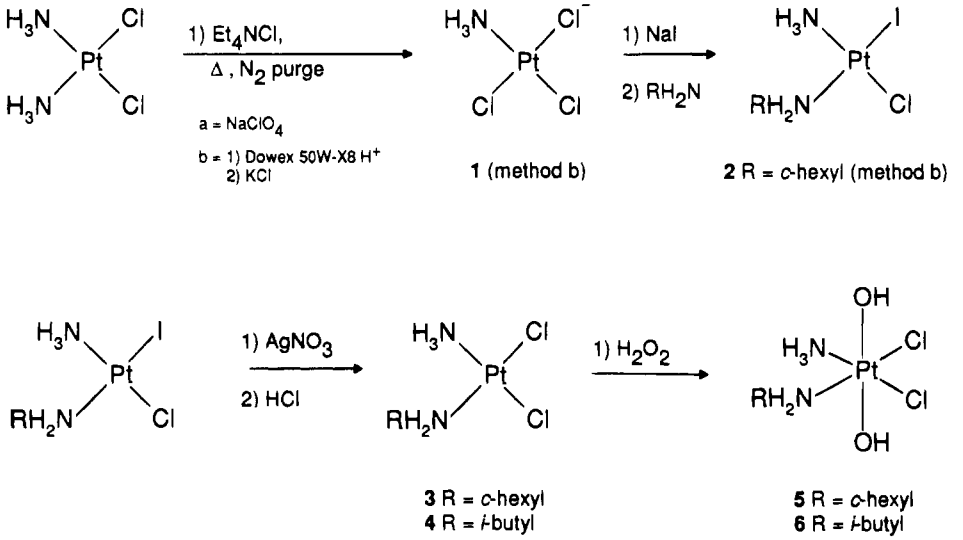
(*OC*-6-54)-(Acetato-*O*)amminedichloro(cyclohexanamine)(pentanoato-*O*)platinum(IV) (16). Stir a suspension of 1.5 g (3.6 mmol) of **5**, 1.3 mL (6.6 mmol) of valeric anhydride, and 0.44 mL (4.4 mmol) of acetic anhydride in 10 mL of dichloromethane for 24 h at RT. Collect the solid by filtration, wash with ether, and stir 30 min in 20 mL of dichloromethane. Filter and set aside unreacted **5** (0.65 g) before removing the CH_2Cl_2 in a vacuum. Chromatograph the resultant oil (0.4 g) on a 7 in. × 1 in. diameter column of silica eluting with 1/1 ethyl acetate/dichloromethane. The first fraction that elutes is c-t-c-$Pt^{IV}Cl_2(O_2C$-*n*-$C_4H_9)_2(NH_3)$(*c*-$C_6H_{11}NH_2)$ (0.092 g). The second fraction (0.168 g) is the desired compound **16**. The final fraction is c-t-c-$Pt^{IV}Cl_2(O_2CCH_3)_2(NH_3)$(c-$C_6H_{11}NH_2)$ (0.082 g). Anal. Calcd for $C_{13}H_{28}Cl_2N_2O_4Pt$: C, 28.79; H, 5.20; N, 5.16; Cl, 13.07. Found: C, 28.97; H, 5.16; N, 5.14, Cl, 13.17. IR (KBr) ν: 3285 (s), 2920 (s), 2845 (m), 1650 (s), 1620 (s), 1565 (m), 1445 (m), 1365 (s), 1290 (s), 1220 (s), 1080 (m), 1040 (m), 930 (m), 895 (w), 750 (w), 695 (m), 335 (m) cm^{-1}.

(*OC*-6-43)-Amminebis(benzoato-*O*)dichloro(cyclohexanamine)platinum(IV) (17). Stir a suspension of 0.5 g (1.2 mmol) of **5**, 5 g (22 mmol) of benzoic anhydride in 36 mL of 1/5 v/v toluene/ether for 3 days. Filter and set aside any undissolved solid, remove the solvent under vacuum, and recrystallize the residue three times from methylene chloride/ether/hexane. Yield: 0.1 g. Anal. Calcd for $C_{22}H_{30}Cl_2N_2O_4Pt \cdot {}^1/_2EtOAc$: C, 39.53; H, 4.52; N, 4.19. Found: C, 39.80; H, 4.52; N, 4.02. IR (KBr) ν: 3180 (s), 3080 (sh), 2923 (s), 2852 (m), 1630 (s), 1572 (s), 1445 (w), 1365 (sh), 1337 (sh), 1316 (s), 1293 (s), 1170 (m), 1125 (m), 1066 (w), 1021 (m), 712 (s), 695 (s), 340 (m) cm^{-1}.

(*OC*-6-54)-Amminedichlorohydroxy(4-methoxybenzoato-*O*)(2-methyl-1-propanamine)platinum(IV) (18). Stir a suspension of 6.6 g (23 mmol) of *p*-methoxybenzoic anhydride and 3.0 g (7.7 mmol) of **6** in 5 mL of toluene at 65 °C. Collect the solid. Stir a suspension of the solid in acetone for 1 h. Filter and air-dry. Collect 0.63 g of **18**. Anal. Calcd for $C_{12}H_{21}N_2Cl_2O_4Pt$: C, 27.54; H, 4.04; N, 5.35; Cl, 13.55. Found: C, 27.58; H, 4.25; Cl, 13.60. IR (KBr) ν: 3480 (s), 3280 (s), 2960 (s), 1625 (s), 1603 (s), 1560 (sh), 1502 (m), 1455 (m), 1415 (w), 1330 (s), 1310 (s), 1295 (s), 1255 (s), 1165 (s), 1135 (w), 1102 (w), 1029 (m), 1015 (m), 850 (m), 840 (m), 772 (m), 696 (w), 665 (m), 585 (sh), 565 (m), 510 (w), 450 (w), 400 (w), 340 (m) cm^{-1}.

(*OC*-6-43)-Amminedichlorobis(4-methoxybenzoato-*O*)(2-methyl-1-propanamine)platinum(IV) (19). Reduce the volume of the acetone solution produced during the synthesis of **18** above and add ether to precipitate 1.5 g of **19**. Anal. Calcd for $C_{20}H_{28}N_2Cl_2O_6Pt \cdot H_2O$: C, 35.48; H, 4.43; N, 4.13; Cl, 10.48. Found: C, 35.33; H, 4.53; N, 4.12 Cl, 10.49. IR (KBr) ν: 3200 (s), 3100 (sh), 2959 (s), 1620 (sh), 1602

Scheme 1 Synthesis of Mixed-Amine Pt(IV) Dihydroxy Complexes



(s), 1572 (s), 1505 (m), 1456 (m), 1415 (w), 1255 (s), 1238 (m), 1201 (w), 1025 (m), 848 (m), 772 (s), 699 (m), 668 (m), 340 (m) cm^{-1}.

(*OC*-6-43)-Amminedichloro(cyclohexanamine)bis(ethyl carbonato-*O*)platinum(IV) (20). Stir a suspension of 1.5 g (3.6 mmol) of **5** and 6 mL of diethyl pyrocarbonate (40 mmol) for 3 days in 50 mL of1/1 v/v CH_2Cl_2/Et_2O. Collect the solid and recrystallize from EtOAc/Et_2O, cooling to −25 °C to obtain 1.2 g (59% yield) of bright yellow crystals. Anal. Calcd for $C_{12}H_{26}Cl_2N_2O_6Pt$: C, 25.72; H, 4.68; N, 5.00; Cl, 12.65. Found: C, 25.83; H, 4.69; N, 4.98; Cl, 12.54. IR (KBr) ν: 3240 (s), 3130 (s), 2980 (w), 2935 (s), 2858 (m), 1672 (s), 1620 (sh), 1570 (s), 1477 (m), 1465 (w), 1450 (m), 1395 (s), 1470 (s), 1322 (w), 1265 (s), 1172 (m), 1100 (s), 1085 (s), 1050 (w), 1005 (w), 854 (m), 799 (m), 690 (m), 532 (w), 465 (w), 418 (m), 345 (m) cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.24 (6H, t, J = 7 Hz), 1.1−2.3 (11H, b), 4.1 (4H, q, J = 7 Hz).

(*OC*-6-43)-Amminedichloro(cyclohexanamine)bis((methylthio)acetato-*O*)platinum(IV) (21). Stir a suspension of 1.14 g (2.8 mmol) of **5** and 1.6 g (8.2 mmol) of α-(methylthio)acetic acid anhydride in 25 mL of 4/1 Et_2O/CH_2Cl_2 at RT for 24 h. Precipitate by adding 25 mL of Et_2O with rapid stirring. Collect and dry the solid in vacuo. Yield: 1.2 g (73% yield). Anal. Calcd for $C_{12}H_{26}Cl_2N_2O_4PtS_2$: C, 24.33; H, 4.42; N, 4.73. Found: C, 24.05; H, 4.37; N, 4.60. IR (KBr) ν: 3200 (s), 3100 (sh), 2916 (s), 2850 (s), 1655 (s), 1622 (s), 1560 (m), 1440 (m), 1420 (m), 1375 (m), 1312 (sh), 1299 (s), 1208 (s), 1260 (w), 1230 (w), 1080 (w), 1025 (m), 985 (m), 943 (m), 899 (m), 790 (w), 732 (m), 701 (m), 618 (m), 530 (m), 450 (w), 335 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.1−1.8 (11H, m), 2.24 (6H, s), 3.33 (4H, dd, J = 24.8 Hz, J = 19.6 Hz).

(*OC*-6-43)-Amminedichloro(cyclohexanamine)bis((methylsulfonyl)acetato-*O*)platinum(IV) (22). Add a solution of 1 g (5.8 mmol) of 3-chloroperoxybenzoic acid (MCPBA) in 10 mL of CH_2Cl_2 to a stirred, nitrogen-purged suspension of 0.344 g (0.58 mmol) of **21** cooled to 0 °C. After 1 h allow to warm to RT and continue stirring for an additional 24 h. Collect the product by vacuum filtration and dry under vacuum overnight. Yield: 0.32 g (84% yield). Anal. Calcd for $C_{12}H_{26}Cl_2N_2O_8PtS_2$: C, 21.96; H, 3.99; N, 4.27. Found: C, 21.67; H, 3.82; N, 4.17. IR (KBr) ν: 3220 (sh), 3185 (s), 3010 (w), 2920 (s), 2925 (m), 1670 (sh), 1641 (s), 1565 (m), 1441 (w), 1305 (s), 1218 (m), 1151 (m), 1105 (s), 1040 (m), 970 (m), 902 (m), 812 (m), 731 (m), 616 (m), 595 (m), 495 (m), 453 (m), 340 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.1−1.4, 1.5−1.8, 2.0−2.1 (11H, m), 3.18 (6H, s), 4.1 (4H, s).

(*OC*-6-43)-Amminedichloro(cyclohexanamine)bis((methylsulfinyl)acetato-*O*)platinum(IV) (23). Stir a suspension of 0.344 g of **21** (0.58 mmol) and 500 μL of 30% H_2O_2 (4.9 mmol) in CH_2Cl_2 at RT for 16 h. Collect the resulting solid and dry in vacuo, obtaining 0.3 g (83% yield). Anal. Calcd for $C_{12}H_{26}Cl_2N_2O_6PtS_2$: C, 23.08; H, 4.20; N, 4.49. Found: C, 22.74; H, 4.13; N, 4.40. IR (KBr) ν: 3220 (s), 3000 (s), 2920 (s), 2955 (m), 1675 (s), 1640 (s), 1449 (w), 1375 (m), 1310 (s), 1200 (m), 1175 (m), 1030 (s), 960 (w), 948 (m), 899 (w), 718 (m), 685 (m), 600 (m), 375 (w), 340 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.1−1.4 (5H, m), 1.5−1.8 (3H, m), 2.0−2.1 (2H, m), 2.74 (6H, d, J = 9 Hz), 4.1 (4H, dd).

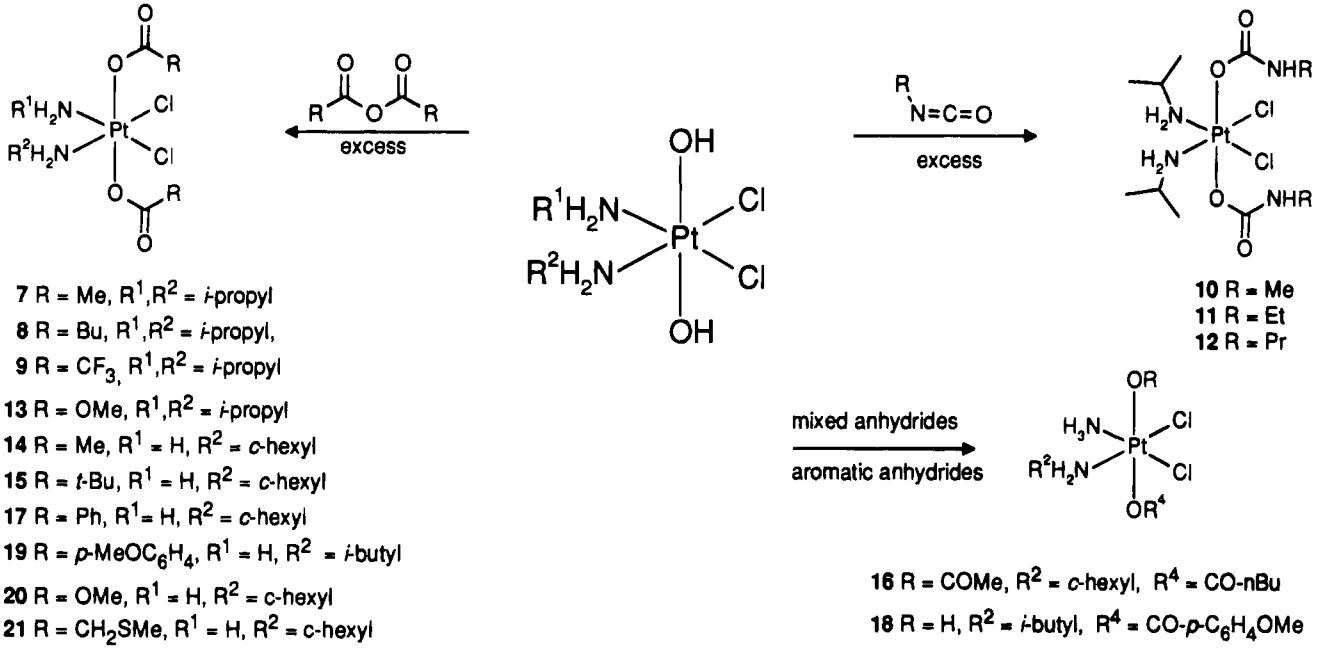
Results

Syntheses of *cis,trans,cis*-$Pt^{IV}Cl_2(OH)_2NH_3(NH_2R)$ (R = cyclobutylamine, isobutylamine), compounds **5** and **6**, are accomplished in four steps in moderate overall yield from cisplatin and the corresponding amine according to Scheme 1. A key intermediate is the $[Pt^{II}Cl_3NH_3]^-$ anion, used as the sodium salt *in situ* or isolated as the potassium salt, $K[Pt^{II}Cl_3NH_3]\cdot{}^1/_2H_2O$ (**1**). Both salts are obtained by a modification of the preparation of the $[Pt^{II}Cl_3NH_3]^-$ anion we described previously.[2] The isobutylamine Pt(II) complex **4** is conveniently prepared pure by reaction of $Na[Pt^{II}Cl_3NH_3]$ prepared *in situ* (method a of Scheme 1) with isobutylamine in a modified Dhara procedure.[8,9] However, the Pt(II) dichloride **3**, prepared from *in situ* $Na[Pt^{II}Cl_3NH_3]$, contains an impurity. Pure **3** can be prepared in two steps (method b of Scheme 1) from isolated **1** ($K[Pt^{II}Cl_3NH_3]$). The intermediate mixed-halo Pt(II) complex **2** is isolated, purified, and subsequently converted to the dichloride by formation of the aquo species with silver nitrate followed by precipitation with HCl. Oxidation of Pt(II) complexes **3** and **4**, with hydrogen peroxide by literature methods, produces the Pt(IV) mixed amine dihydroxy complexes **5** and **6**, respectively. The complexes *cis*-$Pt^{II}Cl_2$(isopropylamine)$_2$ and *cis,trans,cis*-$Pt^{IV}Cl_2(OH)_2$(isopropylamine)$_2$ are prepared by literature methods.[4]

The scope of the carboxylation of hydroxide coordinated to platinum is shown in Scheme 2. Carboxylation is facile, occurring under a variety of conditions. Hence, the carboxylates **7**, **8**, **9**, and **14**, the carbonates **13** and **20**, and the carbamates **10**, **11**, and **12** are conveniently prepared by stirring the corresponding *cis,trans,cis*-$Pt^{II}Cl_2(OH)_2AA'$ (A, A' = ammine, amine) complex at room temperature in the corresponding anhydride, pyrocarbonate, or isocyanate for several hours to days. The carboxylated product is precipitated by addition of a nonpolar solvent such as hexane or ether (or occasionally it precipitates spontaneously) and collected. The product is frequently analytically pure as collected, though sometimes recrystallization is required. Usually the electrophile serves as

(8) Dhara, S. C. *Indian J. Chem.* **1970**, *8*, 193.
(9) Cleare, M. J.; Hoeschele, J. D. *Platinum Met. Rev.* **1973**, *17*, 2.

Scheme 2 Carboxylation of the Pt(IV) Hydroxo Group

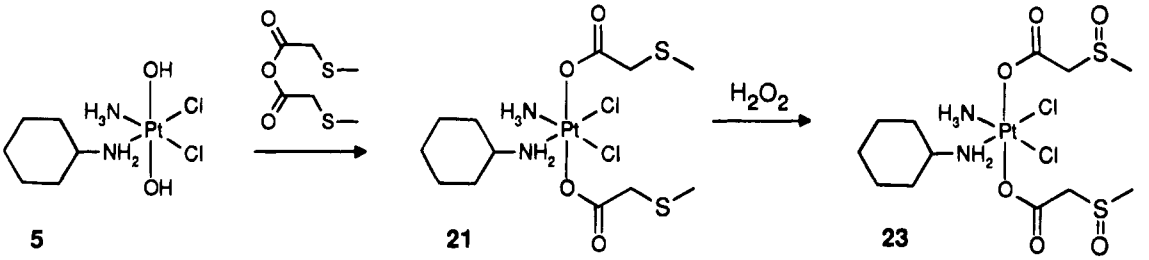


7 R = Me, R^1,R^2 = *i*-propyl
8 R = Bu, R^1,R^2 = *i*-propyl,
9 R = CF_3, R^1,R^2 = *i*-propyl
13 R = OMe, R^1,R^2 = *i*-propyl
14 R = Me, R^1 = H, R^2 = *c*-hexyl
15 R = *t*-Bu, R^1 = H, R^2 = *c*-hexyl
17 R = Ph, R^1 = H, R^2 = *c*-hexyl
19 R = *p*-$MeOC_6H_4$, R^1 = H, R^2 = *i*-butyl
20 R = OMe, R^1 = H, R^2 = c-hexyl
21 R = CH_2SMe, R^1 = H, R^2 = c-hexyl

10 R = Me
11 R = Et
12 R = Pr

16 R = COMe, R^2 = *c*-hexyl, R^4 = CO-nBu
18 R = H, R^2 = *i*-butyl, R^4 = CO-*p*-C_6H_4OMe

Scheme 3 Oxidation of a Pendant Thioether to a Sulfoxide on a Pt(IV) Carboxylate



5 **21** **23**

the solvent, but in certain circumstances, diluting the electrophile in an inert solvent is advantageous. This is the case when the electrophile is valuable, as in preparation of **21**, or when the electrophile is a solid, as in the synthesis of the arenecarboxylates **17**, **18**, and **19**. In other cases, addition of a less polar solvent aids precipitation of a soluble product, as in the preparation of **16**. Conversely, the polar solvent acetone facilitates the separation of the soluble pivalate, **15**, from insoluble starting material.

In some circumstances, compounds containing unsymmetrical trans-oxygen-containing ligands can be obtained. If the carboxylation is carried out in a mixture of two electrophiles of similar reactivities but differing lipophilicities, a mixture of carboxylates is formed. The desired mixed-carboxylate complex of the general formula *cis,trans,cis*-$Pt^{IV}Cl_2(O_2CR)(O_2CR')NH_3(NH_2R'')$ may be separated by chromatography on silica. The optimum statistical yield (50%) can be achieved by accounting for small differences in reactivity between the two electrophiles and adjusting the stoichiometry. For example, when the carboxylation is carried out with a 2/3 molar ratio of acetic anhydride to valeric anhydride, the mixed-carboxylate complex **16** is isolated as 49% of the product mixture (after chromatography with 86% sample recovery) while the remaining 51% of the mixture comprises the two symmetrical carboxylates. Occasionally monocarboxylated complexes *cis,trans,cis*-$Pt^{IV}Cl_2(O_2CR)(OH)NH_3(NH_2R'')$ precipitate from the reaction mixture and may be isolated. This situation occurs with the bis(*p*-methoxybenzoate) **19**, which is separated from the monohydroxy mono(*p*-methoxybenzoate) complex **18** by taking advantage of the fact that **19** is soluble in acetone while **18** is not. Presumably, complete conversion to **19** is made feasible by extending the reaction time. No attempt was made to resolve the racemic, unsymmetrical carboxylato complex **16** or the carboxylato hydroxy complex **18**.

The Pt(IV) carboxylates are kinetically inert and stable to mild oxidation conditions. We took advantage of this to carry out further transformations of the coordinated ligand. Thioethers may be selectively oxidized to sulfoxides or sulfones by judicious choice of oxidizing agent and reaction conditions.[10] Oxidation of the pendant thioethers of **21** to sulfoxides with hydrogen peroxide in a two-phase reaction yielded **23** (Scheme 3), while excess MCPBA oxidized the thioethers to the sulfone complex **22**.

The oxidation of Pt(II) dichloro diamine complexes to Pt(IV) dihydroxy complexes and subsequent carboxylation are readily identified by prominent changes in the infrared spectrum. The hydrogen peroxide oxidation products of platinum(II) dichlorides **3** and **4** are the Pt(IV) hydroxy compounds **5** and **6**, respectively, which are readily identified by their characteristic[11] PtOH stretches at 3527 and 3503 cm^{-1} and PtO streatches at 549 and 538 cm^{-1}. Upon carboxylation, both PtOH and PtO stretches are lost, replaced by a strong C=O stretch of the carboxylate ligand. There is considerable overlap in the stretching frequency of the different carboxylate functional groups. The stretching frequencies of these complexes range from 1587 cm^{-1} for the carbamate **10** to 1675 cm^{-1} for the

(10) March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1985; p 1089.
(11) Nakamoto, K. *Infrared and Raman Spectra of Inorganic Coordination Compounds*, 4th ed.; John Wiley & Sons: New York, 1986; p 383.

carboxylate **23**. The trifluoroacetate **9** lies outside the normal range of carboxylates at 1741 cm^{-1}. The characteristic PtOH stretches are slightly perturbed in the monocarboxylated product **18** where the PtOH shift ~23 cm^{-1} is to lower energy and the PtOH stretch shift ~27 cm^{-1} is to higher energy compared to those for the dihydroxy complex **6**. The other characteristic IR band common to all of these compounds is the PtCl stretch. The Pt(II) starting materials here contain characteristic PtCl stretches near 325 cm^{-1} which shift ~10 cm^{-1} to higher energy upon oxidation. However, the position of the chloride stretch alone is insufficient to assign oxidation state because the range of stretching frequencies among Pt(II) and Pt(IV) complexes is greater than 10 cm^{-1}.

Discussion

We sought a means to systematically modify the trans ligands of the class antitumor compounds of the general formula *cis,-trans,cis*-$Pt^{IV}X_2Y_2AA'$ (X = halide; Y = OH, Cl; A, A' = ammine, amine) in order to examine the effect on their pharmacological properties. The introduction of the kinetically inert trans hydroxy or chloro ligands in such complexes is accomplished by oxidation of the corresponding Pt(II) complex with oxidants such as hydrogen peroxide or chlorine. Conversion of these ligands to carboxylates via substitution reactions is problematic due to the kinetic inertness of Pt(IV). Intermolecular carboxylation of the coordinated hydroxide overcame this problem. The synthesis of compounds of the general formula *cis,trans,cis*-$Pt^{IV}Cl_2(O_2CR)_2AA'$ (A, A' = ammonia or amine; R = alkyl, aryl, alkoxy, or amido) is depicted in Scheme 1. The most notable features in this scheme are convenient *in situ* laboratory-scale preparation of $K[Pt^{II}Cl_3NH_3]$ and reaction of moderately nucleophilic hydroxide coordinated to Pt(IV) with a variety of electrophiles under mild conditions.

Practical syntheses of *cis*-Pt^{II}(amine)$(NH_3)Cl_2$ compounds are via ligand substitution[3,7,12] of $[Pt^{II}(am)Cl_3]^-$ (am = ammine, amine) or bridge-cleaving reactions[13] of $[Pt^{II}(amine)I_2]_2$. The most desirable starting material for synthesizing a variety of *cis*-Pt^{II}(amine)$(NH_3)Cl_2$ complexes is the $[Pt^{II}(NH_3)Cl_3]^-$ anion because the substitution chemistry of this anion is controlled by the trans effect leading to the exclusive formation of *cis*-Pt^{II}(amine)$(NH_3)Cl_2$. In addition, the ammine ligand is common to the entire series of compounds of interest. This minimizes the number of required starting materials. A practical synthesis[3] of $K[Pt^{II}Cl_3NH_3]\cdot{}^1/_2H_2O$ (**1**) based on the Elleman procedure[14] recently appeared; however, it does require an elaborate purification procedure. The method we employed has the principal advantage that $[Pt^{II}Cl_3NH_3]^-$ is prepared *in situ* on a gram scale from the convenient starting material cisplatin with simple equipment. Analytically pure **1** can also be prepared by this route in good yield (55%) without a complex purification step. The $Na[Pt^{II}Cl_3NH_3]$, prepared *in situ*, reacts with small amines ($\leq C_4$), producing crude *cis*-Pt^{II}(amine)$(NH_3)ICl$ complexes which, though not analytically pure, are conveniently converted to the pure dichloride *cis*-Pt^{II}(amine)$(NH_3)Cl_2$. Analytically pure *cis*-Pt^{II}(amine)$(NH_3)ICl$ may be obtained by a procedure similar to the one used for the preparation of mixed-halo complex **2** starting with pure isolated **1**. When $[Pt^{II}Cl_3NH_3]^-$ prepared *in situ* is used to synthesize mixed-amine Pt(II) complexes with larger amines ($\geq C_6$), an impurity coprecipitates in the final product. This is probably the symmetrical *cis*-$Pt^{II}Cl_2(amine)_2$ arising from a small contamination of $Pt^{II}Cl_4^{2-}$. This problem arises with larger amines because the corresponding Pt(II) diamine complex is extremely insoluble in water and is more likely to precipitate than the corresponding complex of a smaller amine. The problem is overcome in the synthesis of **3** by using isolated $K[PtCl_3(NH_3)]$ (**1**) in a two-step synthesis. During the preparation of the mixed-halo intermediate **2**, a small contaminant of *cis*-$Pt^{II}I_2$(cyclohexanamine)$_2$ is easily washed out with acetone. Subsequent conversion of **2** to its aquo species with silver nitrate, followed by precipitation with HCl, produces pure dichloride **3**.

The observation of intramolecular hydrolysis of nitriles,[15] peptides,[16] and phosphate esters[17] in kinetically inert hydroxide complexes established that coordinated hydroxide can be nucleophilic. Intermolecular hydrolysis of propionic anhydride[18] by kinetically inert $Co^{III}(NH_3)_5(^{18}OH)^{2+}$ leads to formation of $Co^{III}(NH_3)_5(^{18}OCOEt)^{2+}$ in 5% isolated yield and 93% retention of the ^{18}O label in the carboxylation product, demonstrating that carboxylation proceeds by nucleophilic attack of hydroxide for kinetically inert metal hydroxides. Trifluoroacetic anhydride, which is commonly used to prepared derivatives of alcohols and amines, has been used to form a volatile trifluoroacetate derivative of *cis,trans,cis*-$Pt^{IV}Cl_2(OH)_2(NH_2\text{-}i\text{-}Pr)_2$ useful for mass spectral analysis.[19] Despite these examples, the nucleophilic character of metal-coordinated hydroxide has not been utilized extensively to synthesize coordination compounds containing carboxyl ligands. The technique is especially suitable to synthesize carboxyl complexes of kinetically inert metal complexes which would be otherwise be difficult to prepare by substitution. The ligand geometry about the platinum center is unaffected by intermolecular carboxylation of the coordinated hydroxide as would be expected on the basis of the earlier studies of Co(III).[18] Single-crystal X-ray studies of carboxylates **7**[20] and **14**[21] confirmed the geometry of the product. The method has broad scope, permitting the synthesis of a wide variety of complexes. As noted under Results, reaction conditions are not critical, provided that the pH of the reaction medium is neither strongly acidic or strongly basic. Three classes of agent that can be used very successfully are as follows: anhydrides, which release a comparatively weak carboxylic acid upon reaction; the pyrocarbonates, which release CO_2 and alcohol; and isocyanates, which do not produce a by-product. Acid chlorides, though very reactive toward the platinum hydroxy complexes, produce complex mixtures of compounds of the general composition $Pt^{IV}Cl_{4-x}(O_2CR)_x(NH_3)(NH_2R')$ ($x = 0-2$). The formation of this mixture is almost certainly due to the generation of free HCl, which can displace both coordinated hydroxide and carboxylate. We were unable to find conditions that were suitable for powerful electrophiles because the starting platinum hydroxide is insoluble. In this circumstance, it is difficult to maintain an adequately buffered reaction medium that will not consume very reactive carboxylating agents before they have an opportunity to react.

(12) Rochon, F. D.; Melanson, R.; Doyon, M. *Inorg. Chem.* **1987**, *26*, 3065−3068.
(13) Rochon, F. D.; Kong, P. C. *Can. J. Chem.* **1986**, *64*, 1894.
(14) Elleman, T. S.; Reidhus, J. W.; Marin, D. S., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 536−541.
(15) Buckingham, D. A.; Morris, P.; Sargeson, A. M.; Zanella, A. *Inorg. Chem.* **1977**, *16*, 1910−1923.
(16) Boreham, C. J.; Buckingham, D. A.; Keene, F. R. *J. Am. Chem. Soc.* **1979**, *101*, 1409−1421. Groves, J. T.; Baron, L. A. *J. Am. Chem. Soc.* **1989**, *111*, 5442−5448.
(17) Jones, D. R.; Lindoy, L. F.; Sargeson, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 7327−7336.
(18) Buckingham, D. A.; Englehardt, L. M. *J. Am. Chem. Soc.* **1975**, *97*, 5915−5917.
(19) Cowens, J. W.; Stevie, F. A.; Alderfer, J. L.; Hansen, G. E.; Pendyala, L .A.; Creaven, P. J. *Int. J. of Mass Spectrom. Ion Phys.* **1983**, *48*, 177−180.
(20) Zubieta, J. Private communication.
(21) Neidle, S.; et al. Submitted for publication in *Acta Crystallogr.*

Under most circumstances, only bis(carboxylate) complexes are isolated. The heterogenous reaction conditions employed should tend to favor formation of dicarboxylated adducts, provided that the monocarboxylated complex is as soluble in the reaction medium as the dihydroxide and has similar reactivity. When the monocarboxylated product is very insoluble in the reaction medium, as for **18**, it can be isolated. This situation most often occurs with the less reactive aromatic anhydrides. Presumably a high concentration of monocarboxylate species builds up and this species precipitates before carboxylation of the second coordinated hydroxy ligand occurs.

The utility of this method to prepare compounds containing functionalized ligands normally considered incompatible with the platinum is demonstrated by the synthesis of compounds **21** and **23**. Formation of platinum thioether or sulfoxide complexes would be favored under substitution conditions for either oxidation state of Pt because of the high affinity platinum has for sulfur. However carboxylation of the Pt(IV) hydroxy complex **14** to form **21** occurs under conditions too mild to effect substitution of coordinated ligands. Pt(IV) carboxylates such as **21** are stable to the oxidation conditions required to oxidize thioethers to sulfoxides or sulfones. Intramolecular substitution by the pendant sulfoxides of **23** does not occur at room temperature because Pt(IV) is kinetically inert.

Biological activities of **14** and several other of the Pt(IV) carboxylates have been reported elsewhere.[22-28] The antitumor activity of complexes of this class was recently confirmed by others.[29] Kelland et al.[23] have reported an extensive preclinical evaluation of **14**. They find that the cytotoxicity profile of **14** is comparable to that of cisplatin. For example, the IC_{50}'s (concentration of compound that inhibits cell growth to 50% of control) of cisplatin and **14** are 4.4 and 1.6 μM, respectively, in SKOV-3, an intrinsically platinum-resistant cell line. In CH1, a platinum-sensitive cell line, the IC_{50}'s of both are 0.1 μM. The phase I clinical trail of orally administered **14** has been completed, and preliminary reports have been presented.[30] This compound was found to be well tolerated by the patients. The dose-limiting toxicity was myleosuppression, and the limited nausea and vomiting were readily controlled by orally administered antiemetic drugs. Phase I clinical trials in the United States and phase II clinical trials in the United Kingdom are in progress.

Conclusion

A series of Pt(IV) carboxylates, carbonates, and carbamates have been prepared by the carboxylation of kinetically inert metal-coordinated hydroxide. This reaction takes place with retention of ligand geometry in the coordination sphere of the complex. We have used this reaction to prepare a variety of Pt(IV) complexes. Currently, **14** (JM-216) is in clinical trails as an *orally active* antitumor agent. The versatile but underutilized carboxylation reaction described here should be applicable to a variety of kinetically inert metal hydroxy complexes.

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(22) Kelland, L. R.; Jones, M.; Gwynne, J. J.; Valenti, M.; Murrer, B.; Barnard, C. F. J.; Vollano, J. F.; Giandomenico, C. M.; Abrams, M. J.; Harrap, K. R. *Int. J. Oncol.* **1993**, *2*, 1042-1048.
(23) Kelland, L. R.; Abel, G.; McKeage, M. J.; Jones, M.; Goddard, P. M.; Valenti, M.; Murrer, B. A.; Harrap, K. R. *Cancer Res.* **1993**, *53*, 2581-2586.
(24) McKeage, M. J.; Morgan, S. E.; Boxall, F. E.; Murrer, B. A.; Hard, G. C.; Harrap, K. R. *Br. J. Cancer* **1993**, *67*, 996-1000.
(25) Loh, S. Y.; Mistry, P.; Kelland, L. R.; Abel, G.; Harrap, K. R. *Br. J. Cancer* **1992**, *66*, 1109-1115.
(26) Mistry, P.; Kelland, L. R.; Loh, S. Y.; Abel, G.; Murrer, B. A.; Harrap, K. R. *Cancer Res.* **1992**, *52*, 6188-6193.
(27) Kelland, L. R.; Mistry, P.; Abel, G.; Loh, S. Y.; O'Neill, C. F.; Murrer, B. A.; Harrap, K. R. *Cancer Res.* **1992**, *52*, 3857-3864.
(28) Kelland, L. R.; Murrer, B. A.; Abel, G.; Giandomenico, C. M.; Mistry, P.; Harrap, K. R. *Cancer Res.* **1992**, *52*, 822-828.
(29) Khokar, A. R.; Deng, Y.; Al-Baker, S.; Yoshida, M.; Siddik, Z. H. *J. Inorg. Biochem.* **1993**, *51*, 677-687. Khokar, A. R.; Deng, Y.; Kido, Y.; Siddik, Z. H. *J. Inorg. Biochem.* **1993**, *50*, 79-87.
(30) McKeage, M. J.; et al. *Proc. Am. Soc. Clin. Oncol.* **1994**, 136 (Abs. 337).