Electrophilic Substitution of (Diamine)tetrahydroxoplatinum(IV) with Carboxylic Anhydrides. Synthesis and Characterization of (Diamine)platinum(IV) Complexes of Mixed Carboxylates

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A novel series of (diamine)platinum(IV) complexes of mixed carboxylates have been synthesized by electrophilic substitution of the tetrahydroxoplatinum(IV) complex (dach)$Pt(OH)_4$ (dach = *trans*-(±)-1,2-diaminocyclohexane) with three different carboxylic anhydrides, pivalic, acetic, and trifluoroacetic anhydrides. Consecutive two-step acylations with two different carboxylic anhydrides in acetone or dichloromethane gave the mixed carboxylate complexes (dach)$Pt(O_2CR)_x(O_2CR')_{4-x}$ (R = $C(CH_3)_3$ or CF_3, R′ = CH_3, x = 1−4) including all the possible stereoisomers, which could be separated and identified by means of HPLC, column chromatography, ^1H NMR, and X-ray crystallography. From analysis of the reaction products we have found that the positions of electrophilic substitution of (dach)$Pt(OH)_4$ were influenced by the kinds of carboxylic anhydrides exhibiting different electrophilicity or steric effects. The initial substitution by the first reactant occurs more favorably on axial OH, but in the case of pivalic anhydride, equatorial substitution is favored probably because of the bulkiness of the pivalate group. Such a result seems to be related to their stereochemical factors rather than to differences in electrophilicity. The lipophilicity of the title complexes was affected not only by the carbon numbers of substituents but also by the conformation of the resulting compound.

Introduction

Six-coordinate (diamine)platinum(IV) complexes have been of great interests[1−10] because of their potential applicability as oral anticancer drugs, as was exemplified by JM216,[11] which has undergone extensive clinical trials. Lipophilicity and water solubility are important physicochemical properties for gastrointestinal absorption of drugs. Many platinum(IV) complexes have been synthesized to modulate such properties by changing the axial ligands by electrophilic substitution of *cis*,*trans*,*cis*-(diamine)$Pt(OH)_2X_2$ (X_2 = halides or dicarboxylates) with carboxylic anhydrides.[8−10] To tune these properties more subtly, variation of the equatorial ligands is also necessary but cannot be easily afforded by conventional synthetic methods. Recently, we have attempted electrophilic substitution of (diamine)$Pt(OH)_4$ with carboxylic anhydrides, which was found to be a facile and efficient method to yield (diamine)$Pt(O_2CR)_4$ (R = C_nH_{2n+1}, n = 1−4).[12] In the previous studies, lipophilicity was modulated by introducing carboxylic anhydrides with different carbon number (n = 1−6). However, in the case of (diamine)Pt-$(O_2CR)_4$, an increase of one carbon in the carboxylate ligand results in an increase of four carbons in the platinum(IV) complex, which is accompanied by a relatively large change of lipophilicity. Therefore, for more fine-tuning of the lipophilicity and water solubility of the platinum(IV) complexes, we have performed electrophilic substitution reactions of intermediate (diamine)tetrahydroxoplatinum(IV) complexes with two different carboxylic anhydrides in a stepwise manner to obtain mixed carboxylatoplatinum(IV) complexes (dach)$Pt(O_2CR)_x(O_2CR')_{4-x}$ (dach = *trans*-(±)-1,2-diaminocyclohexane, R = $C(CH_3)_3$ or CF_3, R′ = CH_3, x = 1−4). We could separate the products with different compositions of the mixed carboxylates and determined the ratios of the stereoisomers formed from the reactions. We report here the synthesis, separation, and characterization of the isomers of the mixed carboxylatoplatinum(IV) complexes.

Experimental Section

Materials and Instrumentation. Potassium tetrachloroplatinate from Kojima and *trans*-(±)-1,2-diaminocyclohexane (dach), pivalic anhydride ($(Piv)_2O$), trifluoroacetic anhydride, and acetic anhydride (Ac_2O) from Aldrich were used as received. The intermediate (dach)$Pt(OH)_4$ was prepared by the literature method.[8,13] For analytical HPLC, samples

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were chromatographed on Capcell PAK C_{18} using aqueous acetonitrile solutions as eluent. Elemental analyses were carried out at the Advanced Chemical Analysis Center, KIST. ^{1}H NMR spectra were recorded on a 300 MHz Varian Gemini NMR spectrometer. IR spectra were measured as KBr pellets on a MIDAC 101025 FT-IR spectrometer. The mass analyses were performed by HP5989A equipped with HP59987A as an electron-spray source. A mixture of methanol and water (80:20) containing 1% formic acid was used as solvent for the mass analysis.

Synthesis of (dach)Pt(OAc)$_4$ (1). This compound was prepared by a method described previously.[12]

Synthesis of (dach)Pt(OPiv)(OAc)$_3$ (2, 3). To a suspension of (dach)Pt(OH)$_4$ (0.379 g, 1 mmol) in acetone (10 mL) was added pivalic anhydride (203 μL, 1 mmol), and the reaction mixture was stirred for 2 h under protection from light. Acetic anhydride (330 μL, 3 mmol) was added to the reaction mixture, which was further stirred for 2 h. The solution mixture was evaporated to dryness under reduced pressure. The solid product was eluted through a silica gel column using a mixed solvent of acetone/hexane (35/75 to 70/30, v/v) and two stereoisomers, (dach)Pt(OPiv)^{eq}(OAc)$_3$ (**2**) and (dach)Pt(OPiv)^{ax}(OAc)$_3$ (**3**), were obtained from the fractions. **2**: yield, 15%. Anal. Calcd for $C_{17}H_{32}N_2O_8Pt\cdot H_2O$: C, 34.1; H, 5.67; N, 4.67. Found: C, 34.2; H, 5.54; N, 4.60. IR (KBr, ν_{max}, cm^{-1}): 2956(w), 1658(s), 1622(s), 1364(s), 1311(s), 1292(s), 1212(m), 704(m) cm^{-1}. ^{1}H NMR (acetone-d_6, ppm): 2.90 (s, 2H), 2.57 (t, 2H), 2.00 (s, 3H, eq-O_2CCH_3), 1.93 (s, 6H, ax-O_2CCH_3), 1.70 (d, 2H), 1.55 (d, 2H), 1.32 (s, 2H), 1.17 (s, 9H, eq-$O_2CC(CH_3)_3$). ESI-MS: m/e = 610 [M + Na]$^+$, 528 [M − CH_3COO]$^+$, 409 [M − 3CH_3COO]$^+$, 366 [M − 3CH_3COO − $(CH_3)_3$]$^+$. **3**: yield, 8%. Anal. Calcd for $C_{17}H_{32}N_2O_8Pt\cdot H_2O$: C, 34.1; H, 5.67; N, 4.67. Found: C, 33.8; H, 5.59; N, 4.60. IR (KBr, ν_{max}, cm^{-1}): 2956(w), 1658(s), 1622(s), 1364(s), 1311(s), 1292(s), 1212(m), 704(m). ^{1}H NMR (acetone-d_6, ppm): 2.90 (s, 2H), 2.57 (t, 2H), 2.02 (s, 6H, eq-O_2CCH_3), 1.95 (s, 3H, ax-O_2CCH_3), 1.70 (d, 2H), 1.55 (d, 2H), 1.32 (s, 2H), 1.11 (s, 9H, ax-$O_2CC(CH_3)_3$).

Synthesis of (dach)Pt(OPiv)$_2$(OAc)$_2$ (4−6). The procedure was the same as described for **2** except for the quantities of pivalic (406 μL, 2 mmol) and acetic anhydrides (220 μL, 2 mmol). The product was obtained as a mixture of three stereoisomers, which were separated on the analytical HPLC but could not be isolated as pure compounds by conventional silica column chromatography. Yield: 12%. Anal. Calcd for $C_{20}H_{38}N_2O_8Pt\cdot 2H_2O$: C, 36.1; H, 6.32; N, 4.21. Found: C, 36.3; H, 6.31; N, 4.12. IR (KBr, ν_{max}, cm^{-1}): 2954(m), 1648(sh), 1624(s), 1364(s), 1300(s), 1210(s). ^{1}H NMR (acetone-d_6, ppm): 2.90 (s, 2H), 2.57 (t, 2H), 1.98−2.00 (s, 3H, eq-O_2CCH_3), 1.92−1.94 (s, 3H, ax-O_2CCH_3), 1.70 (d, 2H), 1.55 (d, 2H), 1.32 (s, 2H), 1.18−1.19 (s, 9H, eq-$O_2CC(CH_3)_3$), 1.11−1.12 (s, 9H, ax-$O_2CC(CH_3)_3$). ESI-MS: m/e = 652 [M + Na]$^+$, 410 [M − 2CH_3COO − $(CH_3)_3CCOO$]$^+$.

Synthesis of (dach)Pt(OPiv)$_3$(OAc) (7, 8). The procedure was the same as described for **2** except for the quantities of pivalic (609 μL, 3 mmol) and acetic anhydrides (110 μL, 1 mmol). The product was obtained as a mixture of two stereoisomers, (dach)Pt(OPiv)$_3$(OAc)^{ax} (**7**) and (dach)Pt(OPiv)$_3$(OAc)^{eq} (**8**). Compound **7** was separated by recrystallization in a solvent pair of acetone and water. Anal. Calcd for $C_{23}H_{44}N_2O_8Pt\cdot 4H_2O$: C, 37.1; H, 6.99; N, 3.77. Found: C, 37.6; H, 6.97; N, 3.67. IR (KBr, ν_{max}, cm^{-1}): 2954(m), 1648(sh), 1624(s), 1364(s), 1300(s), 1210(s). **7**: yield, 20%. ^{1}H NMR (acetone-d_6, ppm): 2.90 (s, 2H), 2.57 (t, 2H), 1.92 (s, 3H, ax-O_2CCH_3), 1.70 (d, 2H), 1.55 (d, 2H), 1.32 (s, 2H), 1.19 (s, 9H, eq-$O_2CC(CH_3)_3$), 1.17 (s, 9H, eq-$O_2CC(CH_3)_3$), 1.11 (s, 9H, ax-$O_2CC(CH_3)_3$). ESI-MS: m/e = 694 [M + Na]$^+$, 571 [M − $(CH_3)_3CCOO$]$^+$, 409 [M − CH_3COO − 2$(CH_3)_3$-$CCOO$]$^+$. **8**: yield, 3%. ^{1}H NMR (acetone-d_6, ppm): 2.00 (s, 3H, eq-O_2CCH_3), 1.18 (s, 9H, eq-$O_2CC(CH_3)_3$), 1.12 (s, 18H, ax-$O_2CC(CH_3)_3$).

Synthesis of (dach)Pt(OPiv)$_4$ (9). The procedure was the same as described for **2** except that only pivalic anhydride (815 μL, 4 mmol) was used. The product was finally recrystallized in a solvent pair of acetone and water. Yield: 65%. Anal. Calcd for $C_{26}H_{50}N_2O_8Pt\cdot H_2O$: C, 42.7; H, 7.11; N, 3.83. Found: C, 43.6; H, 7.10; N, 3.86. IR (KBr, ν_{max}, cm^{-1}): 2954(m), 1635(s), 1310(s), 1210(s). ^{1}H NMR ($CDCl_3$, ppm): 9.80 (br, 2H), 8.23 (br, 2H), 2.54 (s, 2H), 2.29(d, 2H), 1.67 (d, 2H), 1.49 (br, 2H), 1.35 (br, 2H), 1.20 (s, 18H, eq-$O_2CC(CH_3)_3$), 1.11 (s, 18H, ax-$O_2CC(CH_3)_3$).

Synthesis of (dach)Pt(O$_2$CCF$_3$)(OAc)$_3$ (10, 11). To a suspension of (dach)Pt(OH)$_4$ (0.379 g, 1 mmol) in dichloromethane (10 mL) was added trifluoroacetic anhydride (141 μL, 1 mmol). The reaction mixture was stirred for 2 h under protection from light. Acetic anhydride (330 μL, 3 mmol) was added to the reaction mixture, which was further stirred for 2 h. The solution was evaporated to dryness under reduced pressure. The solid product was then eluted on a silica gel column using a mixture of acetone/hexane (50/50, v/v), and two stereoisomers (dach)-Pt(O$_2$CCF$_3$)^{eq}(OAc)$_3$ (**10**) and (dach)Pt(O$_2$CCF$_3$)^{ax}(OAc)$_3$ (**11**) were isolated in pure forms. **10**: yield, 5%. Anal. Calcd for $C_{14}H_{23}F_3N_2O_8Pt$: C, 28.1; H, 3.87; N, 4.67. Found: C, 28.3; H, 3.74; N, 4.60. IR (KBr, ν_{max}, cm^{-1}): 3185(m), 1713(s), 1660(s), 1618(s), 1366(s), 1312-(s), 1188(s). ^{1}H NMR (D_2O, ppm): 2.78 (br, 2H), 2.32 (br, 2H), 2.15 (s, 3H, eq-O_2CCH_3), 2.09 (s, 6H, ax-O_2CCH_3), 1.65 (br, 2H), 1.55 (br, 2H), 1.18 (s, 2H). **11**: yield, 24%. Anal. Calcd for $C_{14}H_{23}F_3N_2O_8Pt$: C, 28.1; H, 3.87; N, 4.67. Found: C, 28.6; H, 3.81; N, 4.59. IR (KBr, ν_{max}, cm^{-1}): 3185(m), 1713(s), 1660(s), 1618(s), 1366(s), 1312(s), 1188(s). ^{1}H NMR (D_2O, ppm): 2.73 (br, 2H), 2.22 (br, 2H), 2.14 (s, 6H, eq-O_2CCH_3), 2.11 (s, 3H, ax-O_2CCH_3), 1.65 (br, 2H), 1.55 (br, 2H), 1.18 (s, 2H). Crystals suitable for X-ray analysis were obtained by recrystallization in aqueous solution.

Synthesis of (dach)Pt(O$_2$CCF$_3$)$_2$(OAc)$_2$ (12−14). The procedure was the same as described for **10** except for the quantities of trifluoroacetic (282 μL, 2 mmol) and acetic anhydrides (220 μL, 2 mmol). The product was obtained as a mixture of three stereoisomers, which were separated on the analytical HPLC but could not be isolated as pure compounds by conventional silica column chromatography. The crystals of **12** were grown in an aqueous mixture solution. Yield: 30%. Anal. Calcd for $C_{14}H_{20}F_6N_2O_8Pt$: C, 25.7; H, 3.09; N, 4.29. Found: C, 24.9; H, 3.11; N, 4.22. IR (KBr, ν_{max}, cm^{-1}): 3196(m), 1725(s), 1713(s), 1660(s), 1620(s), 1366(s), 1312(s), 1188(s) cm^{-1}. ^{1}H NMR (D_2O, ppm): 2.73 (br, 2H), 2.22 (br, 2H), 2.11 (s, 6H, O_2CCH_3), 1.65 (br, 2H), 1.55 (br, 2H), 1.18 (s, 2H).

Synthesis of (dach)Pt(O$_2$CCF$_3$)$_3$(OAc) (15, 16). The procedure was the same as described for **10** except for the quantities of trifluoroacetic (423 μL, 3 mmol) and acetic anhydrides (110 μL, 1 mmol). The product was obtained as a mixture of two stereoisomers, (dach)Pt(O$_2$CCF$_3$)$_3$-(OAc)^{ax} (**15**) and (dach)Pt(O$_2$CCF$_3$)$_3$(OAc)^{eq} (**16**). Yield: 30%. Anal. Calcd for $C_{14}H_{17}F_9N_2O_8Pt$: C, 23.8; H, 2.42; N, 3.96. Found: C, 23.6; H, 2.49; N, 3.87. IR (KBr, ν_{max}, cm^{-1}): 3196(m), 1725(s), 1713(s), 1660(s) 1620(s), 1366(s), 1312(s), 1188(s) cm^{-1}. ^{1}H NMR (D_2O, ppm): 2.73 (br, 2H), 2.22 (br, 2H), 2.16 (s, 3H, O_2CCH_3), 1.65 (br, 2H), 1.55 (br, 2H), 1.18 (s, 2H).

(dach)Pt(O$_2$CCF$_3$)$_4$ (17). This compound was prepared according to a method in the literature.[12]

X-ray Structure Determination. All the X-ray data were collected on an Enraf-Nonius CAD4 automated diffractometer equipped with a Mo X-ray tube and a graphite crystal monochromator. The orientation matrix and unit cell dimensions were determined from 25 machine-centered reflections in the 2θ range of from 15° to 25°. The variations of intensities were monitored by a repeated check of intensities of three reflections every 1 h during the data collection period. Absorption corrections were applied by empirical ψ scan on three reflection planes with a χ value of ∼90°. A direct or Patterson method (SHELXS-86)[14] was employed to locate the platinum atom. Subsequent cycles of Fourier map and least-squares refinements located other atoms (SHELXL-97).[15] All the nonhydrogen atoms were refined anisotropically. Hydrogen atoms were included in the structure factor calculation using a riding model. All the calculations were carried out using VAX and PC computers. The crystallographic data for **7** and **11** are listed in Table 1.

Results and Discussion

Synthesis and Characterization. The successive acylation of (dach)Pt(OH)$_4$ with pivalic or trifluoroacetic anhydride and

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Table 1. Crystallographic Data for **7** and **11**

	7	**11**
formula	$C_{23}H_{44}N_2O_8Pt$	$C_{23}H_{44}N_2O_8PtC_{14}$ $H_{23}F_3N_2O_8Pt\cdot(^1/_2)C_3H_6O$
fw	671.69	628.47
cryst syst	triclinic	monoclinic
space group	$P\bar{1}$ (No.2)	$C2/c$ (No.15)
a (Å)	9.583(3)	4.279(3)
b (Å)	10.542(3)	2.516(4)
c (Å)	15.728(3)	16.732(6)
α (deg)	104.52(3)	90.0
β (deg)	90.13(3)	102.33(2)
γ (deg)	110.73(3)	90.0
vol (Å^3)	1424.3(7)	4789(2)
Z	2	8
d(calcd), g/cm^3	1.566	1.743
μ (mm^{-1})	4.970	5.925
F(000)	676	2448
cryst size (mm)	0.30 × 0.35 × 0.55	0.25 × 0.25 × 0.30
θ_{max} (deg)	25	25
index ranges	$h, \pm k, \pm l$	$h, k, \pm l$
reflns collected	4926	2939
parameters refined	307	269
goodness of fit	1.124	1.047
final R indices $[I > 2\sigma(I)]$		
R_1[a]	0.0429	0.0450
wR2[b]	0.1209	0.1278

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] wR2 = $\{\sum(F_o^2 - F_c^2)^2/\sum wF_o^4\}^{1/2}$, where $w = 1/\{\sigma^2F_o^2 + (0.0197P)^2 + 0.00P\}$ and where $P = \{\max(F_o^2,0) + 2F_c^2\}/3$.

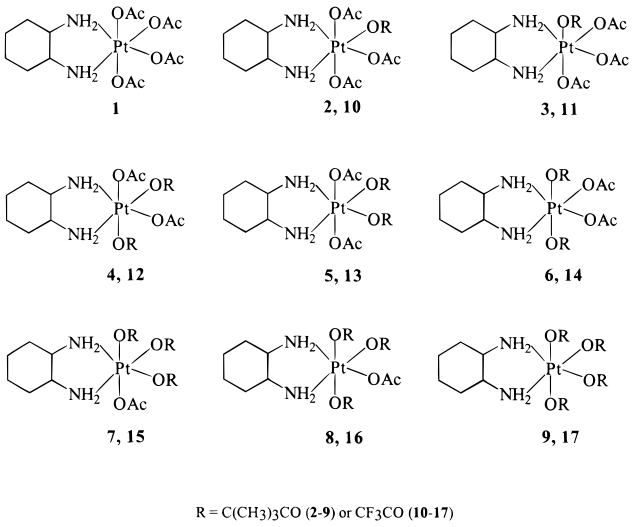

Figure 1. Stereoisomers of (dach)Pt$(O_2CR)_x(OAc)_{4-x}$ (R = $C(CH_3)_3$ or CF_3, $x = 1-4$).

acetic anhydride resulted in the formation of the mixed carboxylate complexes (dach)Pt$(O_2CR)_x(OAc)_{4-x}$ (R = $C(CH_3)_3$ or CF_3, $x = 1-4$) including all possible stereoisomers as shown in Figure 1. When anhydrides were added to (dach)Pt$(OH)_4$ suspended in acetone or dichloromethane, the reaction mixture became clear after a few minutes even at room temperature. Thus, electrophilic substitution reaction of (dach)Pt$(OH)_4$ with carboxylic anhydrides seems to be relatively fast, but the yield of the desired product from the stoichiometric ratio of the reactants was low because other byproducts with different composition were formed. For example, the yield of **2** + **3** was only 23% with many byproducts of different compositions. Separation of this reaction mixture was attempted by silica column chromatography. In the case of the complexes **1**−**9**, their R_f values of TLC in the solvent mixture of acetone/hexane (50/50) were 0.10, 0.33, 0.40, 0.66, 0.78, 0.94 for the complexes **1**, **2**, **3**, **4** + **5** + **6**, **7** + **8**, **9**, respectively. Thus, we could isolate the reaction mixture of the stereoisomers **2** and **3** into pure forms by column chromatography, but the reaction mixtures of stereoisomers **4** + **5** + **6** and **7** + **8** could not be separated by this method. Although these stereoisomeric mixtures of **4** + **5** + **6** and **7** + **8** could not be separated into pure forms by column chromatography, all the stereoisomers could be identified on HPLC. Therefore, all the reaction mixtures were subjected to HPLC to determine the ratio of isomers. The reaction of (dach)Pt$(OH)_4$ with an excess amount of a carboxylic anhydride resulted in only fully substituted complexes, (dach)Pt$(OR)_4$. However, when (dach)Pt$(OH)_4$ reacted with less than 4 equiv of a carboxylic anhydride, the product was always obtained as a mixture of partially substituted carboxylate complexes, (dach)Pt$(OR)_x(OH)_{4-x}$ ($x = 1-4$). Among the partially substituted products, (dach)Pt$(OPiv)_3(OH)^{ax}$ could be purely isolated by silica column chromatography. This trisubstituted pivalate complex was recrystallized and subjected to X-ray analysis[16] and further reacted with acetic anhydride, which afforded the mixed carboxylate complex (dach)Pt$(OPiv)_3(OAc)^{ax}$ in nearly 100% yield, implying that the remaining hydroxide group reacted with the second acetic anhydride without ligand interconversion.

The stereochemistry of the isomers has been determined with reference to that of complexes **7** and **11**, which were subjected to X-ray crystallography. Coordination of all four carboxylate ligands to the platinum(IV) atom in the complexes could be clearly confirmed from their IR and ^{1}H NMR spectra, since uncoordinated free carboxylates, that is, carboxylic acids, show quite different carbonyl stretching frequencies and proton resonances. For example, free acetic and pivalic acids show the asymmetric carbonyl stretching frequencies at approximately 1700 cm^{-1} whereas the coordinated carboxylates show them at 1600−1650 cm^{-1}. Also the mass spectral data of the mixed carboxylate complexes (**2**, **4**−**6**, **7**) showed clearly their parent peaks, which excludes the possibility of solvation by carboxylic acid. In addition, our previous work on the tetracarboxylatoplatinum(IV) complexes[12] and the crystal structural data[16] of (dach)Pt$(OPiv)_3(OH)^{ax}$ has shown clearly that the proton resonances of the axial carboxylate group appear in the more upfield region compared with those of the equatorial ones. Likewise, ^{1}H NMR spectra of **1** and **2** as well as of **10** and **11** showed two apparently distinguished singlets for substituted acetate or pivalate. The resonances of the axial carboxylate groups appeared in the more upfield region by 0.06−0.07 ppm compared with those of equatorial ones. In the case of complex **7**, the methyl protons of the pivalate groups appeared as two singlets at 1.19 and 1.17 ppm for the equatorial groups and as one singlet at 1.11 ppm for the axial group. It seems that the chemical environments of the methyl protons of the two equatorial groups are not equal probably because of the presence of asymmetric substituents at the axial position. In the IR spectra, the mixed carboxylatoplatinum(IV) compounds showed two carbonyl bands in the range 1622−1658 cm^{-1} for **1**−**8** and 1620−1720 cm^{-1} for **10**−**16**, probably due to the asymmetric carboxylate stretching of the two kinds of the carboxylate groups coordinated to the platinum(IV) atom.

(16) X-ray analysis of (dach)Pt$(OPiv)_3(OH)^{ax}$: tetragonal system, space group $P\bar{4}2_1c$, $a = 21.161(3)$ Å, $b = 21.161(6)$ Å, $c = 12.816(3)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 5739(2)$ Å^3, $Z = 8$, $R = 0.0639$ for 1849 unique observed reflections. Details of the structure determination are given in the Supporting Information.

Table 2. Analysis of the Composition of the Stereoisomeric Mixtures by HPLC[a]

mole ratio of A/A′	ratio of the isomer[b]	reaction 1	reaction 2	reaction 3
1:3	eq/ax	65/35[d]	25/75[c]	20/80[d]
2:2	eq,eq/eq,ax/ax,ax	43/54/4[c]	29/51/20[c]	
3:1	eq,eq,ax/eq,ax,ax	91/9[c]	61/39[d]	

[a] Reaction 1: successive reactions with pivalic (A) and acetic anhydrides (A′). Reaction 2: successive reactions with acetic (A) and pivalic anhydrides (A′). Reaction 3: successive reactions with trifluoroacetic (A) and acetic anhydrides (A′). [b] eq or ax designates the position substituted by the first reactant. [c] Analysis condition: H_2O/CH_3CN, 50/50. [d] Analysis condition: H_2O/CH_3CN, 85/15.

The ratios of the stereoisomers of the products from the successive two-step acylation were determined by HPLC, and the results are listed in Table 2. Here, we have studied the position of substitution by the first reactant in the electrophilic substitution reaction of the tetrahydroxoplatinum(II) complex, in which the second reactant was used to facilitate the separation of the products by enhancing lipophilicity. The ratios of the isomers shown in the table indicate the ratios of the positions substituted by the first reactant. First of all, this result clearly indicates that the position of substitution by the first reactant is dependent on the kind of anhydride. For example, in the case of the consecutive reactions with pivalic and acetic anhydrides (reaction 1) in a mole ratio of 1:3, pivalic anhydride reacted preferentially with equatorial OH, as is seen from the ratio of eq/ax = 65/35. On the other hand, when acetic or trifluoroacetic anhydride was used as a first reactant, the major product was obtained as a result of the preferential attack on the axial OH (eq/ax (**10**/**11**) = 20/80 in reaction 3). It seems that the initial substitution by the first electrophilic reagent occurs more favorably on axial OH, but in the case of pivalic anhydride, equatorial substitution is favored because of its bulkiness. Such results may be related to the different stabilization energy of the resulting compound depending on both electronic and steric effects of the electrophilic reagents. In the case of the products disubstituted by the first reactant, all possible stereoisomers resulted in the mole ratios of (eq,eq)/(eq,ax)/(ax,ax) = 43/54/4 (**4**/**5**/**6**) and 29/51/21 (**12**/**13**/**14**) for reactions 1 and 2, respectively. In both cases, the complexes disubstituted by the first reactant at both the equatorial and axial positions were the major products regardless of the position of the initial substitution. Such distributions of the isomers imply that the second electrophilic substitution occurred mainly on the equatorial position. The product disubstituted by pivalate at both axial positions was only 4%, and such a result is probably due to the unfavorable stabilization energy for a certain stereochemistry of the product depending on the substituent. A theoretical study based on the overall thermodynamic energy calculation for each isomer, depending on the nature of the electrophile and the kind of diamine, is being undertaken.

Crystal Structures of 7 and 11. Although many platinum(IV) complexes are known, mixed carboxylatoplatinum(IV) complexes are extremely rare. Moreover, no crystal structure of mixed carboxylatoplatinum(IV) complexes has been reported to our knowledge. Here, we have studied two crystal structures of **7** and **11** bearing the same carrier amine ligand, dach, and a different combination of carboxylates. In this work, the crystallographic results served as supplementary data for confirming the HPLC and NMR data. The crystals of **11** were grown in the solution of isomeric mixtures and confirmed as the major product among them. The carrier ligand, dach, in the compounds coordinates to the platinum(IV) atom through two amine nitrogen atoms in cis mode as a typical bidentate ligand.

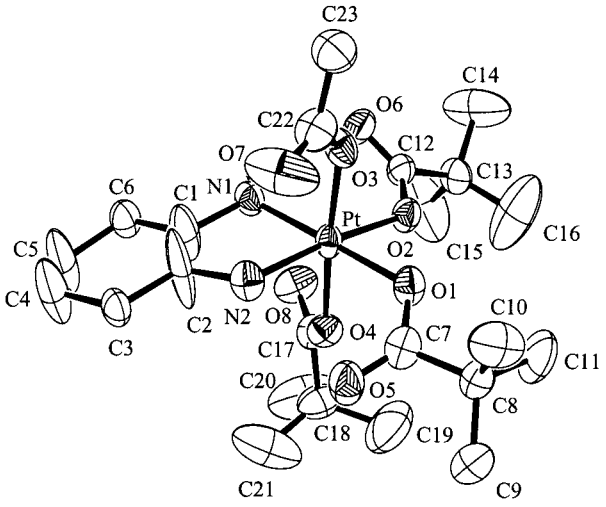

Figure 2. ORTEP drawing of (dach)Pt($O_2CC(CH_3)_3$)$_3$(OAc)^{ax} with an atomic labeling scheme.

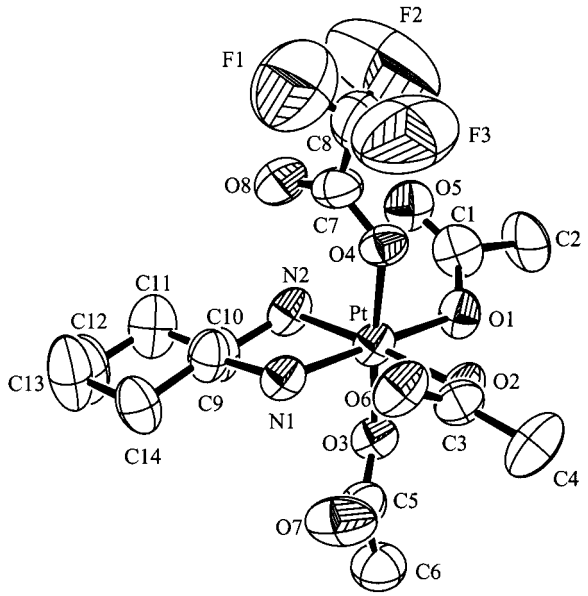

Figure 3. ORTEP drawing of (dach)Pt(O_2CCF_3)^{ax}(OAc)$_3$ with an atomic labeling scheme.

The molecular structures with their atomic labeling schemes of complexes **7** and **11** are depicted in Figures 2 and 3, respectively. Selected bond lengths and angles are listed in Table 3. The local geometry around the platinum(IV) atom in both complexes is a distorted octahedron similar to other platinum(IV) complexes[12,17,18] with the same carrier ligand, dach. However, it is somewhat surprising that the present mixed carboxylate complexes **7** and **11** exhibit a little less distortion around their Pt(IV) atoms compared with the sterically less hindered tetraacetatoplatinum(IV) complex, (dach)Pt(O_2CCH_3)$_4$.[12] The bite angle, N(1)−Pt−N(2), and its opposite angle on the square plane, O(1)−Pt−O(2), of both complexes are all around 81−82°, which is nearly the same as the corresponding angles (82−83°) of the tetracetatoplatinum(IV) complex, but the axial

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Table 3. Selected Bond Lengths (Å) and Angles (deg) for **7** and **11**

	7	**11**
Pt−N(1)	2.043(6)	2.019(10)
Pt−N(2)	2.029(6)	2.031(10)
Pt−O(1)	2.021(5)	2.007(8)
Pt−O(2)	2.008(5)	2.020(8)
Pt−O(3)	1.999(5)	1.983(9)
Pt−O(4)	1.998(5)	1.983(9)
N(1)−Pt−N(2)	82.2(2)	82.0(4)
N(1)−Pt−O(2)	99.6(2)	99.1(3)
N(2)−Pt−O(1)	96.1(2)	97.2(3)
O(1)−Pt−O(2)	82.2(2)	81.6(3)
O(1)−Pt−O(3)	91.1(2)	84.1(3)
O(1)−Pt−O(4)	86.5(2)	91.8(3)
O(3)−Pt−O(4)	175.51(17)	174.9(3)

O(3)−Pt−O(4) is 175.51(17)° and 174.9(3)° in the present complexes **7** and **11**, respectively, compared with 170.9(2)° in the tetraacetate analogues.[12] Another interesting aspect of the present mixed carboxylate complexes is that the equatorial Pt−O bond distances are slightly longer than the axial ones. Such a structural feature is also consistent with what has been observed in the tetracarboxylatoplatinum(IV) complexes.[12] For example, in the crystal structure of **11** the Pt−O bonds in the equatorial positions (2.007(8) and 2.020(8) Å) are longer than those in the axial positions (1.983(9) Å). Moreover, the axial Pt−O bond length (1.983(9) Å) is clearly shorter than the average axial Pt−O bond distance of 2.035(3) Å reported for JM216.[19]

Lipophilicity. The lipophilic and hydrophilic balance of a compound is critical for drug absorption and transport. There are many studies of the use of HPLC to determine the hydrophobicity of drugs.[20,21] Although we have not employed the special HPLC stationary phase as reported, the partition coefficients of the tetracarboxylatoplatinum(IV) complexes were determined in an octanol/water system in our previous work,[22] and we have found that the complexes are eluted in the order of their lipophilicity at the HPLC conditions. The relative retention times measured for the title complexes under the reverse-phase conditions are given in Table 4. The complexes fully substituted by pivalate or trifluoroacetate were eluted much more slowly than the tetraacetatoplatinum(IV) complex, which was eluted first among all the complexes. Thus, the mixed carboxylatoplatinum(IV) complexes were eluted between the two extremes in the order of their lipophilicity. The factors influencing the lipophilicity of a complex were not only the number of lipophilic substituents but also the conformation of the resulting compound, which probably lead to the different polarities of the complexes. A comparison of isomers in the table shows that complex **2** is eluted before **3** and that **8** is eluted before **7**. The complex bearing one different substituent at the equatorial position exhibits more polar character. Among the disubstituted isomers, the complex with two pivalate groups at equatorial positions retained more lipophilicity than the complex with two pivalate groups at axial positions. The mechanism of action of antitumor platinum(IV) complexes has not been clearly elucidated yet, but it has been shown that many platinum(IV) complexes should be reduced to platinum(II) species before binding to DNA. Although such a reduction mechanism was not clearly understood, it has been reported that the reduction rates are affected principally by the axial ligands.[5,23] In this sense, the present complexes with different stereochemistry are expected to exhibit differences in antitumor activity.

Table 4. Relative Retention Time of the Complexes on the Reverse-Phase HPLC[a]

complex	relative retention	complex	relative retention
1	2.85	**8**	14.7
2	14.7	**9**	29.0
3	17.2	**10**	12.0
4	5.7	**11**	8.98
5	6.8	**12**	5.33
6	4.7	**17**	16.1
7	22.2		

[a] Analysis condition for **1**, **9**: H_2O/CH_3CN, 80/20 for 0 min, 20/80 for 20 min, 20/80 for 40 min (1 mL/min). For **2**, **3, 10, 11**: H_2O/CH_3CN, 85/15. For **4**−**8 12, 17**: H_2O/CH_3CN, 50/50.

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Supporting Information Available: Tables listing crystallographic data, non-hydrogen positional parameters, bond distances and angles, and anisotropic and isotropic thermal parameters and an ORTEP drawing and mass spectra for the present compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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