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Subtle Ligand/Media Effects. Modulation of *cis/trans* Isomerism in Hydrogen Peroxide Oxidation of Pt(II) to Pt(IV) Complexes

Young-A Lee, Kyung Ho Yoo, and Ok-Sang Jung*

Materials Chemistry Laboratory, Korea Institute of Science and Technology, Seoul 136-791, Korea

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The modulation of *cis/trans* isomerism on the oxidation of Pt^{II} to Pt^{IV} via subtle ligand/media effects has been established. The reaction of $[Pt^{II}(O\text{-}O)(dpda)]$ (O-O = 1,1-cyclobutanedicarboxylate (cbdc), dibenzylmalonate (dbm); dpda = 2,2-dimethyl-1,3-propanediamine) with hydrogen peroxide in acetic acid produces *cis*-$[Pt^{IV}(O_2CCH_3)_2(O\text{-}O)(dpda)]$, while the reaction in acetic anhydride gives *trans*-$[Pt^{IV}(O_2CCH_3)_2(O\text{-}O)(dpda)]$. The crystal structures of *cis*-$[Pt^{IV}(O_2CCH_3)_2(cbdc)(dpda)]$ (orthorhombic *Pbca*, $a = 11.148(2)$ Å, $b = 14.188(5)$ Å, $c = 23.425(3)$ Å, $V = 3705(2)$ Å^3, $Z = 8$, $R = 0.0525$) and *trans*-$[Pt^{IV}(O_2CCH_3)_2(cbdc)(dpda)]\cdot 3H_2O$ (monoclinic $P2_1/c$, $a = 11.479(2)$ Å, $b = 13.426(3)$ Å, $c = 14.640(5)$ Å, $\beta = 108.73(2)°$, $V = 2136.8(9)$ Å^3, $Z = 4$, $R = 0.0251$) have been solved and refined. The AcO–Pt–AcO angle (87.4(5)°) of the *cis* isomer presents a striking contrast to that (172.5(1)°) of the *trans* isomer. The *trans* isomer is retained in aqueous solution, but the *cis* isomer is very slowly converted to the *trans* isomer in both water and acetic acid.

The ability to control the *cis/trans* isomerism by means of chemical triggers is of central importance in useful platinum complexes such as oral antitumor (pro)drugs and mechanistic intermediates. We keenly feel the necessity of such a *cis/trans* modulation, especially when we attempt the synthesis of Pt^{IV} compounds from the oxidation of Pt^{II} precursor.[1–3] The oxidation of Pt^{II} with hydrogen peroxide has been shown to proceed with *trans*-bis(hydroxo) addition and the retention of the stereochemistry.[4–6] On the other hand, little is known about *cis* addition. The oxidative addition of Pt^{II} with dibenzoyl peroxide gives a *cis*-$Pt^{IV}(OOCPh)_2$ isomer as a minor product along with a major *trans* isomer.[7] It was reported that oxidation of a platinum(II) complex with (diacetoxyiodo)benzene afford *cis*-bis(acetato)platinum(IV) complexes in very low yield.[8] However, selective *cis* addition of carboxylates remains unexplored. In this context, this is the first report demonstrating the stereospecific oxidation of Pt^{II} to Pt^{IV} complexes via delicate differences in the synthetic media. In the present study, it is found that modulation of the *cis/trans* isomerism can be achieved in the hydrogen peroxide oxidation of Pt^{II} to Pt^{IV} complexes, in which the structures of the products are examined by both single crystal X-ray diffractometry and $^1H/^{13}C$ NMR. Such a delicate tuning of the stereochemistry could facilitate the development of anticancer (pro)drugs and other desirable materials, and may be utilized in the field of solvent recognition.[9,10]

Experimental

Materials and Instrumentation. Reagent grade potassium tetrachloroplatinate(II) (Kojima) was used as received. $[Pt^{II}(cbdc)(dpda)]\cdot 2H_2O$ (cbdc = 1,1-cyclobutanedicarboxylate; dpda = 2,2-dimethyl-1,3-propanediamine) and $[Pt^{II}(dbm)(dpda)]$ (dbm = dibenzylmalonate) were prepared by the literature methods.[11,12] ^1H, ^{13}C, and ^{195}Pt NMR spectra were recorded on a Varian Gemini 300 instrument operating at 300.00, 75.48, and 64.39 MHz, respectively. The chemical shifts are given relative to internal Me_4Si (^1H and ^{13}C) and external $Na_2[PtCl_6]$ (^{195}Pt) for the indicated nuclei. The infrared spectra (the 4000–400 cm^{-1}) of the compounds as KBr disks were measured on a Perkin Elmer 16F PC model FT-IR spectrophotometer. Elemental analyses were performed at the Advanced Analysis Center at KIST.

***cis*-$[Pt^{IV}(O_2CCH_3)_2(cbdc)(dpda)]$.** A 30% aqueous solution of H_2O_2 (1 mL) was added to a solution of $[Pt^{II}(cbdc)(dpda)]\cdot 2H_2O$ (0.47 g, 1.0 mmol) in acetic acid (20 mL). The mixture solution was then stirred for 6 h at room temperature. The filtrate was evaporated to dryness. The crude product was recrystallized from water to give colorless crystals in 85% yield. mp 218 °C (decomp). Anal. Calcd for $C_{15}H_{26}N_2O_8Pt$: C, 32.32; H, 4.70; N, 5.03%. Found: C, 32.20; H, 4.58; N, 4.98%. ^1H NMR (300.00 MHz, D_2O) δ 0.84 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 1.65–1.81 (m, 2H, NCH_2), 1.81–1.92 (m, 2H, CH_2), 1.90 (s, 3H, $OOCCH_3$), 1.99 (s, 3H, $OOCCH_3$), 2.10–2.23 (m, 2H, NCH_2), 2.27–2.49 (m, 2H, CH_2), 2.51–2.57 (m, 2H, CH_2). ^{13}C NMR (75.48 MHz, D_2O) δ 15.7, 22.1, 22.2, 22.8, 24.0, 28.1, 34.2, 35.8, 49.2, 49.8, 55.9, 179.7 (C=O), 180.2 (C=O), 181.4 (C=O), 182.2 (C=O). ^{195}Pt NMR (65.39 MHz, D_2O) δ 1787.3. IR (KBr) $\nu(COO)_{asym}$, 1680, 1624; $\nu(COO)_{sym}$, 1368, 1344, 1316, 1298 cm^{-1}.

***trans*-$[Pt^{IV}(O_2CCH_3)_2(cbdc)(dpda)]$.** This was prepared in the same manner as the *cis* product, except that acetic anhydride was employed instead of acetic acid (82% yield). mp 224 °C (decomp). Anal. Calcd for $C_{15}H_{26}N_2O_8Pt\cdot 3H_2O$: C, 29.46; H, 5.27; N 4.58%. Found: C, 29.30; H, 5.20; N, 4.51%. ^1H NMR (300.00 MHz, D_2O) δ 0.86 (s, CH_3, 6H), 1.82 (q, CH_2, 2H), 1.90 (s, $OOCCH_3$, 6H), 2.07 (s, NCH_2, 4H), 2.42 (t, CH_2, 4H). ^{13}C NMR (75.48 MHz, D_2O) δ 15.7, 22.3, 22.9, 31.2, 35.2, 50.3, 57.2, 180.8 (C=O), 181.8 (C=O). ^{195}Pt NMR (65.39 MHz, D_2O) δ 1757.6. IR (KBr) $\nu(COO)_{asym}$, 1680, 1624; $\nu(COO)_{sym}$, 1364, 1346, 1316, 1298 cm^{-1}.

***cis*-$[Pt^{IV}(O_2CCH_3)_2(dbm)(dpda)]$.** This was prepared in the same manner as the *cis* product, except that [$\mathrm{Pt^{II}}$(dbm)(dpda)] was employed instead of [$\mathrm{Pt^{II}}$(cbdc)(dpda)]·$2H_2O$ (Yield, 80%). mp 212 °C (decomp). Anal. Calcd for $C_{26}H_{34}N_2O_8Pt$: C, 44.76; H, 4.91; N, 4.02%. Found: C, 44.20; H, 4.78; N, 4.08%. ^{1}H NMR (300.00 MHz, Me_2SO-d_6) δ 1.03 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.62–1.85 (m, 2H, NCH_2), 1.90 (s, 3H, $OOCCH_3$), 2.79–2.90 (m, 2H, NCH_2), 3.32 (s, 3H, $OOCCH_3$), 3.35 (s, 4H, CCH_2), 6.68–7.20 (m, 10H, C_6H_5), 8.15–8.47 (br, 4H, NH). IR (KBr) $\nu(\mathrm{COO})_{\mathrm{asym}}$, 1620 (br); $\nu(\mathrm{COO})_{\mathrm{sym}}$, 1312 $\mathrm{cm^{-1}}$ (br).

***trans*-[$\mathrm{Pt^{IV}}$(O_2CCH_3)$_2$(dbm)(dpda)].** This was prepared in the same manner as the *cis*-[$\mathrm{Pt^{IV}}$(O_2CCH_3)$_2$(dbm)(dpda)] product, except that acetic anhydride was employed instead of acetic acid (81% yield). mp 211 °C (decomp). Anal. Calcd for $C_{26}H_{34}N_2O_8Pt$: C 44.76, H 4.91, N, 4.02%. Found: C 44.30, H 4.71, N 4.00%. ^{1}H NMR (300.00 MHz, Me_2SO-d_6) δ 0.89 (s, 6H, CH_3), 1.86 (s, 6H, $OOCCH_3$), 2.06 (br, 4H, NCH_2), 3.30 (dd, 4H, CCH_2), 6.86–7.37 (m, 10H, C_6H_5). IR (KBr) $\nu(\mathrm{COO})_{\mathrm{asym}}$, 1672, 1628; $\nu(\mathrm{COO})_{\mathrm{sym}}$, 1366, 1262 $\mathrm{cm^{-1}}$.

Crystal Structure Determination. All X-ray data were collected on an Enraf-Nonius CAD4 automatic diffractometer with graphite-monochromated MoKα (λ = 0.71073 Å) at ambient temperature (20(1) °C). The unit cell parameters were determined based on 25 well-centered reflections by using a least-squares procedure. During the data collection, three standard reflections monitored every hour did not show any significant intensity variation. The data were corrected for Lorentz and polarization effects, and empirically for absorption (azimuthal ψ-scans of six reflections). The structures were solved by the Patterson method (SHELXS-97), and were refined by full-matrix least-squares techniques (SHELXL-97).[13] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed at the calculated positions. Crystal parameters and procedural information corresponding to data collection and structure refinement are given in Table 1 and 2.

Further details concerning the crystal structure investigation of *cis*-[$\mathrm{Pt^{IV}}$($OOCCH_3$)$_2$(cbdc)(dpda)] and *trans*-[$\mathrm{Pt^{IV}}$($OOCCH_3$)$_2$(cbdc)(dpda)]·$3H_2O$ are available on request from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ, (U.K.), free of charge, by quoting the publication citation and the deposition numbers 176880 and 176881.

Table 1. Crystallographic Data for *cis*-[$\mathrm{Pt^{IV}}$(O_2CCH_3)$_2$(cbdc)(dpda)] and *trans*-[$\mathrm{Pt^{IV}}$(O_2CCH_3)$_2$(cbdc)(dpda)]·$3H_2O$

	cis-	*trans-*
Formula	$C_{15}H_{26}N_2O_8Pt$	$C_{15}H_{26}N_2O_8Pt\cdot 3H_2O$
Fw	557.47	611.52
Space group	*Pbca*	*P*2$_1$/*c*
a/Å	11.148(2)	11.479(2)
b/Å	14.188(5)	13.426(3)
c/Å	23.425(3)	14.640(5)
β/deg		108.73(2)
V/Å^3	3705(2)	2136.8(9)
Z	8	4
d_{cal}/g cm^{-3}	1.999	1.901
μ/mm^{-1}	7.619	6.625
R $\{I > 2\sigma(I)\}$	$R1$ = 0.0525	0.0251
	$wR2$ = 0.1284	0.0692

$R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$.

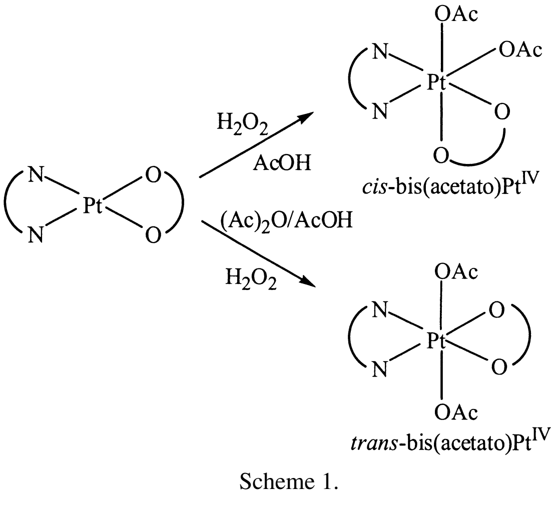
$wR2 = [\Sigma w(F_o^2-F_c^2)^2/\Sigma wF_o^2]^{1/2}$.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for *cis*-[$\mathrm{Pt^{IV}}$(O_2CCH_3)$_2$(cbdc)(dpda)] and *trans*-[$\mathrm{Pt^{IV}}$(O_2CCH_3)$_2$(cbdc)(dpda)]·$3H_2O$

	cis-	*trans-*
Pt–O(1)	2.01(1)	1.988(4)
Pt–O(3)	1.980(9)	2.003(3)
Pt-O(5)	2.03(1)	2.004(3)
Pt-O(7)	2.02(1)	1.999(3)
Pt-N(1)	2.06(1)	2.033(5)
Pt-N(2)	2.05(1)	2.014(4)
O(1)–Pt–O(3)	93.5(1)	96.9(1)
O(1)–Pt–O(5)	87.2(5)	87.6(2)
O(1)–Pt–O(7)	82.1(5)	91.2(2)
O(3)–Pt–O(5)	98.5(5)	96.3(2)
O(3)–Pt–O(7)	172.3(5)	91.2(1)
O(5)–Pt–O(7)	87.4(5)	172.5(1)
O(1)–Pt–N(1)	179.2(6)	176.7(2)
O(3)–Pt–N(1)	87.1(5)	84.7(2)
O(5)–Pt–N(1)	91.9(6)	94.9(2)
O(7)–Pt–N(1)	97.7(6)	85.9(2)
O(1)–Pt–N(2)	87.4(5)	83.4(2)
O(3)–Pt–N(2)	86.2(5)	178.9(2)
O(5)–Pt–N(2)	173.1(5)	84.7(2)
O(7)–Pt–N(2)	87.6(5)	87.8(2)
N(1)–Pt–N(2)	93.4(6)	94.9(2)

Results and Discussion

Syntheses. The oxidation of [$\mathrm{Pt^{II}}$(cbdc)(dpda)] in acetic acid by adding an aqueous 30% H_2O_2 solution exclusively yields *cis*-[$\mathrm{Pt^{IV}}$($OOCCH_3$)$_2$(cbdc)(dpda)]. On the other hand, *trans*-[$\mathrm{Pt^{IV}}$($OOCCH_3$)$_2$(cbdc)(dpda)] is only given when acetic anhydride is employed instead of acetic acid (Scheme 1). Since acetic anhydride immediately reacts with water to give acetic acid, the latter reaction should not be regarded as a reaction in pure acetic anhydride. Based on a simple estimation, the latter reaction must be considered as occurring in a mixture solvent consisting of acetic anhydride and acetic acid in a mole ratio of ca. 2:1. In either case, the product yield and selectivity



Scheme 1.

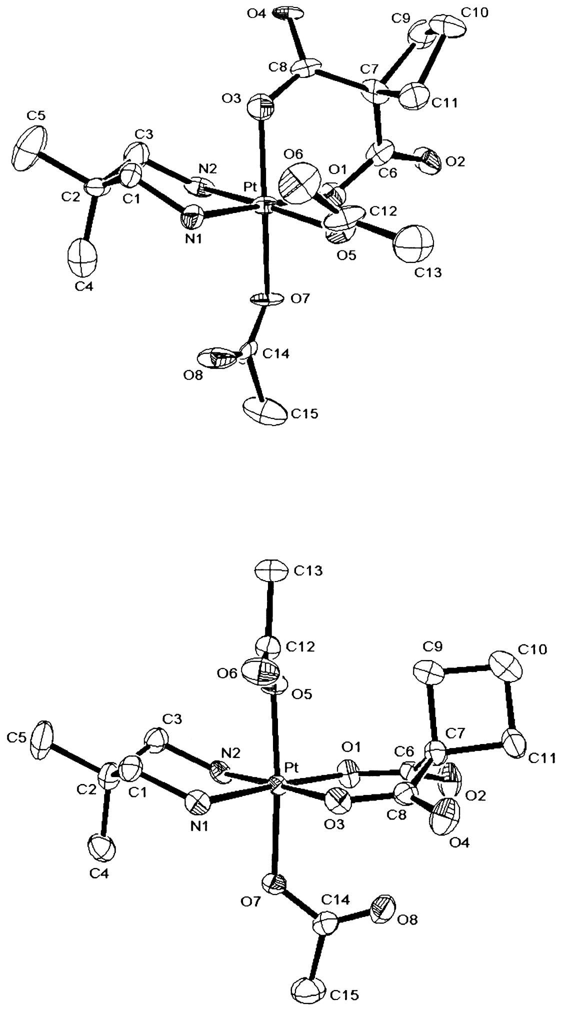


Fig. 1. ORTEP drawings of *cis*-[Pt^{IV}(O$_2$CCH$_3$)$_2$(cbdc)(dpda)] (top) and *trans*-[Pt^{IV}(O$_2$CCH$_3$)$_2$(cbdc)(dpda)]·3H$_2$O (bottom), where water molecules and hydrogen atoms are omitted for clarity.

were not affected neither by the change in the mole ration of reactants nor by the extension of reaction time. Exactly the same solvent-assisted modulation of the *cis/trans* isomerism was achieved in the H$_2$O$_2$ oxidation of [Pt^{II}(dbm)(dpda)] (see Experimental Section). All the platinum(IV) compounds described above were obtained as white solids that are soluble in common polar organic solvents and even in water.

Structures. The crystal structures of *cis*-[Pt^{IV}(OOCCH$_3$)$_2$-(cbdc)(dpda)] ([*cis*-cbdc]) and *trans*-[Pt^{IV}(OOCCH$_3$)$_2$(cbdc)-(dpda)] ([*trans*-cbdc]) are depicted in Fig. 1. For [*cis*-cbdc], the local geometry around the platinum(IV) atom approximates to a typical octahedral arrangement with two monodentate acetates coordinated in a *cis* position (O(5)–Pt–O(7) = 87.4(5)°). Concomitantly, a carboxylato moiety of the anionic cbdc in Pt^{II} species is converted to an axial site (O(1)–Pt–O(3) = 93.1(5)°) in [*cis*-cbdc]. In contrast, the corresponding angle (O(5)–Pt–O(7)) of [*trans*-cbdc] is 172.5(1)°, in which the chelate mode of the cbdc ligand is retained in two equatorial sites. Both isomers are discrete molecules with no close intermolecular contacts. The neutral amine ligand is bonded to the platinum(IV) in a bidentate fashion. No other exceptional features are observed. ^{1}H NMR spectrum of [*trans*-cbdc] exhibits relatively symmetric features because of its structural symmetry is higher than that found with [*cis*-cbdc], and therefore the assignments are straightforward. To the contrary, each corresponding component in [*cis*-cbdc] is observed as a pair of different resonances, where the assignments are unambiguously given based on the ^{1}H/^{13}C COSY NMR spectra. In a ^{13}C NMR spectra of [*cis*-cbdc], four carbonyl signals are observed in the range of 179–183 ppm, indicating that two carbonyl groups of either acetates or cbdc are magnetically inequivalent in solution (Supporting Information). On the other hand, only two carbonyl signals are observed in a ^{13}C NMR spectrum of [*trans*-cbdc] (Supporting Information). The ^{195}Pt NMR spectra of [*cis*-cbdc] and [*trans*-cbdc] in D$_2$O both consist of a singlet (δ = 1787 ppm for [*cis*-cbdc]; δ = 1758 ppm for [*trans*-cbdc]), reflecting the presence of a single platinum species in each solution. It is also conformed from the time-course of ^{1}H

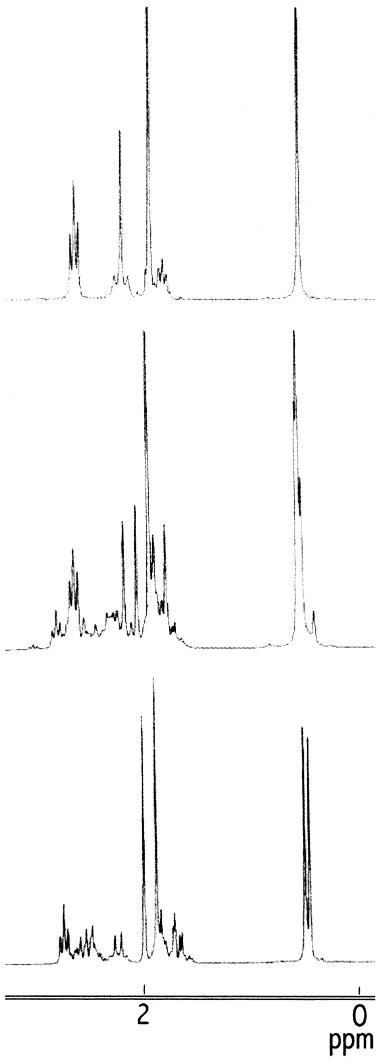


Fig. 2. ^{1}H NMR spectra of *trans*-[Pt^{IV}(O$_2$CCH$_3$)$_2$(cbdc)-(dpda)]·3H$_2$O (a) and *cis*-[Pt^{IV}(O$_2$CCH$_3$)$_2$(cbdc)(dpda)] (b) after leaving for 3 weeks in aqueous solution. Spectrum *b* reveals the presence of both the *cis* and *trans* isomers in the mole ration of 3:7. A spectrum recorded right after dissolution of a pure *cis* product is depicted in *c* for comparison.

NMR that [*trans*] is stable for a month in D_2O and that [*cis*] is very slowly converted into [*trans*] in D_2O (Fig. 2). After 3 weeks, [*cis*] was isomerized into [*trans*] by about 70%. However, [*trans*] does not undergo isomerization into [*cis*]. It means that this isomerization is an irreversible process.

Mechanistic Aspect. Why does the present oxidation selectively produce only one isomer in each medium? One is conducted in acetic acid in the presence of a small amount of water (ca. 3.5%), while the other in a 2:1 mixture of acetic anhydride and acetic acid, presumably in the presence of water. In the latter case, hydrogen peroxide may react with acetic anhydride to give peroxyacetic acid[14] and therefore the role of peroxyacetic acid should also be taken into consideration to account for the observed phenomena. First, *trans* → *cis* isomerization may be excluded since it is observed to be very slow in aqueous media. In fact, [*cis*-cbdc] undergos very slow isomerization into [*trans*-cbdc], ruling out an acid-catalyzed *trans* → *cis* isomerization. Second, *trans*-[$Pt^{IV}(OH)_2$(cbdc)(dpda)] does not react with acetic acid under the same reaction condition. This fact suggests that the turnstile mechanism[15] via the formation of a *trans*-bis(hydroxo)platinum(IV) intermediate is not involved in the selective formation of [*cis*-cbdc]. Third, the reaction of [Pt^{II}(cbdc)(dpda)] with peroxyacetic acid did not produce [*cis*-cbdc], indicating that peroxyacetic acid does not make any contribution to the formation of [*cis*-cbdc]. Studies on more detailed mechanisms are underway.

In conclusion, the present exclusive routes to *cis/trans*-bis(carboxylato)platinum(IV), for the first time, demonstrate that a delicate difference between acetic acid and acetic anhydride critically affects the geometrical isomerism of the product as well as the reactivity. This work may become a new landmark leading to rational synthetic strategies to obtain desirable geometrical isomers in coordination chemistry. Further experiments aimed at clarifying the mechanistic aspects and pervasive applications are in progress.

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