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Reaction of Tetrahydroxo(2,2-dimethylpropanediamine)platinum(IV) with Trimethylsilylchoride. Pentacoordinative Si···OH Interaction Labilizing the $Pt^{IV}-OH$ Bond

Kwan Mook Kim and Youn Soo Sohn*

Inorganic Chemistry Laboratory, Korea Institute of Science
and Technology, Seoul 130-650, Korea

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Introduction

A great deal of efforts has been made to find platinum(IV) anticancer drugs[1−8] along with platinum(II) complexes, but unfortunately none of those has been approved yet for use in humans. The synthetic variety of platinum(IV) complexes is limited due to their intrinsic inertness of Pt^{IV}−ligand bonds. The general synthetic route to platinum(IV) complexes is oxidation of predesigned platinum(II) complexes by hydrogen peroxide or halogens. In particular, the most popular pathway to preparing orally active platinum(IV) complexes[4−6] is oxidation of platinum(II) complexes A_2PtX_2 (A_2 = diamine, X = halide or carboxylate) to axial dihydroxy platinum(IV) complexes followed by carboxylation of their hydroxy ligands. However, little was reported on the electrophilic substitution reaction of tetrahydroxoplatinum(IV) complexes, although a few papers[1,2] described preparation of tetrahydroxoplatinum(IV) complexes. To our knowledge there is only one report on direct derivatization of $[Pt(OH)_4(NH_3)(c\text{-}C_6H_{11}NH_2)]$[5] using acetic anhydride as an electrophilic reagent. Similarly, we could also prepare tetracarboxylatoplatinum(IV) complexes by reacting tetrahydroxoplatinum(IV) complexes with acetic anhydride or acyl halide in the presence of triethylamine as an HCl acceptor in dichloromethane solution.[9] However, when we reacted tetrahydroxoplatinum(IV) complexes with trimethylsilylchloride as an electrophilic reagent, we could obtain only axially substituted disiloxyplatinum(IV) complexes instead of tetrasiloxyplatinum (IV) complexes. More surprising is that one or two of the equatorial hydroxide ligands were replaced by a chloride ion available in the reaction solution. Here we report the structures and properties of the disiloxyplatinum(IV) complexes.

Experimental Section

Materials and Instrumentation. Reagent grade potassium tetrachloroplatinate(II) (Kojima), 2,2-dimethylpropanediamine (dmpda) (Aldrich), trimethylsilyl chloride (Aldrich), and hydrogen peroxide (30%, Junsei) were used without further purification. Triethylamine (Aldrich) and dichloromethane (Baker) were purified by distillation over barium oxide and calcium hydride as drying agents. Dried THF (Baker) was obtained by distillation over sodium metal and benzoquinone.

Elemental analysis was performed by the Advanced Analysis Center at KIST. ^{1}H NMR spectra were recorded on a Varian Gemini-300 NMR spectrometer relative to $SiMe_4$ as an external standard.

Preparation of $(dmpda)Pt(OH)_4$. $(dmpda)Pt(SO_4)$(2.0 g, 4.66 mmol) prepared according to the known procedure[10] was oxidized with excess hydrogen peroxide(30%) in an aqueous solution at room temperature. The reaction solution was evaporated to minimum volume, and excess acetone was added. The precipitate thus obtained was dissolved in water and treated with anion-exchange resin (Amberlite IRA-420C, Aldrich). The concentrated solution was treated with methanol to obtain $(dmpda)Pt(OH)_4$ in 62.1% yield. Anal. Calcd for $C_5H_{18}N_2O_4Pt$: C, 16.4; H, 4.97; N, 7.67. Found: C, 16.7; H, 4.96, N, 7.01. ^{1}H NMR (D_2O): 2.43 (s (J_{Pt-H} = 27 Hz), 4H, methylene), 1.01 (s, 6H, methyl).

Synthesis of *cis,trans,cis*-$(dmpda)Pt(OSiMe_3)_2(OH)Cl$ (1). Trimethylsilyl chloride (2.5 mL) was dropped into a rapidly stirred solution of $(dmpda)Pt(OH)_4$ (1.0 mmol) suspended in a mixture of THF(20 mL) and triethylamine (5 mL) at room temperature. After 4 h, the resultant precipitate (Et_3NHCl) was filtered out and the filtrate was extracted with diethyl ether (300 mL). The ether layer was washed with water several times and then dried with $MgSO_4$. Concentration by evaporation of the dried solution resulted in a pale yellow crystalline compound in 71.5% yield. Anal. Calcd for $C_{11}H_{33}N_2O_3Si_2ClPt\cdot H_2O$: C, 24.2; H, 6.46; N, 5.13; Cl, 6.49. Found: C, 24.0; H, 6.55; N, 5.32; Cl, 6.18. ^{1}H NMR (acetone-d_6): amine ligand, 2.57 (br (J_{Pt-H} = 24 Hz), 2H, methylene), 2.47 (br (J_{Pt-H} = 30 Hz), 2H, methylene), 1.11 (s, 6H, methyl), 6.27 (br, 2H, NH_2), 5.13 (br, 2H, NH_2); siloxy ligand, 0.12 (s, 18H, methyl).

Synthesis of *cis,trans,cis*-$(dmpda)Pt(OSiMe_3)_2Cl_2$ (2). The compound was prepared by the same procedure used for **1**, but the reaction was performed at boiling temperature for 4 h. A yellow crystalline compound was obtained in 68.0% yield. Anal. Calcd for $C_{11}H_{32}N_2O_2Si_2Cl_2Pt$: C, 24.2; H, 5.90; N, 5.13; Cl, 13.0. Found: C, 24.1; H, 6.04; N, 4.91; Cl, 12.1. ^{1}H NMR(acetone-d_6): amine ligand, 5.70 (br, 4H, NH_2), 2.51 (t (J_{Pt-H} = 30 Hz), 4H, methylene), 1.14 (s, 6H, methyl); siloxy ligand, 0.09 (s,18H, methyl).

X-ray Structure Determination. All the X-ray data was 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 variation of intensities was 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 2 or 3 reflection planes with a χ value of near 90°. A direct or Patterson method (SHELXS-86)[11] was employed to locate the platinum atom. Subsequent cycles of Fourier map and least-squares refinements located other atoms (SHELXS-93).[12] Only Pt, Si, and Cl atoms were refined anisotropically for **2** because of unstable refinement, but all nonhydrogen atoms were refined anisotropically for **1**. 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 **1** and **2** are listed in Table 1.

Results and Discussion

Synthesis and Properties. The reaction of $(dmpda)Pt(OH)_4$ with trimethylsilyl chloride in THF solution containing triethy-

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Table 1. Crystallographic Data for **1** and **2**

	1	**2**
empirical formula	$C_{11}H_{33}C_{l1}N_2O_3Pt_1Si_2 \cdot H_2O$	$C_{10}H_{56}C_{l4}N_4O_8Si_2Pt_2$
fw	546.13	1061.11
cryst syst	monoclinic	orthorhombic
space group	$P2_1/c$ (No. 14)	$Pbca$ (No. 61)
a, Å	11.925(2)	13.5700(13)
b, Å	16.789(5)	23.4054(12)
c, Å	13.609(4)	30.802(4)
β, deg	113.55(2)	
V, Å^3	2497.7(11)	9783(2)
Z	4	8
d_{calcd}, g/cm^3	1.452	1.441
μ, mm^{-1}	5.832	6.105
θ range, deg	1.86−24.97	1.74−22.86
index ranges	$h, k, \pm l$	h, k, l
no. of reflcns obsd	2272	1866
no. of indep reflcns $\{I > 2\sigma(I)\}$	2151 [R(int) = 0.0259]	1866
refinement method	full-matrix least-squares on F^2	
data-to-parameter ratio	2151/190	1866/239
GOF on F^2	1.003	1.093
final R indices $\{I > 2\sigma(I)\}^a$	R1 = 0.0576, wR2 = 0.1369	R1 = 0.0834, wR2 = 0.168
R indices (all data)^b	R1 = 0.0632, wR2 = 0.1413	R1 = 0.1086, wR2 = 0.185
largest diff. peak and hole, e A^{-3}	1.075 and −0.814	1.670 and −1.187

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR2 = \{\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4\}^{1/2}$, where $w = 1/\{\sigma^2F_o^2 + (aP)^2 + bP\}$.

lamine as an HCl acceptor at room temperature afforded only disiloxyplatinum(IV) complexes in contrast to carboxylation reactions in which tetracarboxylatoplatinum(IV) complexes are easily obtained. Surprisingly, instead of further silylation, one of the two equatorial hydroxide ligands was replaced with a chloride ion available from the reaction solution. Extension of the reaction time to several hours resulted in the same reaction product. When the reaction was performed at refluxing condition, both equatorial hydroxide ligands were replaced by chloride ions. These disiloxyplatinum(IV) complexes are insoluble in water and nonpolar organic solvents but fairly soluble in organic solvents such as alcohol, acetone and diethyl ether.

^{1}H NMR spectra of **1** and **2** are shown in Figure 1. Resonances of the methyl protons of two axial siloxy groups in both compounds **1** and **2** appear as a singlet at 0.12 and 0.09 ppm, respectively, indicating large shielding effects by silicon atoms. The two spectra are apparently distinguished in the regions of methylene protons of the dmpda ligand which are expanded in the ellipsoids above each peak in the figure: four methylene protons of **1** exhibit two peaks centered at 2.57 ppm (2H) and 2.47 ppm (2H), whereas those in **2** exhibit a single peak centered at 2.51 ppm (4H). The splitting of those protons of **1** seems to be related with the asymmetric environment of the ligands (OH, Cl) trans to two amine nitrogens. The peak at 2.57 ppm in the spectrum of **1** is a triplet because of coupling with the adjacent amine protons and the peak at 2.47 ppm appears as a broad singlet which changes to a sharp singlet when it is decoupled from the amine protons. Both resonances are also coupled with the ^{195}Pt atom, exhibiting different coupling constants of 24 Hz for the peak at 2.57 ppm and 30 Hz for the peak at 2.47 ppm. The methylene protons of **2** also couples with amine protons and ^{195}Pt ($J_{\text{Pt-H}} = 30$ Hz) resulting in a triplet with the satellite peaks.

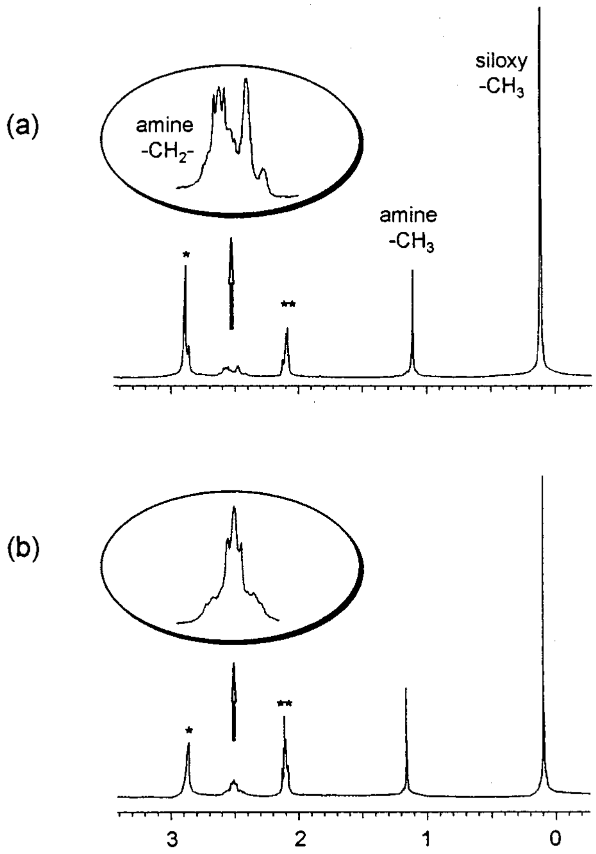

Figure 1. ^{1}H NMR spectra of **1** (a) and **2** (b) in acetone-d_6 (*, water peak; **, acetone peak). Amine -CH$_2$- peaks are expanded in the ellipsoids.

Figure 2 depicts the molecular structure of **1** with an atomic labeling scheme. Bond distances and angles for **1** are listed in Table 2. The carrier ligand dmpda in compound **1** coordinates to the platinum(IV) atom through two amine nitrogens in cis mode with a bite angle (N(1)−Pt−N(2)) of 93.6(12)°, forming a six-membered metallacyclic ring of chair conformation. The two siloxy groups are located in axial positions with normal Pt−O distances[13,14] of 1.963(13) Å (Pt−O(1)) and 1.93(2) Å (Pt−O(2)). Two equatorial positions are occupied by OH$^-$ and Cl$^-$ ligands. The Pt−Cl distance (2.314(5) Å) also falls in the range of usual Pt−Cl distances.[15,16]

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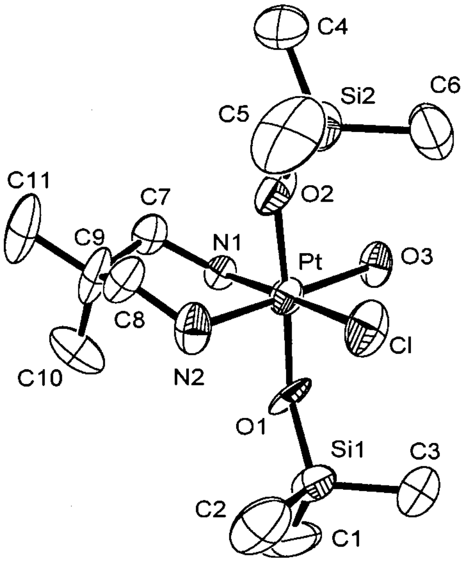

Figure 2. ORTEP drawing of (dmpda)Pt(OSiMe$_3$)$_2$Cl(OH) (**1**) with an atomic labeling scheme.

Table 2. Selected Bond Distances (Å) and Angles (deg) for **1**

Pt−O(2)	1.93(2)	Pt−O(1)	1.963(14)
Pt−N(2)	2.02(2)	Pt−O(3)	2.047(11)
Pt−N(1)	2.038(13)	Pt−Cl	2.314(5)
O(2)−Pt−N(2)	91.5(7)	O(1)−Pt−N(2)	90.2(7)
O(2)−Pt−O(3)	88.1(6)	O(1)−Pt−O(3)	90.1(6)
O(2)−Pt−N(1)	87.8(6)	O(1)−Pt−N(1)	83.9(6)
N(2)−Pt−N(1)	91.6(6)	O(3)−Pt−N(1)	88.0(5)
O(2)−Pt−Cl	93.6(4)	O(1)−Pt−Cl	94.7(4)
N(2)−Pt−Cl	88.3(5)	O(3)−Pt−Cl	92.1(4)
O(1)−Si(1)−C(1)	106.8(10)	O(1)−Si(1)−C(3)	110.9(10)
C(1)−Si(1)−C(3)	107.9(13)	O(1)−Si(1)−C(2)	113.7(10)
C(1)−Si(1)−C(2)	107.4(14)	C(3)−Si(1)−C(2)	109.9(12)
O(2)−Si(2)−C(5)	112.7(13)	O(2)−Si(2)−C(6)	111.7(11)
C(5)−Si(2)−C(6)	110(2)	O(2)−Si(2)−C(4)	105.1(10)
C(5)−Si(2)−C(4)	106.5(14)	C(6)−Si(2)−C(4)	110.7(13)
Si(1)−O(1)−Pt	137.4(9)	Si(2)−O(2)−Pt	138.1(8)

The two siloxy groups are oriented toward the chlorine atom as shown in the Figure. The distances of Si···Cl are 3.60 Å (Si(1)···Cl) and 3.54 Å (Si(2)···Cl), shorter than the sum of the van der Waals radii[17] of Si (2.1 Å) and Cl (1.7−1.9 Å), implying a significant interaction between Si and Cl atoms. The pentacoordinative Si···Cl interaction is also reflected in bond angles around Si atoms. The space inside of O(1), C(2), and C(3) is opened toward the chlorine atom, and the angles of O(1)−Si(1)−C(2) (113.7(10)°), O(1)−Si(1)−C(3) (110.9(10)°), and C(2)−Si(1)−C(3) (109.9(12)°) are larger than those of O(1)−Si(1)−C(1) (106.8(10)°), C(1)−Si(1)−C(3) (107.9(13)°) and C(1)−Si(1)−C(2) (107.4(14)°). This phenomenon is also observed for the atoms around Si(2).

cis,trans,cis-(dmpda)Pt(OSiMe$_3$)$_2$Cl$_2$ crystallizes in the orthorhombic unit cell with space group of *Pbca* (No.61). There are two molecules with a disordered chloroform molecule in the asymmetric unit. The molecular structure of one of the two molecules in the asymmetric unit is depicted in Figure 3, and its bond distances and angles are listed in Table 3. The molecular structure of the compound is similar to that of **1** in its coordination mode except for two equatorial ligands that are all chlorines.

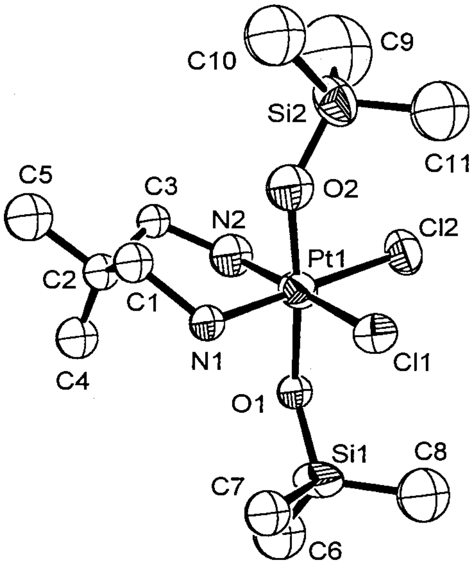

Figure 3. ORTEP drawing of one of the two conformers of (dmpda)-Pt(OSiMe$_3$)$_2$Cl$_2$ (**2**) with an atomic labeling scheme.

Table 3. Selected Bond Lengths (Å) and Angles (deg) for **2**

Pt(1)−O(2)	1.97(4)	Pt(1)−O(1)	2.05(3)
Pt(1)−N(2)	2.01(4)	Pt(1)−N(1)	2.00(3)
Pt(1)−Cl(1)	2.30(2)	Pt(1)−Cl(2)	2.32(2)
O(2)−Pt(1)−N(2)	93(2)	O(1)−Pt(1)−N(2)	83(2)
O(2)−Pt(1)−N(1)	84(2)	O(1)−Pt(1)−N(1)	92(2)
N(2)−Pt(1)−N(1)	96(2)	O(2)−Pt(1)−Cl(1)	86.9(12)
O(1)−Pt(1)−Cl(1)	96.9(10)	N(1)−Pt(1)−Cl(1)	82.5(12)
O(2)−Pt(1)−Cl(2)	93.4(12)	O(1)−Pt(1)−Cl(2)	90.3(10)
N(2)−Pt(1)−Cl(2)	88.3(14)	Cl(1)−Pt(1)−Cl(2)	93.4(6)
O(1)−Si(1)−C(7)	110(2)	O(1)−Si(1)−C(8)	114(3)
C(7)−Si(1)−C(8)	109(3)	O(1)−Si(1)−C(6)	103(2)
C(7)−Si(1)−C(6)	111(3)	C(8)−Si(1)−C(6)	111(3)
O(2)−Si(2)−C(10)	102(3)	O(2)−Si(2)−C(11)	110(3)
C(10)−Si(2)−C(11)	112(3)	O(2)−Si(2)−C(9)	116(3)
C(10)−Si(2)−C(9)	112(4)	C(11)−Si(2)−C(9)	106(4)
Si(1)−O(1)−Pt(1)	132(2)	Si(2)−O(2)−Pt(1)	138(3)

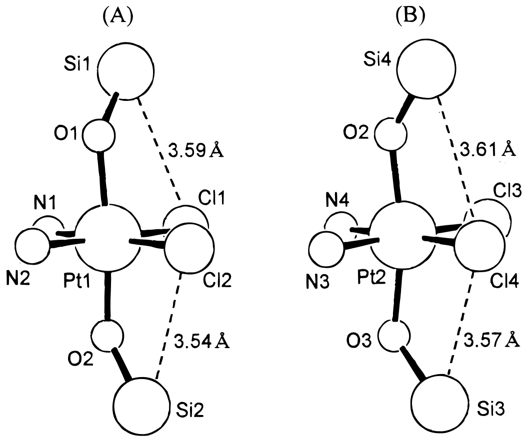

Figure 4. PLUTON diagram showing Si···Cl interaction in two conformers of (dmpda)Pt(OSiMe$_3$)$_2$Cl$_2$ (**2**).

The two molecules in the asymmetric unit closely resemble each other in their bond distances, but they have quite different conformations of ligands around the platinum(IV) atom. Figure 4 shows in a PLUTON diagram the framework of neighboring atoms around platinum(IV) for the two molecules. The orientation of Si atoms in the two molecules are different. The Si(1)

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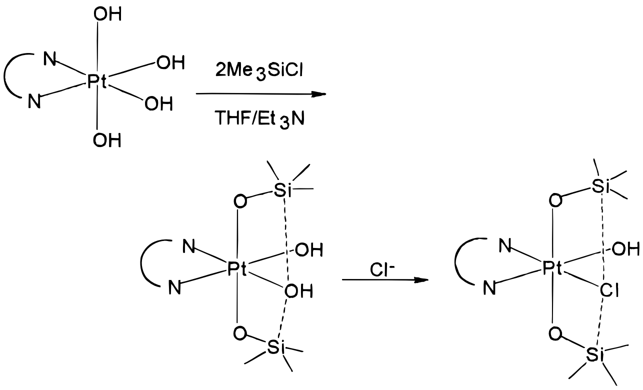
and Si(2) atoms in molecule A are oriented toward Cl(1) and Cl(2), respectively, but both Si(3) and Si(4) atoms in molecule B are directed only to Cl(4). In other words, the two molecules A and B are in a conformational isomeric relation in the solid state, which may be the first example of transition metal complexes. The distances between Si and Cl atoms are in the van der Waals interaction range of 3.5−3.7 Å. The bond angles around Si atoms also indicate the Si···Cl pentacoordinative interaction as in the case of compound **1**.

Reaction Mechanism. The reactions of (dmpda)Pt(OH)$_4$ with excess trialkylsilyl chloride at room and refluxing temperatures resulted in the formation of **1** and **2**, respectively. In both reactions only two silyl groups were introduced at axial positions by electrophilic substitution at the axial hydroxide ligands. Such introduction of two silyl groups in trans positions is certainly more favorable sterically than any cis positions, and therefore, silyl substitution at axial hydroxide ligands seems natural. However, an interesting question is why further substitution by a silyl group does not occur at the equatorial hydroxide groups, which are instead replaced by a chloride ion. It is seen from the molecular model that there is no critical steric hindrance for the third silyl group to attack on the equatorial hydroxide group, but it is presumed that once two silyl groups are introduced at axial positions, silicon atoms may interact with the oxygen atom of the equatorial hydroxy groups in the same fashion as with the chlorine atom, as was aforementioned in the X-ray structures of these siloxy complexes. Such a pentacoordinative Si···OH interaction seems to weaken and labilize the Pt−OH bond so that nucleophilic substitution by a chloride ion may easily take place. The second equatorial hydroxide group is replaced by a chloride ion at the higher energy condition. Therefore, as shown in Scheme 1, we propose that the reaction of the tetrahydroxoplatinum(IV) with trimethylsilyl chloride proceeds initially via electrophilic substitution at axial hydroxide groups, but once the axial substitution reactions are completed, nucleophilic substitution of the equatorial hydroxide groups by chloride ion follows without further silyl substitution by assistance of pentacoordinative Si···OH interaction. Such pentacoordinative interactions[18,19] of the silicon atom are found in many organic silicon compounds influencing the reactions, but such an interaction has not been found in platinum complexes.

Scheme 1



In summary, only disiloxyplatinum(IV) complexes were obtained from the reaction of (dmpda)Pt(OH)$_4$ with trialkylsilyl chloride, in contrast to the reaction with acetic anhydride producing tetraacetatoplatinum(IV) complexes. The electrophilic substitution reaction of (dmpda)Pt(OH)$_4$ with trialkylsilyl chloride at room temperature is followed by nucleophilic substitution of one of the two equatorial hydroxide groups by chloride ion available from the reaction solution. The same reaction at refluxing temperature resulted in displacement of another remaining hydroxy group by a chloride ion. The crystal structures of **1** and **2** show interesting pentacoordinative Si···Cl interactions, which afford the two molecules in the asymmetric unit of **2** to be in a conformational isomeric relation. The nucleophilic substitution of the hydroxide ligand by chloride ion is presumed to be assisted by a pentacoordinative Si···O interaction, which may be the first example of platinum complexes.

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Supporting Information Available: Tables of crystallographic details, non-hydrogen positional parameters, bond distances and angles, anisotropic thermal parameters of non-hydrogen atoms, and hydrogen coordinates and isotropic thermal parameters for **1** and **2** (13 pages). Ordering information is given on any current masthead page.

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