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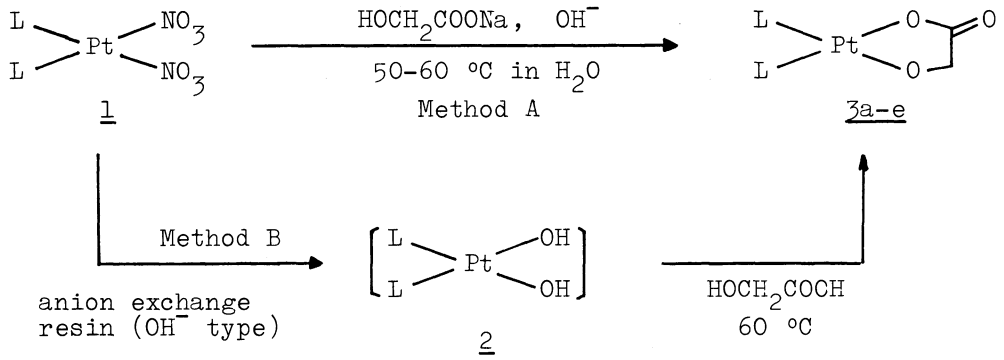
SYNTHESIS OF (GLYCOLATO-O,O')DIAMMINEPLATINUM(II) AND ITS RELATED COMPLEXES

Tetsushi TOTANI,* Katsutoshi AONO, Michihiro KOMURA, and Yasuko ADACHI
Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553

Glycolatoplatinum(II) complexes, $[Pt(OCOCH_2O)L_2]$, having a novel five-membered ring structure were obtained by adding an equimolar quantity of glycolic acid to cis-$[Pt(OH)_2L_2]$ (L: NH_3, amines) in water followed by heating. These complexes have also been obtained by reaction of cis-$[Pt(NO_3)_2L_2]$ with sodium glycolate in neutral aqueous solution. These complexes have been characterized by SIMS, IR, and NMR spectroscopy.

Since cisplatin, cis-dichlorodiammineplatinum(II), has proven to be effective on a variety of human cancers, a number of platinum complexes have been synthesized.[1] Among them there are antitumor dicarboxylato derivatives such as (1,1-cyclobutanedicarboxylato)diammineplatinum(II),[2] and (oxalato)(R,R-1,2-cyclohexanediamine)platinum(II).[3] While, non-ionic bidentate glycolatoplatinum(II) complex has not yet been known.

We now report a new class of neutral glycolatoplatinum(II) complexes having a novel ring structure in which glycolate is bound to the platinum ion as a bidentate ligand. These complexes were synthesized by method A and/or B as shown in Scheme 1, where each L denotes monodentate ammonia, alkylamine ligands or each L taken together forms a bidentate ligand in the case of cyclic (or acyclic) diamine.



Scheme 1.

Synthesis of (glycolato-O,O')diammineplatinum(II) (3a): In method A, cis-$[Pt(NO_3)_2(NH_3)_2]$ (1a) (2.0 mmol) was dissolved in H_2O (30 cm^3) and sodium glycolate (2.0 mmol) was added thereto. The mixture was adjusted to pH 7 with sodium hydroxide solution and stirred for 3 h. The resulting solution was concentrated at 50-60 °C under reduced pressure and remained solid was filtered, washed with a small amount of chilled water and dried *in vacuo* to yield 0.56 mmol (170 mg) of 3a. (Found: C; 7.77, H; 2.71, N; 9.34, Pt; 64.14%. Calcd for $C_2H_8N_2O_3Pt$: C; 7.92, H; 2.66, N; 9.24, Pt; 64.34%). In method B, a solution of 12.0 mmol of 1a in H_2O (150 cm^3) was passed through a column packed with anion exchange resin, Diaion SA10A (OH^- type, 160 cm^3). To the eluate was added 12.0 mmol of glycolic acid and the mixture was allowed to react for 24 h at room temperature. After additional heating for 6 h at 55 °C, the resulting solution was concentrated to give crystalline solid. The solid was filtered and crystallized from water to give 5.2 mmol (1.6 g) of colorless to slightly yellowish crystals of 3a. (Found: C; 7.75, H; 2.75, N; 9.41, Pt; 63.96%). According to method B, since the reaction of 1 to produce 2 proceeds quantitatively,[4] glycolic acid was used in an equivalent amount to 1. The reaction of 2 to afford 3 is usually completed within several hours at 58-60 °C. Method B was applicable to obtain all the complexes (3a-e). As these complexes are soluble and adequately stable in water under neutral conditions (unstable in acidic conditions), they could be readily purified by recrystallization from water. The solubility of 3a-e in water are listed in Table 1 along with their characterization data.

Table 1. Characterization data of the glycolatoplatinum(II) complexes $[Pt(OCOCH_2O)L_2]$

Compound[a]	L		Method	Yield/%[b]	Dp/°C[c]	δCH_2[d]	^1H NMR (J_{Pt-H})[e]	Solubility[f] / %
3a	NH_3	NH_3	A, B	A, 28: B, 43	130-	4.55	(34)	1.4
3b	$MeNH_2$	$MeNH_2$	B	44	170-	4.55	(34)	>10
3c	Me_2CHNH_2	Me_2CHNH_2	B	69	200-	4.52	(34)	4
3d	$H_2NCH_2CH_2NH_2$		A, B	A, 15: B, 51	165-	4.52	(33)	2.3
3e	DACH[g]		B	85	223-226	4.52	(34)	2.4

a) All complexes (3a-e) gave satisfactory elemental analyses and spectral data (IR, ^1H NMR). b) The isolated yield were calculated based on the nitrato complexes (1) used. c) All complexes decomposed without melting except for 3e. d) D_2O solution, δ from TMS as external reference in 90 MHz ^1H NMR. e) Coupling constants (Hz) between ^{195}Pt and ^1H. f) Solubility in water at room temperature. g) DACH: R,R-1,2-cyclohexanediamine.

The five-membered ring structure for the bidentate glycolato ligand was clearly established by analytical data and chemical evidence. ^1H NMR of 3a in D_2O (Fig. 1)

exhibited a singlet methylene signal at 4.55δ accompanied by satellite signals in the intensity ratio of 17:66:17[5] due to ^{195}Pt-H coupling (J_{Pt-H} = 34 Hz)[6] suggesting the presence of the Pt-O-CH_2 bond. ^{13}C NMR signals of methylene and carbonyl group of 3a were reasonably observed at 69.4 (singlet signal with satellites) and 195.9 (singlet signal) ppm, respectively from dioxane as an external reference. The spin-spin coupling between ^{195}Pt and ^{13}C of the methylene signal (19 Hz) is also attributed to the Pt-O-CH_2 bond. The ^{195}Pt NMR signal of this complex was detected at -30 ppm from K_2PtCl_4 as the external reference ($J_{Pt-^{14}N}$ = 230 Hz, quintet) and the IR spectrum revealed an intense absorption band at 1615 cm^{-1} due to the carbonyl

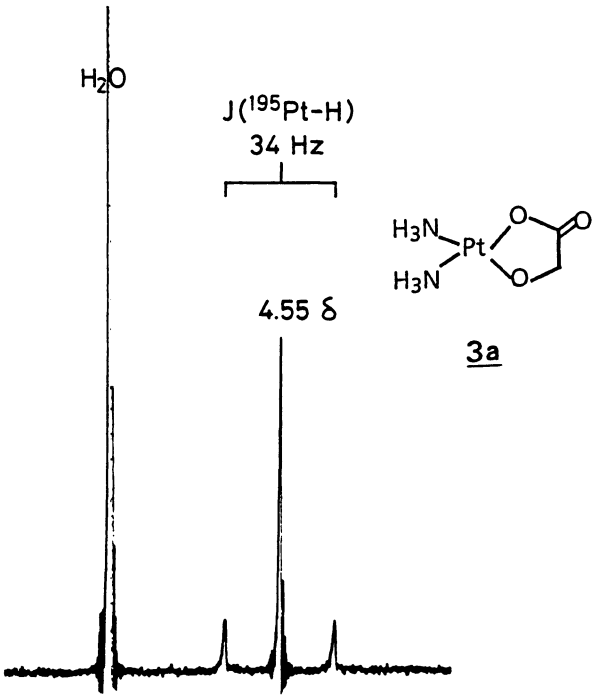


Fig. 1. ^{1}H NMR spectrum of (glycolato-O,O') platinum(II) (3a) in D_2O (external reference, TMS).

(1a) cis-$[Pt(OH)_2(NH_3)_2]$ + $HOCH_2COOH$ + $nHOCH_2COONa$ ⟶ $[Pt(OCOCH_2O)(NH_3)_2]$ (3a) (1)

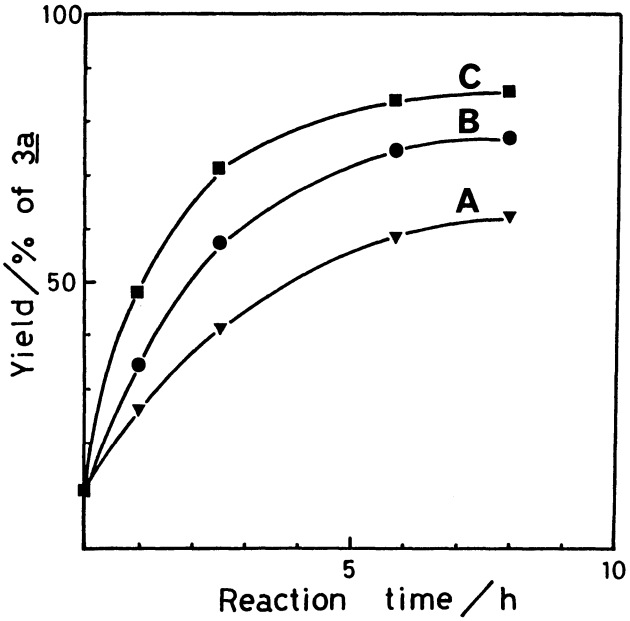


Fig. 2. Formation rate of 3a in the reaction of 1a with glycolate at 59 ± 2 °C. $[HOCH_2COONa]$ = none (curve A), 0.1 M (curve B), and 0.4 M (curve C). [1a] = 0.1 M and $[HOCH_2COOH]$ = 0.1 M.

group. An absorption band at 395 cm^{-1} was tentatively assigned to Pt-O stretching mode.[7] Protonated molecular ion peaks, MH^+ of 3a measured by means of SIMS at m/z = 303 (^{194}Pt, 33%), 304 (^{195}Pt, 34%) and 305 (^{196}Pt, 25%) strongly supported the structure shown in Fig. 1. The possible ionic structure of $[Pt(OCOCH_2OH)(NH_3)_2](OH)$ was excluded by the above mass spectral data in addition to the chemical evidence, i.e., 0.1% solution of 3a in water was neutral to slightly acidic, pH 6.85. If 3a takes the above structure, the presence of hydroxide ion would make the pH alkaline. Another possible polymeric structure, $+Pt(OCOCH_2O)(NH_3)_2+_m$ (m = 2, 3, ···), was also ruled out by mass spectral data which were consistent with the monomeric form as depicted in Fig. 1.

Figure 2 shows the relationship between reaction time and the yield of 3a *in situ*[8] for various molar ratios of sodium glycolate (n = 0, 1, and 4) based upon the reaction equation shown in Eq. 1. As the molar ratio of sodium glycolate for cis-$[Pt(OH)_2(NH_3)_2]$ increases (n = 0 to 4), the formation rate of 3a is accelerated and its yield can be significantly improved. However, the yield of 3a approaches to the limiting value of ca. 80% (n = 4) and remains constant at this state regardless of further increase of sodium glycolate ($n > 4$) and/or the reaction time (> 6 h).

In conclusion, non-ionic glycolatoplatinum(II) complexes having a novel five-membered ring structure were successfully obtained. The chemical structure of (glycolato-O,O')diammineplatinum(II) (3a) as a typical example of the complexes was confirmed by using mainly MS and NMR spectroscopy. The *in situ* yield of 3a was found to be improved by adding excess of glycolate ion.

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References

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4) The solution of 2 obtained from the aqueous solution of 1 by passing through the anion exchange resin (OH^- type) was quantitatively titrated with hydrochloric acid giving $[PtCl_2L_2]$.
5) Natural abundance of ^{195}Pt is 33.8% and its spin quantum number I = 1/2.
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8) Yield of 3a was determined by HPLC method.

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