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Note

Synthesis of water-soluble (tri(hydroxymethyl)phosphine)gold(I) complexes containing a nucleoside ligand

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Abstract

Water-soluble (tri(hydroxymethyl)phosphine)gold(I) complexes containing a nucleoside ligand, $[Au(Nuc)\{P(CH_2OH)_3\}]^+NO_3^-$ (Nuc = Guo, Ado, Cyd) have been synthesized by the reaction of $AuCl(P(CH_2OH)_3$ with the corresponding nucleoside in the presence of silver nitrate in ethanol at room temperature.

Key words: Gold complexes; Nucleoside complexes; Phosphine complexes

Gold(I) complexes carrying tertiary phosphine ligands such as triethylphosphine [1] and 1,2-bis(diphenylphosphino)ethane [2] have recently attracted attention as a novel family of possible metal containing antitumor drugs [3]. Though understanding of the interaction mechanism of the transition metal reagents with nucleosides is potentially important, coordination chemistry of gold complexes with nucleosides has been little explored. We previously reported series of gold(I) and (III) complexes having both triarylphosphine and nucleoside ligands [4–6]. The low solubility of these complexes in water is one of the essential problems especially for clinical purposes. In order to overcome this problem we have chosen tri(hydroxymethyl)phosphine [7] as a candidate to stabilize the gold(I)–nucleoside bond.

The ligand exchange reaction of chloro(cyclooctene)gold(I) [8] with a stoichiometric amount of tri(hydroxymethyl)phosphine in ethanol at room temperature gave a colorless powder of $AuCl\{P(CH_2OH)_3\}$ (**1**) in 83% yield [9].

$$Au(C_8H_{14})Cl + P(CH_2OH)_3 \longrightarrow \underset{\mathbf{1}}{AuCl[P(CH_2OH)_3]} \qquad (1)$$

^1H NMR of **1** in DMSO-d_6 shows a doublet at δ 4.13 for the methylene protons and a singlet at δ 5.59 for the hydroxyl group. Both signals are shifted downfield from those of free tri(hydroxymethyl)phosphine, being consistent with its coordination to Au(I) metal. In D_2O only the methylene signal was observed as a singlet (0.66 ppm from ext. dioxane). The signal of the hydroxyl proton was not observed due to fast H–D exchange with the solvent. The IR spectrum also shows a characteristic ν(OH) band at 3300 cm^{-1} and the ν(C=C) band of cyclooctene disappears.

Complex **1** showed no reactivity toward nucleosides in DMSO-d_6. However, when the chloride leaving group was replaced by the NO_3^- anion, gold(I) complexes having a nucleoside ligand, $[Au(Nuc)\{P(CH_2OH)_3\}]^+$-$NO_3^-$, were cleanly isolated. Attempted trials to isolate the cationic gold(I) intermediate by metathetical displacement of **1** with $AgNO_3$ failed in ethanol to induce the deposition of Au metal. Thus the reactions were performed in the presence of nucleosides such as guanosine (Guo), adenosine (Ado) and cytidine (Cyd) to give colorless solutions with grey precipitates of AgCl. Drying the filtrate solution and recrystallization of the residual solid in ethanol/hexane gave a colorless powder of $[Au(Nuc)\{P(CH_2OH)_3\}]^+NO_3^-$ (Nuc = Guo (**2**), Ado (**3**), Cyd (**4**)) in 46–65% yields**.

$$AuCl[P(CH_2OH)_3] + Nuc \xrightarrow[-AgCl]{+AgNO_3} [Au(Nuc)\{P(CH_2OH)_3\}]^+NO_3^- \qquad (2)$$

Nuc = Guo (**2**), Ado (**3**), Cyd (**4**)

These complexes were thermally stable and were characterized by elemental analysis and IR and NMR spectroscopy. Table 1 summarizes the NMR data for these complexes. The IR spectrum of **2** shows char-

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Yield, m.p. and analytical data for **1–**4**. **1**: 81%, m.p. = 105–106 °C. *Anal.* Found: C, 10.74; H, 2.74. Calc. for $C_3H_9O_3ClPAu$: C, 10.11; H, 2.55%. **2**: 65%, m.p. = 157–158 °C. *Anal.* Found: C, 23.52; H, 3.39; N, 12.29. Calc. for $C_{13}H_{22}N_6O_{11}PAu$: C, 23.43; H, 3.33; N, 12.61%. **3**: 46%, m.p. = 145–146 °C. *Anal.* Found: C, 24.49; H, 4.15; N, 12.72. Calc. for $C_{13}H_{22}N_6O_{10}PAu$: C, 24.01; H, 3.41; N, 12.92%. **4**: 47%, m.p. = 97–99 °C. *Anal.* Found: C, 23.04; H, 3.58; N, 8.28. Calc. for $C_{12}H_{22}N_4O_{11}PAu$: C, 23.01; H, 3.54; N, 8.95%.

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TABLE 1. Selected ^{1}H NMR data of $[Au(Nuc)\{P(CH_2OH)_3\}]^+NO_3^-$

Complex	Nuc	^{1}H NMR^a							
		H2	H5	H6	H8	NH	NH_2	OH	CH_2
1								5.59	4.13
2	Guo				8.52 (0.60)	11.13 (0.44)	6.82 (0.34)	5.75 (0.16)	4.25 (0.12)
3	Ado	8.37 (0.23)			8.67 (0.30)		8.37 (1.01)	5.68 (0.09)	4.26 (0.13)
4	Cyd		6.04 (0.32)	8.18 (0.40)			8.73, 8.02 (1.58, 0.86)	5.67 (0.08)	4.23 (0.10)

^{a}In DMSO-d_6 at room temperature. Chemical shifts are referred to TMS. Numbers in parentheses indicate downfield chemical shift change in ppm from free Nuc and **1**. Chemical shift change of signals due to ribose was within 0.1 ppm.

acteristic ν(CO) and δ(NH) bands at 1694 and 1610 cm^{-1} which are almost the same as those of free Guo, suggesting that these substituents are free from coordination. In ^{1}H NMR of **2** in DMSO-d_6, the signals assignable to NH, H8 and NH_2 appear at δ 11.13, 8.52 and 6.82, respectively. They are considerably shifted to lower field in comparison with those of free Guo. In particular, the chemical shift change of H8 is the largest, suggesting coordination of the neighboring N7 atom to Au, similar to other Guo coordinated gold and platinum complexes [9]. The methylene and hydroxyl signals are observed at δ 4.25 and 5.75, which are slightly shifted downfield. This fact indicates that the hydroxyl group is not involved in the coordination of Guo. Signals due to the ribose entities except for H1′ were not observed due to extensive broadening probably caused by fast H–D exchange processes.

Similar downfield chemical shift changes were observed for **3** and **4**. Only a slight change of the methylene and hydroxyl protons suggests a weak interaction of the tri(hydroxymethyl)phosphine ligand with these nucleosides. For **3**, the NH_2 and H2 protons appear at δ 8.37 and the H8 proton at δ 8.67. The coordination mode of Ado in **3** is not clear at present from the chemical shift change, though possible sites for coordination are the N7 and N1 atoms. In the case of **4**, the NH_2 protons in the Cyd ligand appear as two singlets at δ 8.73 and 8.02 which are largely shifted downfield by 1.58 and 0.86 ppm from those of free Cyd. Signals due to the H5 and H6 protons are found at δ 6.04 and 8.18 which are shifted by 0.32 and 0.40 ppm downfield from free Cyd, respectively. These results suggest the coordination of N3 in Cyd to Au.

When the corresponding free nucleoside was added to DMSO-d_6 solutions of **2**–**4**, the signals of the coordinated nucleosides gradually shifted to the chemical shift of the free nucleoside. This indicates that the coordinated nucleoside ligand is exchanging with free nucleoside in solution probably by an associative mechanism [6].

$$[Au(Nuc)\{P(CH_2OH)_3\}]^+NO_3^- + Nuc \rightleftharpoons [Au(Nuc)_2\{P(CH_2OH)_3\}]^+NO_3^- \quad (3)$$

All of these complexes isolated here were water soluble, as expected, and **4** is even hygroscopic under ambient conditions. Further developments in the present line would afford a new area of anticancer reagents.

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