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Preparation and Crystal Structure of New Gold(I) Complexes Linked to Pyrimidines

Takashi Amagai, T. Ken Miyamoto,* Hikaru Ichida, and Yukiyoshi Sasaki
Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113
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Two new gold(I) complexes linked to pyrimidines, (5-fluoro-2′-deoxyuridinato-N^3)(triphenylphosphine)-gold(I) (**1**) and [5-fluoro-1-(tetrahydro-2-furanyl)-2,4(1*H*,3*H*)-pyrimidinedionato-N^3](triphenylphosphine)gold(I) (**2**) were synthesized and characterized by ^{31}P, ^{1}H NMR and IR spectra. The structure of **2** was determined by an X-ray diffraction method. A linear, two-coordination around gold(I) has been shown. In order to estimate the possible alteration of **1** and **2** in vivo, several factors such as the effect of pH, and reactions with thiol, thiophenol, and imidazole were examined.

For a long time, gold(0) have been used as antirheumatoid drugs.[1] Recent progress in medicinal chemistry has led to a new finding that auranofin [(2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranosato-*S*)-(triethylphosphine)gold(I)] has not only antirheumatoid but anticancer activities.[2,3] Other gold(I) phosphine complexes, e.g. [bis[1,2-bis(diphenylphosphino)-ethane]gold(I) chloride] also show anticancer activities.[4] In these gold(I) compounds, a lot of thiolate or chloride complexes have been investigated extensively;[5] however, antitumor activities of gold(I) complexes containing nitrogen ligands have been not well-characterized.

Organic derivatives of 5-fluorouracil have been widely known as anticancer drugs. They contain nitrogen atoms, which can coordinate to metal atoms. By using these ligands, we have successfully synthesized new compounds.

In this paper, the preparation and crystal structure of these compounds are described. Additionally, the reactions of the complexes to thiol and imidazole are also mentioned.

Experimental

Materials. Chloro(triphenylphosphine)gold(I) were prepared by the literature method,[5] and further recrystallized from tetrahydrofuran (THF). Two pyrimidines, e.g., 5-fluoro-2′-deoxyuridine (5FdUrd) and 5-fluoro-1-(tetrahydro-2-furanyl)-2,4(1*H*,3*H*)-pyrimidinedione (tegafur) were offered by Mitsui Pharmaceutical Inc. Reagent grade solvents were used without further purification.

Measurements. Elemental analysis were carried out by analytical technicians in this department. ^{31}P NMR spectra at 36.4 MHz were recorded with a JEOL FX90Q in 10 mm-tubes using a 85% H_3PO_4 solution as an external reference. ^{1}H NMR spectra at 60 MHz were obtained with a Hitachi R24B in 5 mm-tubes. IR spectra were measured with a Hitachi 260-30.

Preparation of (5-Fluoro-2′-deoxyuridinato-N^3)(triphenylphosphine)gold(I) (1). All procedures were performed under an Ar atmosphere. Chloro(triphenylphosphine)-gold(I) 1.87 g (3.78 mmol), 5FdUrd 1.94 g (7.89 mmol) and KOH 0.43 g (7.66 mmol) were dissolved in H_2O (30 ml)/THF (30 ml). The solution was stirred at 50—60 °C; then the product was obtained as precipitation by evaporation of THF. The solid was filtered off and recrystallized from THF with addition of diethyl ether. (2.23 g; 83.8% yield) Calcd for $C_{27}H_{25}N_2O_5AuFP$ (M.W.=704.45): C, 46.04; H, 3.58; N, 3.98%. Found: C, 45.87; H, 3.79; N, 3.81%.

Preparation of [5-Fluoro-1-(tetrahydro-2-furanyl)-2,4-(1*H*, 3*H*)-pyrimidinedionato-N^3](triphenylphosphine)gold(I) (2). The complex was prepared by the same procedure as that of **1**. From chloro(triphenylphosphine)gold(I) 3.06 g (6.19 mmol), tegafur 2.98 g (14.9 mmol) and KOH 0.74 g (13.2 mmol), 2.53 g of **2** were obtained. (62.1% yield) Calcd for $C_{26}H_{23}N_2O_3AuFP$ (M.W.=658.42): C, 47.43; H, 3.52; N, 4.25%. Found: C, 47.05; H, 3.55; N, 3.96%.

Crystal Structure Determination. X-Ray diffraction intensities were measured on a Rigaku automated four-circle diffractometer with Mo *Kα* radiation at room temperature. Calculations were carried out with UNICS3 programs on a HITAC M-680H/M-682H computer at the Computer Centre of the University of Tokyo.[7]

Crystal dimensions were 0.6×0.15×0.15 mm. Intensities were collected for $4^\circ \leqq 2\theta \leqq 55^\circ$ by the ω–2θ scan technique. Independent 2722 points were collected and 2470 reflections with $F_o \leqq 2.5\sigma(F_o)$ were used for calculation. The position of the Au atom was determined by the heavy-atom method. Other atoms, except for H atoms, were located from subsequent Fourier syntheses. The positional and thermal parameters were refined by a block-diagonal least-squares method. The final *R*-value was 0.076.

Crystallographic data of **2** are as follows: Formula $C_{26}H_{23}N_2O_3AuFP$ (F.W.=658.42), monoclinic, space group $P2_1/n$, a=10.200(2) Å, b=26.115(5) Å, c=9.344(2) Å, β=102.05(3)°, V=2434 Å^3, D_x=1.797 g cm^{-3}, Z=4, μ=61.34 cm^{-1}. The atomic parameters are listed in Table 1. The complete F_o–F_c data are deposited as Document No. 8866 at the Office of the Editor of Bull. Chem. Soc. Jpn.

Examination of the Chemical Stability. A. Effect of pH. Since each complex has an extremely low solubility in H_2O, reactions were performed in two-layer solvents ($CHCl_3$–H_2O). A solution of each complex (0.2 mmol) in $CHCl_3$ (10 ml) was added to excess hydrochloric acid (pH=2, 40 ml), excess amount of aqueous KOH (pH=12, 40 ml) or 10 ml of distilled H_2O (pH=6). The solution was shaken vigorously for ten minutes in a separatory funnel. The organic layer was separated. The organic solution was evaporated to dryness and the residue was characterized by the ^{1}H NMR and IR spectra.

B. Reaction of 1 and 2 with Methanethiol, *p*-Toluenethiol, or Imidazole. Ethanethiol (0.4 mmol), *p*-toluenethiol (0.4 mmol), or imidazole (0.4 mmol) was added to a chloroform solution (10 ml) containing each complex (0.2 mmol). The solution was shaken vigorously for 10 minutes. Unreacted methanethiol, *p*-toluenethiol or imidazole was extracted into the aqueous KOH phase as potassium salts. The products in $CHCl_3$ were isolated by evaporation and characterized by the ^1H NMR and IR spectra.

Results and Discussion

Preparation and Characterization of 1 and 2. Compound **1** was obtained as a powdery solid, while **2** was obtained as colorless transparent pillar crystals. We also tried to prepare analogous (triethylphosphine)gold(I) derivatives; however, preparations of the products were unsuccessful under the present exprimental conditions.

Table 1. Positional Parameters ($\times 10^3$) and Isotropic Temperature Factors for Non-Hydrogen Atoms in **2**

Atom	x	y	z	B_{eq}/Å
Au	476.7(1)	376.5(1)	594.6(1)	4.0
P	332.3(6)	317.8(2)	642.3(7)	3.6
F	860(2)	519(1)	705(2)	8.3
O(1)	487(2)	429(1)	305(2)	6.6
O(2)	708(2)	440(1)	775(2)	6.3
O(3)	700(3)	545(1)	182(2)	8.8
N(1)	654(2)	486(1)	359(2)	4.6
N(2)	593(2)	434(1)	540(2)	3.5
C(1)	395(2)	343(1)	936(3)	5.2
C(2)	404(3)	332(1)	1088(3)	6.9
C(3)	368(3)	287(1)	1134(3)	5.6
C(4)	312(3)	249(1)	1033(3)	5.9
C(5)	301(3)	258(1)	880(3)	4.9
C(6)	344(2)	305(1)	837(2)	3.5
C(7)	74(3)	351(1)	660(3)	5.6
C(8)	−54(3)	370(1)	601(3)	5.7
C(9)	−88(3)	381(1)	450(3)	5.7
C(10)	3(3)	373(1)	360(3)	6.9
C(11)	130(3)	352(1)	420(2)	4.9
C(12)	162(2)	342(1)	567(3)	3.9
C(13)	235(3)	228(1)	497(3)	5.6
C(14)	256(3)	178(1)	444(3)	5.7
C(15)	382(3)	159(1)	453(3)	5.9
C(16)	492(3)	188(1)	518(3)	4.5
C(17)	480(3)	238(1)	568(2)	4.6
C(18)	347(2)	255(1)	559(2)	3.3
C(19)	575(2)	449(1)	399(2)	4.0
C(20)	693(2)	455(1)	647(3)	3.8
C(21)	770(2)	495(1)	602(3)	4.7
C(22)	752(2)	511(1)	459(3)	4.1
C(23)	631(3)	500(1)	196(3)	6.6
C(24)	685(3)	458(1)	111(3)	6.3
C(25)	825(3)	477(1)	112(4)	6.8
C(26)	803(4)	535(1)	99(4)	9.2

Coordination of 5-fluorouracil derivatives to gold(I) in **1** and **2** was confirmed by the ^{31}P, ^1H NMR and IR spectra.

^{31}P NMR of **1** (δ 31.7 in $CDCl_3$-THF) and **2** (δ 31.8 $CDCl_3$), proved to be upfield shifts, compared with that of chloro(triphenylphosphine)gold(I) (δ 33.4 in $CDCl_3$). The ^{31}P upfield shifts were also observed for other (triethylphosphine)gold(I)-(nitrogen ligand) compounds.[8,9] Thus, ^{31}P shifts imply that the nitrogen atom links to the gold(I) atom.

^1H NMR spectral data of **1** and **2** are summarized in Table 2. For **1**, the peak of pyrimidine H(6) proton shows an upfield shift, compared to that of free 5FdUrd, and overlaps with that of fifteen phenyl protons. While, for **2**, the peak of pyrimidine H(6) proton also shows an upfield shift compared with that of free tegafur, it does not overlap with fifteen phenyl protons. ^1H NMR results suggest again that those upfield shifts are caused by a coordination of the pyrimidines.

IR data of **1** and **2** are shown in Table 3. Characteristic absorption bands due to C=O were found in the range 1530—1660 cm^{-1} in these compounds. The C=O absorption peaks shift to a lower frequency than those of the free 5FdUrd or tegafur in the range 1650—1720 cm^{-1}. These results mean that the C=O bonds increase the single-bond character by the coordination, i.e., a part of bond electrons of C=O move toward nitrogen-gold(I) link.

Structure of 2. The molecular structure of **2** is illustrated in Fig. 1 by the use of ORTEP program.[10] Selected bond lengths and angles are listed in Table 4. Au(I) has almost a linear coordination. The lengths of Au-N and Au-P, and the angle of P-Au-N, agree with those of (phthalimidate)(triethylphosphine)gold(I) and (adeninate)(triethylphosphine)gold(I).[8,9] A deformation of ligands resulting through coordination is not found, except that the N(2) atom is slightly pulled toward the Au(I) atom; also, tetrahydrofuranyl moiety rotates around C(23)-N(1) bond. This rotation is

Table 3. IR Data for **1**, **2**, 5FdUrd, and Tegafur (KBr Disk)

Compound	ν/cm^{-1}
5FdUrd	3400, 1720, 1690, 1480, 1360, 1270, 1140, 1040
1	3400, 1650, 1600, 1520, 1430, 1100, 690, 540
tegafur	3040, 1720, 1690, 1650, 1470, 1400, 1270, 1070
2	3050, 1650, 1610, 1530, 1430, 1260, 1100, 700

Table 2. ^1H NMR Data for **1**, **2**, 5FdUrd, and Tegafur

Compound	δ			Solvent	Internal reference
	Phenyl protons	Pyrimidine proton	Other protons		
5FdUrd		8.10(1H; d)	2.35(2H, m), 4.00(1H, m), 4.35(2H, m), 6.30(1H, m)	D_2O	DSS
1	7.3 7.6(16H; m)		2.15(2H, m), 3.70(5H, m), 4.35(1H, m), 6.20(1H, m)	$CDCl_3$	TMS
tegafur		7.70(1H; d)	1.90(2H, m), 2.10(2H, m), 4.00(2H, m), 5.80(1H, m)	$CDCl_3$	TMS
2	7.3 7.5(15H; m)	7.20(1H; d)	2.00(4H, m), 4.00(2H, m), 5.95(1H, m)	DMSO-d_6	TMS

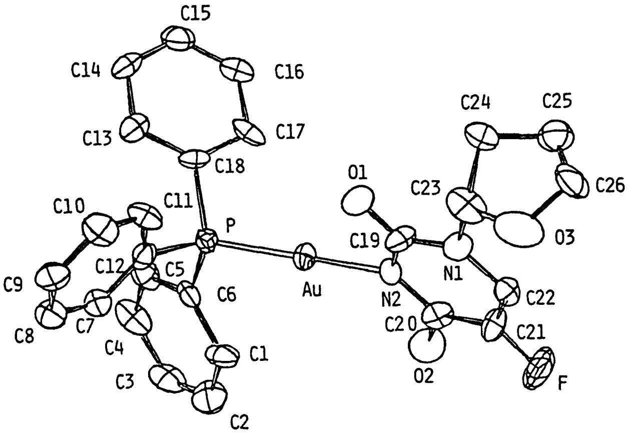

Fig. 1. Molecular structure of **2** showing the numbering system.

Table 4. Selected Bond Lengths (l/Å) and Angles (ϕ/°)

Bond length (l/Å)			
Au-P	2.235(7)	Au-N(2)	2.042(24)
P-C(6)	1.829(20)	F-C(21)	1.339(30)
O(1)-C(19)	1.233(27)	O(2)-C(20)	1.237(34)
O(3)-C(23)	1.390(39)	O(3)-C(26)	1.454(52)
N(1)-C(19)	1.360(34)	N(1)-C(22)	1.382(30)
N(1)-C(23)	1.536(34)	N(2)-C(19)	1.350(27)
N(2)-C(20)	1.389(30)	C(13)-C(14)	1.428(38)
C(13)-C(18)	1.364(35)	C(14)-C(15)	1.364(43)
C(15)-C(16)	1.385(39)	C(16)-C(17)	1.401(37)
C(17)-C(18)	1.413(37)	C(20)-C(21)	1.422(36)
C(21)-C(22)	1.375(39)	C(23)-C(24)	1.523(41)
C(24)-C(25)	1.510(44)	C(25)-C(26)	1.532(37)

Bond angle (ϕ/°)	
P-Au-N(2)	174.5(6)
Au-P-C(6)	114.5(8)
Au-N(2)-C(19)	119.3(16)
Au-N(2)-C(20)	119.3(17)
C(23)-O(3)-C(26)	109.6(24)
C(19)-N(1)-C(22)	122.5(20)
C(19)-N(1)-C(23)	117.7(18)
C(22)-N(1)-C(23)	119.8(23)
C(19)-N(2)-C(20)	121.3(23)
N(1)-C(19)-N(2)	120.5(19)
N(2)-C(20)-C(21)	116.5(24)
C(20)-C(21)-C(22)	122.7(21)
N(1)-C(22)-C(21)	116.4(22)
O(3)-C(23)-C(24)	108.3(26)
C(23)-C(24)-C(25)	101.8(22)
C(24)-C(25)-C(26)	101.6(25)
C(3)-C(26)-C(25)	104.2(28)

caused by stacking of the bulky triphenylphosphine group in the crystal. Substituent fluorine has only little effect on the molecular structure of pyrimidine skeleton.[11]

Examination of the Chemical Stability of 1 and 2. Compound **1** was stable against neutral or alkaline solutions (pH=12; aqueous KOH), but under acidic conditions (pH=2; hydrochloric acid), **1** was transformed to chloro(triphenylphosphine)gold(I). Compound **2** was stable under the above conditions. The instability of **1** is attributable to the existance of hydroxyl groups in **1**; polar hydroxyl groups may accelerate the reactions by hydrogen bond or proton affinity.

Both **1** and **2** reacted with methanethiol, *p*-toluenethiol or imidazole. In each case, the corresponding phosphine thiolate gold(I) complexes or phosphine imidazolato gold(I) complex were formed. These facts suggest that **1** and **2** have a possibility to react with a protein containing a cysteine or histidine residue in vivo.

Antitumor Activity. Preliminary antitumor antimal tests against Mouse Leukemia L1210 were carried out using female CDF_1 mice. While **2** showed comparable activity to tegafur, compound **1**, however, indicated an enhanced activity, compared with 5FdUrd. Further animal tests by use of Lymphocytic Leukemia P388 are in progress.

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