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Gold(I) complexes with biologically active thiolate ligands

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Abstract

The reaction of ethanolic solutions of Na(SR) (SR = 4-oxo-2-thioxopyrimidines) with [AuClL] (L = PPh_3, PPh_2Me and $AsPh_3$) gives [Au(SR)L]; when PPN[$AuCl_2$] or NBu_4[$AuBr(C_6F_5)$] are used instead, PPN[$Au(SR)_2$] and NBu_4[$Au(C_6F_5)(SR)$] are obtained. The structure of [$Au(SR^1)(PPh_3)$] has been established by X-ray diffraction, and shows a linear coordination at gold involving the phosphine phosphorus and the exocyclic sulfur atom of the organic ligand.

Keywords: Crystal structures; Gold complexes; Thiolate complexes

1. Introduction

The widespread applications of gold compounds containing gold–sulfur bonds, as 'liquid-gold' in ceramics [1], as gold–thiol interphases [2], in biochemistry [3] and medicine (chrysotherapy) [4], have stimulated research in this area. Thiolate gold(I) complexes, such as myocrisin, allochrysine or solganol, have been used as antiarthritic drugs since the 1920s [5]; more recently these compounds have been supplemented by phosphine complexes, e.g. auranofin ("Ridaura") which was approved for clinical use in 1985 [4]. Thiolate gold(I) complexes ([Au(SR)]$_n$, e.g. solganol and myocrisin) have been tested for anticancer activity, but they are not very cytotoxic; analogous phosphine complexes, [Au(SR)(PEt_3)] are extremely cytotoxic and active against P388 leukemia [6]. In addition, solganol has some inhibitory effects on HIV-1 (the etiologic agent of AIDS) [7].

In this paper we report the synthesis and characterization of thiolate gold(I) complexes [Au(SR)L], [$Au(SR)_2$]$^-$ or [$Au(C_6F_5)(SR)$]$^-$ with phosphine or arsine ligands L (L = PPh_3, PPh_2Me and $AsPh_3$). The compounds SRH, 3-aryl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydro[1]benzothieno[2,3d]-pyrimidines and 3-tolyl-4-oxo-2-thioxo-1,2,3,4-tetrahydro-quinazolines, were chosen on the basis of their previously known medical properties (Fig. 1); such organic

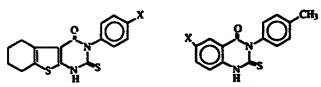

Fig. 1.

derivatives have shown biological activity against tuberculosis [8], as anticonvulsants [9], as antimalarial agents [10], against microorganisms [11], as electroshock and chemishock protection agents and central system nerve depressants [9].

2. Experimental

The C, H, N and S analyses were carried out on a Perkin-Elmer 2400 Microanalyser. Conductivity measurements were carried out in approximately 5×10^{-4} mol dm^{-3} acetone solutions, with a Jenway 4010 conductimeter. The melting points were measured in a Gallenkamp apparatus and are uncorrected. The infrared spectra were recorded (4000–200 cm^{-1}) on a Perkin-Elmer 599 spectrophotometer, using Nujol mulls between polyethylene sheets. The NMR spectra were recorded on a Bruker ARX 300 spectrometer in $CDCl_3$. Chemical shifts are cited relative to $SiMe_4$ (external, ^1H), 85% H_3PO_4 (external, ^{31}P) and $CFCl_3$ (external, ^{19}F). Mass

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Table 1
Analytical and spectroscopic data for products

	Complex	Analysis (%) [a]				Λ_M [b]	M.p. (°C)	Yield (%)	m/z (%)	ν_{as}(C=S) [c] (cm^{-1})	$^{31}P\{^1H\}$ [f]
		C	H	N	S						
1	[Au(SR^1)(PPh_3)]	51.95 (52.35)	3.5 (3.75)	3.4 (3.45)	7.85 (7.95)	1	230	79	803[M^+](63)	1167	37.4(s)
2	[Au(SR^2)(PPh_3)]	52.8 (53.45)	3.2 (3.8)	3.45 (3.55)	7.75 (8.15)	4	212 [d]	82	787[M^+](60)	1196	37.4(s)
3	[Au(SR^3)(PPh_3)]	51.6 (52.1)	3.4 (3.3)	3.65 (3.7)	4.2 (4.2)	1	209 [d]	73	761[M^+](67)	1100	37.3(s)
4	[Au(SR^4)(PPh_3)]	54.0 (54.55)	3.35 (3.6)	3.6 (3.85)	4.1 (4.4)	6	204	41	727[M^+](73)	1101	37.8(s)
5	[Au(SR^2)(PPh_2Me)]	49.4 (49.7)	3.6 (3.85)	3.55 (3.85)	8.45 (8.85)	7	125	56	725[M^+](42)	1173	21.6(s)
6	[Au(SR^3)(PPh_2Me)]	47.75 (48.1)	2.75 (3.3)	3.75 (4.0)	4.5 (4.6)	2	197 [d]	36	699[M^+](67)	1104	22.2(s)
7	[Au(SR^4)(PPh_2Me)]	50.0 (50.6)	3.25 (3.6)	3.8 (4.2)	4.25 (4.8)	14	132	52	665[M^+](22)	1105	20.5(s)
8	[Au(SR^1)($AsPh_3$)]	49.15 (49.6)	3.4 (3.55)	3.2 (3.3)	7.5 (7.5)	2	212 [d]	54	847[M^+](84)	1167	
9	[Au(SR^2)($AsPh_3$)]	50.25 (50.6)	3.55 (3.6)	3.2 (3.35)	7.5 (7.7)	4	192	81	831[M^+](65)	1165	
10	[Au(SR^3)($AsPh_3$)]	47.5 (47.75)	3.0 (3.1)	3.3 (3.5)	3.9 (3.95)	[c]	219 [d]	60	805[M^+](100)	1107	
11	[Au(SR^4)($AsPh_3$)]	51.15 (51.45)	3.0 (3.35)	4.1 (3.65)	4.75 (4.2)	[c]	208	37	771[M^+](44)	1185	
12	PPN[Au(SR^4)$_2$]	61.9 (62.4)	4.2 (4.1)	5.45 (5.5)	4.95 (5.05)	106	195	15	731[M^-](100)	1116	
13	NBu_4[Au(C_6F_5)(SR^2)]	49.75 (50.1)	5.4 (5.45)	4.95 (4.5)	6.8 (6.9)	109	189 [d]	67	691[M^-](100)	1197	
14	NBu_4[Au(C_6F_5)(SR^4)]	50.5 (50.8)	5.1 (5.4)	3.55 (3.65)	4.8 (4.8)	109	155 [d]	37	631[M^-](100)	1019	

[a] Calculated values are given in parentheses.
[b] In acetone, values in Ω^{-1} cm^2 mol^{-1}.
[c] Low solubility.
[d] Decomposes without melting.
[e] Data for free ligands: SR^1H 1172, SR^2H 1225, SR^3H 1134 and SR^4H 1200 cm^{-1}.
[f] In $CDCl_3$. δ in ppm.

spectra were recorded on VG Autospec FAB Technique, using 3-nitrobenzylalcohol as matrix. The elemental analyses, conductivities, melting points, yield, and spectroscopic data of the new complexes are listed in Table 1.

2.1. Syntheses

The starting materials [AuCl(PPh_3)] [12], [AuCl(PPh_2Me)] [12], [AuCl($AsPh_3$)] [13], PPN[$AuCl_2$] [14], NBu_4[$AuBr(C_6F_5)_2$] [12] and (SRH) [15] were prepared according to literature methods. All reactions were carried out in air using absolute ethanol as solvent without further purification.

2.1.1. [Au(SR)L]: {L = PPh_3 R = R^1 1, R^2 2, R^3 3, R^4 4; L = PPh_2Me R = R^2 5, R^3 6, R^4 7; L = $AsPh_3$ R = R^1 8, R^2 9, R^3 10, R^4 11}

To an ethanolic solution (30 cm^3) of the corresponding ligand SRH [R = R^1 (0.034 g, 0.1 mmol), R^2 (0.033, 0.1 mmol), R^3 (0.030 g, 0.1 mmol), or R^4 (0.027 g, 0.1 mmol)] was added 5 cm^3 of an ethanolic NaOH solution (0.1 M). After 15 min [AuClL] [L = PPh_3 (0.049 g, 0.1 mmol), PPh_2Me (0.043 g, 0.1 mmol), or $AsPh_3$ (0.054 g, 0.1 mmol)] was added. After 3 h of stirring, the solutions were concentrated to 5 cm^3; addition of hexane (15 cm^3) led to precipitation of white solids.

2.1.2. PPN[Au(SR^4)$_2$] 12

To an ethanolic solution (30 cm^3) of SR^4H (0.027 g, 0.1 mmol) was added 5 cm^3 of an ethanolic NaOH solution (0.1 M). After 15 min PPN[$AuCl_2$] (0.040 g, 0.05 mmol) was added. After 2 h of stirring the solution was filtered through diatomaceous earth; on partial removal of the solvent a yellow complex was obtained.

2.1.3. NBu_4[Au(C_6F_5)(SR)]: {R = R^2 13, R^4 14}

To an ethanolic solution (30 cm^3) of the corresponding ligand SRH [R = R^2 (0.033, 0.1 mmol), R^4 (0.027 g, 0.1 mmol)] was added 5 cm^3 of an ethanolic NaOH solution (0.1 M). After 15 min NBu_4[$AuBr(C_6F_5)$] (0.069 g,

0.1 mmol) was added. After 3 h of stirring the solutions were concentrated to 5 cm^3; addition of hexane (15 cm^3) led to precipitation of white solids. ^{19}F NMR (ppm) **13**: δ −115.0 (m, 2F, F*o*), −161.4 (t, $^3J_{FpFm}$ = 20.3 Hz, 1F, F*p*), −163.2 (m, 2F, F*m*). **14**: δ −115.2 (m, 2F, F*o*), −161.6 (t, $^3J_{FpFm}$ = 20.2 Hz, 1F, F*p*), −163.4 (m, 2F, F*m*).

2.2. Crystal structure determination of [Au(SR')(PPh$_3$)]

2.2.1. Crystal data

1, $C_{35}H_{30}AuN_2O_2PS_2$, M_r = 802.67, monoclinic, space group *C*2/*c*, a = 19.088(2), b = 14.248(2), c = 23.502(3) Å, β = 104.950(10)°, U = 6175.4(13) Å^3, Z = 8, D_c = 1.727 Mg m^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 4.987 mm^{-1}, $F(000)$ = 3168, T = −100°C.

2.2.2. Data collection and reduction

Single crystals were obtained by a slow diffusion of *n*-hexane into a dichloromethane solution of complex **1**. A colourless prism 0.40 × 0.25 × 0.20 mm was used to collect 5717 intensities to $2\theta_{max}$ 50° (Siemens R3 diffractometer, monochromated Mo Kα radiation) of which 5332 were independent (R_{int} = 0.046). An absorption correction based on Ψ scans was applied, with transmission factors 0.649–0.768. Cell constants were refined from setting angles of 48 reflections in the range 2θ = 5.7–25°.

2.2.3. Structure solution and refinement

The structure was solved by the heavy-atom method and subjected to full-matrix least-squares refinement on F^2 (SHELXL-93) [16]; all non-H atoms were refined anisotropically, H atoms were included using a riding model or rigid methyls. Refinement proceeded to $wR(F^2)$ 0.058 for 5331 reflections, 389 parameters and 336 restraints, conventional $R(F)$ 0.031, $S(F^2)$ = 0.884, max. $\Delta\rho$ = 0.79 e Å^{-3}.

3. Results and discussion

In the compounds SRH (Fig. 1) the hydrogen atom bonded to nitrogen can be removed by base in alcoholic solution. Addition of [AuClL] to a freshly prepared ethanolic solution of Na(SR) leads to the following gold complexes:

$$[AuClL] + Na(SR) \rightarrow [Au(SR)L] + NaCl \quad (1)$$

L = PPh_3 R = R' **1**, R^2 **2**, R^3 **3**, R^4 **4**
L = PPh_2Me R = R^2 **5**, R^3 **6**, R^4 **7**
L = $AsPh_3$ R = R' **8**, R^2 **9**, R^3 **10**, R^4 **11**

The elemental analyses are in agreement with the proposed stoichiometry and the acetone solutions are non-conducting. The IR spectra lack the characteristic ν_{st}(N–H) ≈ 3200 cm^{-1}. The free ligands show C=S stretching frequencies higher than those of the new complexes **1–11** (Table 1) suggesting a lower C–S bond order in the latter, and thus coordination by the exocyclic sulfur of the ligand.

The ^1H NMR spectra lack the singlet at δ > 9 ppm (N–H) of the free ligands. The phosphine complexes show a singlet in $^{31}P\{^1H\}$ NMR spectra; in the PPh_3 derivatives this resonance appears at δ ≈ 37 ppm, which is a normal value for a P–Au–S but not for a P–Au–N (≈29 ppm) arrangement [17]. These data also suggest coordination through a sulfur atom of the ligand.

The mass spectra (FAB+) of **1–11** show the parent peak at *m*/*z* values and intensities shown in Table 1. It is noteworthy that $[M+AuL]^+$ fragments are present in all the cases with lower intensities than parent peaks. The addition of AuL^+ (L = PPh_3, PPh_2Me, $AsPh_3$) fragments in the mass spectra of thiolate gold complexes, by FAB$^+$ or electrospray technique, has been recently reported [18].

The structure of complex [Au(SR')(PPh_3)] **1** has been established by single crystal X-ray diffraction (Fig. 2). Atomic coordinates are shown in Table 2 and selected bond lengths and angles in Table 3. The gold atom in **1** exhibits the expected linear geometry defined by the phosphorus atom of the triphenylphosphine and the sulfur atom of the thiolate ligand; the angle P–Au–S is 177.77(5)°. Unlike some other phosphinegold(I) thiolate complexes, there are no short intermolecular contacts in the lattice, probably because the bulkiness of this thiolate ligand prevents further contacts between the gold atoms. The Au–P distance is 2.257(1) Å and is very similar to those found in [Au(SR')PPh_3] (SR' = $SC_5N_4H_3$ (purine-6-thiolate) [19]; $SC_4N_2H_3$ (pyrimidine-2-thiolate) [20]; $SC_4N_2H_3$ (2-thiouracil) [21]) derivatives, which lie in the range 2.237(2), 2.253(2) and 2.248(2) Å, respectively. The Au–S(1) bond length is 2.323(1) Å, slightly longer than those in the latter complexes [2.287(1), 2.310(3) and 2.298(2) Å]. The S(1)–C(1) distance is 1.730(5) Å, as expected for a C(sp^2)–S single bond, and the N(1)–C(1) bond is the shortest in the six-membered heterocycle at 1.325(6) Å. The Au···N(1) distance,

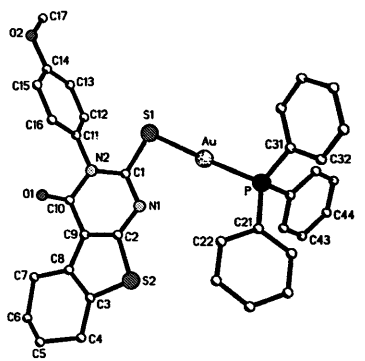

Fig. 2. The molecule of complex **1** in the crystal, showing the atom numbering scheme. Hydrogen atoms are omitted for clarity. Atomic radii are arbitrary.

Table 2
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **1**

	x	y	z	U_{eq} [a]
Au	2528.4(1)	−784.7(2)	6724.5(1)	22.7(1)
P	2979.1(8)	451.9(10)	7303.5(6)	23.2(3)
S(1)	2060.7(7)	−2089.1(9)	6160.9(6)	24.4(3)
S(2)	999.8(8)	982.1(9)	4921.1(6)	27.2(3)
N(1)	1493(2)	−582(3)	5535(2)	20.1(10)
N(2)	1101(2)	−2070(3)	5106(2)	19.4(10)
O(1)	253(2)	−2239(3)	4231(2)	32.9(10)
O(2)	1578(2)	−5936(3)	5154(2)	40.4(10)
C(1)	1512(3)	−1511(4)	5563(2)	19.7(11)
C(2)	1048(3)	−219(3)	5036(2)	20.7(11)
C(3)	382(3)	840(4)	4238(2)	23.1(11)
C(4)	91(3)	1646(4)	3836(2)	28.1(13)
C(5)	−167(4)	1293(4)	3219(3)	44(2)
C(6)	−631(3)	439(4)	3175(3)	44(2)
C(7)	−297(3)	−392(4)	3545(2)	29.7(13)
C(8)	218(3)	−87(4)	4111(2)	22.8(12)
C(9)	607(2)	−693(4)	4573(2)	19.8(10)
C(10)	607(3)	−1700(4)	4595(2)	22.2(12)
C(11)	1204(3)	−3078(4)	5127(2)	21.4(12)
C(12)	814(3)	−3649(4)	5403(2)	24.9(13)
C(13)	927(3)	−4618(4)	5413(2)	25.9(13)
C(14)	1427(3)	−4991(4)	5151(2)	28.9(13)
C(15)	1819(3)	−4416(4)	4870(2)	28.2(13)
C(16)	1713(3)	−3466(4)	4852(2)	26.3(13)
C(17)	1224(4)	−6540(4)	5474(3)	49(2)
C(21)	3067(3)	1498(4)	6896(2)	23.3(12)
C(22)	2989(3)	1445(4)	6291(2)	30.0(13)
C(23)	2999(3)	2246(4)	5957(3)	37.4(15)
C(24)	3089(3)	3109(4)	6226(3)	34.9(14)
C(25)	3166(3)	3176(4)	6825(3)	31.5(14)
C(26)	3153(3)	2382(4)	7160(2)	26.8(12)
C(31)	3852(3)	180(4)	7800(2)	24.9(12)
C(32)	4372(3)	852(5)	8030(2)	39.1(14)
C(33)	5037(3)	594(5)	8392(3)	49(2)
C(34)	5197(3)	−309(5)	8527(3)	48(2)
C(35)	4682(4)	−998(5)	8301(3)	57(2)
C(36)	4018(3)	−745(5)	7942(2)	42.6(15)
C(41)	2387(2)	841(4)	7752(2)	22.7(11)
C(42)	1805(3)	1422(4)	7500(2)	31.5(14)
C(43)	1328(3)	1698(4)	7817(3)	35.5(14)
C(44)	1408(3)	1398(4)	8383(3)	35.5(14)
C(45)	1976(3)	810(5)	8637(2)	36.5(13)
C(46)	2469(3)	534(3)	8323(2)	28.2(12)

[a] U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

2.992 Å, may correspond to a very weak interaction but scarcely perturbs the almost ideal linearity at the gold centre.

Some anionic derivatives have been obtained by reacting anionic gold(I) complexes, containing one or two halides, with the SR ligand in the appropriate molar ratio (1:1 or 1:2). Three examples that may be regarded as general procedures are as follows:

$$PPN[AuCl_2] + 2Na(SR^4) \rightarrow \underset{\mathbf{12}}{PPN[Au(SR^4)_2]} + 2NaCl \quad (2)$$

$$NBu_4[AuBr(C_6F_5)] + Na(SR) \rightarrow \underset{R=R^2\ \mathbf{13},\ R^4\ \mathbf{14}}{NBu_4[Au(C_6F_5)(SR)]} + NaBr \quad (3)$$

Table 3
Selected bond lengths (Å) and angles (°) for **1**

Au–P	2.257(1)	Au–S(1)	2.323(1)
S(1)–C(1)	1.730(5)	S(2)–C(2)	1.731(5)
S(2)–C(3)	1.742(5)	N(1)–C(1)	1.325(6)
N(1)–C(2)	1.360(6)	N(2)–C(1)	1.403(6)
N(2)–C(10)	1.425(6)	C(2)–C(9)	1.370(7)
C(3)–C(8)	1.372(7)	C(8)–C(9)	1.435(7)
C(9)–C(10)	1.436(7)		
P–Au–S(1)	177.77(5)	C(1)–S(1)–Au	98.3(2)
C(2)–S(2)–C(3)	91.4(3)	C(1)–N(1)–C(2)	115.2(4)
C(1)–N(2)–C(10)	123.6(4)	N(1)–C(1)–N(2)	121.8(5)
N(1)–C(1)–S(1)	121.3(4)	N(2)–C(1)–S(1)	116.9(4)
N(1)–C(2)–C(9)	128.0(5)	N(1)–C(2)–S(2)	120.4(4)
C(9)–C(2)–S(2)	111.5(4)	C(8)–C(3)–C(4)	125.0(5)
C(8)–C(3)–S(2)	112.0(4)	C(4)–C(3)–S(2)	122.9(4)
C(3)–C(8)–C(9)	111.7(5)	C(3)–C(8)–C(7)	122.1(5)
C(9)–C(8)–C(7)	126.2(5)	C(2)–C(9)–C(8)	113.4(5)
C(2)–C(9)–C(10)	118.1(5)	C(8)–C(9)–C(10)	128.5(5)
N(2)–C(10)–C(9)	113.2(4)		

The acetone solutions of complexes **12–14** show conductivity values in agreement with a formulation as 1:1 electrolytes [22]. Complexes **13**, **14** show in the ^{19}F NMR spectra three groups of resonances in a 2:1:2 ratio for the *ortho*, *para* and *meta* fluorine atoms in accordance with other pentafluorophenyl complexes.

The mass spectra (FAB −) of complexes **12–14** show the corresponding anion as the base peak. Higher *m/z* fragments are present at *m/z* 1195 (6%, **12**) $[M+AuSR^4]^-$, 1055 (17%, **13**) $[M+Au(C_6F_5)]^-$, 995 (23%, **14**) $[M+Au(C_6F_5)]^-$. These data show the high stability of the anions and that the fragment addition to thiolate gold complexes also occurs in negative FAB conditions.

The coordination through the sulfur atoms in complexes **12–14** is similarly supported by the IR data. The characteristic ν_{st}(N–H) of the ligand are absent in the IR of the new complexes, which also show a decrease in the ν_{st}(C=S) frequencies.

Supplementary material

Full details of the structure determination have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany. Any request for this material should quote a full literature citation and the reference number CSD 405 368.

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