Inorg. Chem. **2007**, *46*, 6236–6238

Novel Gold(I) 7-Azacoumarin Complex: Synthesis, Structure, Optical Properties, and Cytotoxic Effects

José S. Casas,*,† Eduardo E. Castellano,‡ María D. Couce,§ Olga Crespo,⊥ Javier Ellena,‡ Antonio Laguna,⊥ Agustín Sánchez,† José Sordo,† and Carmen Taboada†

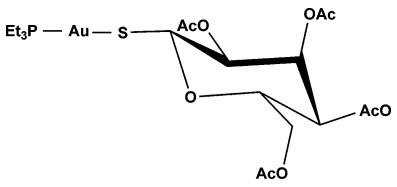
Departamento de Química Inorgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, 15782 Santiago de Compostela (Galicia), Spain, Instituto de Física de Sao Carlos, Universidade de São Paulo, Caixa Postal 369, CEP 13560, Sao Carlos, São Paulo, Brazil, Departamento de Química Inorgánica, Facultade de Ciencias, Universidade de Vigo, 36310 Vigo (Galicia), Spain, and Departamento de Química Inorgánica, Facultad de Ciencias, Instituto de Ciencias de Materiales de Aragón, Universidad de Zaragoza-CSIC, E50009 Zaragoza, Spain

Received May 4, 2007

A mixture of pyridoxalrhodanine, triethylphosphinegold(I) chloride, and sodium methoxide in methanol unexpectedly afforded the azacoumarin complex [Au(TS)(PEt_3)] [HTS = 5-(hydroxymethyl)-8-methyl-3-thiol-7-azacoumarin], which was characterized by X-ray diffractometry. Its crystals consist of independent molecules in which the metal atom is bound to the azacoumarin [Au–S = 2.9458(18) Å] and the phosphine [Au–P = 2.262(2) Å] in an almost linear arrangement [P1–Au1–S1 = 176.93(7)°]. The complex showed better in vitro antitumor activity than cisplatin against the cisplatin-resistant cell line A2780cis.

Gold(I) coordination compounds have been attracting considerable interest, mainly because of their applications in medicine as antiarthritic[1] and antitumor[2] agents. There is also growing interest in their optical properties because of the phosphorescence exhibited by some systems, which is potentially exploitable in organic light-emitting devices.[3]

Among the most promising gold(I) derivatives for cancer treatment are the phosphinegold(I) thiolates [Au(RS)(PR_3)], which are structurally related to the antiarthritic drug auranofin (I).[4]



(I)

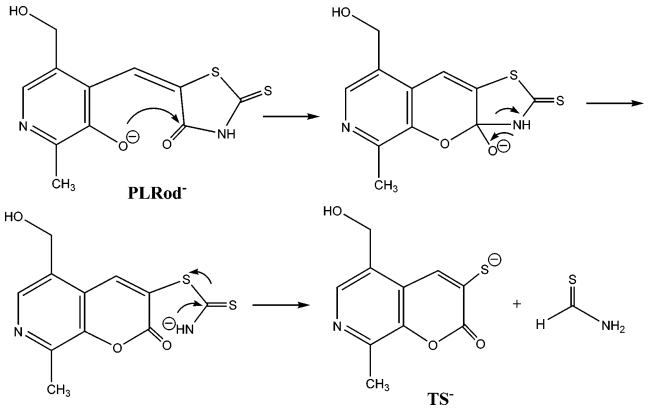
Because their antitumor activity is influenced by the nature of their thiolate ligand (as well as by their phosphine ligand),[4] we decided to explore the anticancer behavior of [Au(RS)(PEt_3)] complexes containing unconventional and/or biologically active thiols.[5] Pyridoxalrhodanine (HPLRod; see Scheme 1), which we expected to evolve to its thiol form under deprotonation and coordination to the metal,[6] was our first choice because its 5′-*O*-phosphono derivative has proven chemotherapeutical potential.[7] However, when HPLRod was reacted with [AuCl(PEt_3)] and sodium methoxide in MeOH (vide infra), the product was not the expected complex [Au(PLRod)(PEt_3)] but [Au(TS)(PEt_3)] [HTS = 5-(hydroxymethyl)-8-methyl-3-thiol-7-azacoumarin; see Scheme 1].[8]

* To whom correspondence should be addressed. E-mail: qiscasas@usc.es.
† Universidade de Santiago de Compostela.
‡ Universidade de São Paulo.
§ Universidade de Vigo.
⊥ Universidad de Zaragoza.

(1) Eisler, R. *Inflamm. Res.* **2003**, *52*, 487−501.
(2) Kostova, I. *Anticancer Agents Med. Chem.* **2006**, *6*, 19−32.
(3) Evans, R. C.; Douglas, P.; Winscom, J. W. *Coord. Chem. Rev.* **2006**, *250*, 2093.
(4) Tiekink, E. R. R. *Gold Bull.* **2003**, *36*, 117−124.
(5) Casas, J. S.; Castellano, E. E.; Couce, M. D.; Ellena, J.; Sánchez, A.; Sordo, J.; Taboada, C. *J. Inorg. Biochem.* **2006**, *100*, 1858−1860.
(6) Escobar-Godoy, R.; Guiraúm Pérez, A. *Analyst* **1986**, *111*, 1297−1299.
(7) Kesel, A. J.; Sonnenbichler, I.; Polborn, K.; Gürtler, L.; Klinkert, W. E. F.; Modolell, M.; Nussler, A. K.; Oberthür, W. *Bioorg. Med. Chem.* **1999**, *7*, 359−367.
(8) A solution of HPLRod (0.08 g, 0.28 mmol) in MeOH (5 mL) was brought to pH ∼9.2 by the addition of NaOMe, after which 0.10 g (0.28 mmol) of [AuCl(PEt_3)] was added, and the mixture was stirred for 2 h at room temperature. Storage of the resulting red solution in the refrigerator for 2 days afforded yellow crystals that were filtered out, vacuum dried, and identified as [Au(TS)(PEt_3)]. Yield: 57%. Mp: 170 °C. Anal. Calcd for $C_{16}H_{23}AuNO_3PS${[PEt_3Au(TS)]}: C, 35.6; H, 4.4; N, 2.6; S, 5.9. Found: C, 35.5; H, 4.2; N, 2.6; S, 5.8. IR (cm^{-1}): ν(OH) 3486s, ν(C=O) 1696s, ν(C=C) + ν(C=N) 1567m, ν(ring) 1519m, ν(C=S) 1078m, ν(Au−P) 393w, ν(Au−S) 384w. LSIMS(+) [PEt_3Au(TS)H]: 538.1 (10.8%). ^{1}H NMR ($CDCl_3$, ppm): δ[C4H] 8.29s(1), δ[C6H] 8.22s(1), δ[C5aH_2] 4.80s(2), δ[OH] 4.77br-(1), δ[C8aH_3] 2.64s(3), δ[P−C20H_2] 1.86dc(6) [^3J(^{1}H−^{1}H) = 7.6 Hz, ^2J(^{1}H−^{31}P) = 10.0 Hz], δ[P−C21H_3] 1.22dt(9) [^3J(^{1}H−^{1}H) = 7.6 Hz, ^3J(^{1}H−^{31}P) = 18.6 Hz]. ^{13}C{^{1}H} NMR ($CDCl_3$, ppm): δ[C2] 165.1, δ[C9] 145.7, δ[C5] 143.4, δ[C6] = 142.0, δ[C4] 132.7, δ[C8] 126.7, δ[C3] not observed, δ[C10] 124.0, δ[C5a] 60.1, δ[C20] 18.0d [^1J(^{13}C−^{31}P) = 35.1 Hz], δ[C8a] 18.5, δ[C21] 9.0. ^{31}P{^{1}H} NMR ($CDCl_3$, ppm): 37.3.

10.1021/ic700861a CCC: $37.00
Published on Web 06/30/2007

Scheme 1. Possible Evolution of HPLRod during the Formation of the Gold(I) Complex [Au(TS)(PEt_3)] [HTS = 5-(hydroxymethyl)-8-methyl-3-thiol-7-azacoumarin]



A plausible mechanism for the evolution of the ligand in this reaction is shown in Scheme 1. The hydrolysis of HPLRod to an α-mercaptopropenoate in the presence of sodium methoxide (which is known to occur to other rhodanine derivatives[9]) will be followed by a nucleophilic attack on the carboxyl carbon by the deprotonated −OH group of the pyridine ring, which would lead to 7-azacoumarin and thiocyanic acid[10] through a process resembling the previously reported transformation of 3-(2-hydroxyphenyl)-2-sulfanylpropenoic acid to 3-sulfanylcoumarin in the presence of $SnPh_3OH$.[11]

The present reaction occurs to some extent even in the absence of gold(I): the negative-ion electrospray ionization time-of-flight mass spectrometry (ESI-TOF/MS) spectrum of an equimolar solution of HPLRod and NaOMe in methanol showed a signal at *m*/*z* (%) 222 (62) that is attributable to the TS^- anion. However, in these conditions, the base peak in the MS spectrum corresponds to $PLRod^-$ and no azacoumarin can be isolated from the solution, whereas the ESI-TOF/MS spectrum of a 1:1:1 mixture of HPLRod, [AuCl(PEt_3)], and NaOMe has a base peak attributable to the azacoumarin species [Au(TS)PEt-2H]. It is therefore likely that the presence of the triethylphosphinegold(I) cation stabilizes the TS^- anion by interacting with the sulfur atom.

This reaction is noteworthy because it prepares both the ligand and the complex in a one-pot reaction; the synthesis of azacoumarins is not easy,[12] and [Au(TS)(PEt_3)] is, as far as we know, the first gold−coumarin complex to have been isolated and identified structurally. Furthermore, this ligand may have interesting optical[13] properties, and the cytotoxic effects of azacoumarins are also beginning to be explored[14] (and in the present case may be synergically reinforced by the presence of the phosphinegold moiety).

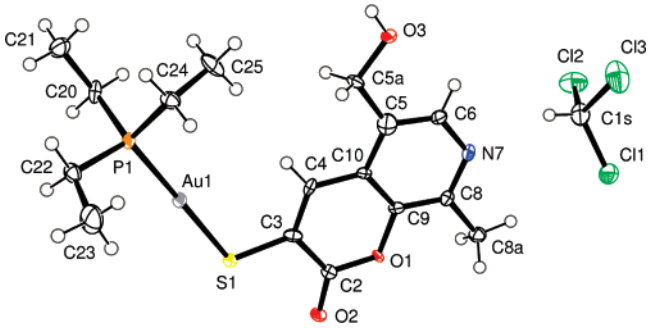


Figure 1. Molecular structure of [Au(TS)(PEt_3)]·$CHCl_3$ in its crystal form. Selected bond lengths (Å) and angles (deg): Au1−P1 2.262(2), Au1−S1 2.310(2), C3−S1 1.735(8), O3−C5A 1.414(9), N7−C8 1.339(10), N7−C6 1.360(10), C9−C8 1.381(11), C9−C10 1.387(10), C9−O1 1.404(9), C6−C5 1.377(11), C10−C5 1.415(10), C10−C4 1.436(11), C8−C8A 1.490(11), C5A−C5 1.498(10), C2−O1 1.363(9), C2−O2 1.212(9), C2−C3 1.452(10), C4−C3 1.377(10); P1−Au1−S1 176.93(7), C3−S1−Au1 106.1(3).

Recrystallization of [Au(TS)(PEt_3)] from $CHCl_3$ afforded crystals suitable for X-ray diffractometry that proved to be [Au(TS)(PEt_3)]·$CHCl_3$ (Figure 1).[15]

In these crystals, the TS^- anion coordinates to the metal through an Au−S bond that is practically collinear with the Au−P bond [Au−S = 2.310(2) Å, Au−P = 2.262(2) Å, and S−Au−P = 176.93(7)°].

The azacoumarin rings are planar [root mean square = 0.0186 and 0.0031] and form a dihedral angle of 1.72(0.27)°, and the bond lengths and angles in this moiety differ by less than 0.05 Å and 1°, respectively, from those found in an iminoazacoumarin.[18] The length of the C3−S1 bond in the present compound, 1.735(8) Å, suggests that the ligand evolves only partially to its thiol form upon metalation. The molecules of [Au(TS)(PEt_3)] are arranged in the crystal lattice in layers connected by intermolecular hydrogen bonds [O3H···O2# = 0.82, 2.06, and 2.839(7) Å and 157.6° and O3H···S3# = 0.82, 2.77, and 3.363(6) Å and 130.6°, where # = $-x + 1$, $y + 1/2$, $-z + 3/2$].

The IR bands assigned to ν_{Au-P} (393 cm^{-1}) and ν_{Au-S} (384 cm^{-1}) are at positions similar to those reported in other gold(I) thiolates.[19] The NMR spectra[8] recorded in $CDCl_3$ corroborate the evolution of HPLRod to the TS^- anion.

In the solid state, [Au(TS)(PEt_3)] is only slightly luminescent at room temperature and slightly more at 77 K.

In these conditions and in solution in CH_2Cl_2 or MeOH at 77 K, its emission spectrum shows one or two bands in

(9) Gränacher, C. *Helv. Chim. Acta* **1922**, *5*, 610−624.
(10) Girard, M. L.; Dreux, C. *Bull. Soc. Chim. Fr.* **1968**, *8*, 3461−3468.
(11) Alvarez-Boo, P.; Casas, J. S.; Couce, M. D.; Fernández-Moreira, V.; Freijanes, E.; García-Martínez, E.; Sordo, J.; Vázquez-López, E. *Eur. J. Inorg. Chem.* **2005**, 4425−4429.
(12) Brufola, G.; Fringuelli, F.; Piermatti, D.; Pizzo, F. *Heterocycles* **1997**, *45* (9), 1715−1721.
(13) Fletcher, A. N.; Pietrak, M. N.; Bliss, D. E. *Appl. Phys. B* **1987**, *B42* (2), 79−83.
(14) Kulkarni, M. V.; Kulkarni, G. M.; Lin, C. H.; Sun, C. M. *Curr. Med. Chem.* **2006**, *13*, 2795−2818. Kostova, I. *Curr. Med. Chem.: Anti-Cancer Agents* **2005**, *5*, 29−46. Okamoto, T.; Kobayashi, T.; Yoshoda, S. *Curr. Med. Chem.: Anti-Cancer Agents* **2005**, *5*, 47−51.
(15) $C_{17}H_{24}AuCl_3NO_3PS$, M = 656.72, monoclinic, space group $P2(1)/c$, a = 17.580(4) Å, b = 18.597(4) Å, c = 6.8252(17) Å, α = 99.831°, V = 2198.7(9) $Å^3$, Z = 4, D_c = 1.984, μ = 7.241 mm^{-1}, λ(Mo Kα) = 0.710 73 Å, T = 120 K. The total number of data is 3863 [θ range (deg): 1.61−25.00], R value for equiv reflns = 0.0385 [$I > 2\sigma(I)$]. Data collection was performed using a SMART CCD 1000 diffractometer; an empirical absorption correction was applied using *SADABS*,[16] and the structure was subjected to full-matrix least-squares refinement using *SHELXL-97*.[17]
(16) Sheldrick, G. M. *SADABS*; University of Göttingen: Göttingen, Germany, 2000.
(17) Sheldrich, G. M. *SHELXL-97, Program for the refinement of crystal structures*; University of Göttingen: Göttingen, Germany, 1997.
(18) Kovalenko, S. M.; Vyacheslav, N. B.; Zhuravel, V. P. C. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2004**, *E60*, o187−o189.
(19) El-Etri, M. M.; Scovell, W. M. *Inorg. Chem.* **1990**, *29*, 480−484.

Table 1. Emission and Excitation Maxima for [Au(TS)(PEt_3)] (in Nanometers)

	298 K		77 K	
	λ_{emis}	λ_{exc}	λ_{emis}	λ_{exc}
solid	625, 670	375	650	375, 425
CH_2Cl_2	440	325, 425	650, 675	375, 425
methanol	425	330	517	330
	525, 575	475	650, 700	475

the 600−700 nm region (see Table 1).[20] These bands may be due to intraligand transitions because a solution of NaTS prepared in situ by the reaction of NaOMe with HPLRod (see above) shows a single band at about 600 nm. A higher-energy emission band that appears between 425 and 517 nm when the complex is excited at ca. 300 nm in CH_2Cl_2 at room temperature or in MeOH at room temperature or 77 K may be due to a ligand−metal charge transfer from the thiolate sulfur atom to the gold atom; such charge-transfer processes have often been observed in gold thiolate derivatives.[21,22]

(20) Emission and excitation spectra were recorded at room temperature and 77 K from finely pulverized mixtures with KBr and from 10^{-3} M solutions in methanol and dichloromethane, using a Jobin−Yvon Horiba Fluorolog FL-3-11 spectrometer with band pathways of 3 nm for both excitation and emission.

(21) Forward, J. M.; Bohmann, D.; Fackler, J. P., Jr.; Staples, R. J. *Inorg. Chem.* **1995**, *34*, 6330.

(22) Yam, V. W. W.; Lam, C. H.; Fung, W. K. M.; Cheung, K. K. *Inorg. Chem.* **2001**, *40*, 3435.

Table 2. In Vitro Activity of [Au(TS)(PEt_3)] against A2780 and A2780cis Cells (IC_{50}, μM)

	A2780	A2780cis
[Au(TS)(PEt_3)]	0.30	0.59
cisplatin	0.51	4.2

Preliminary screening of [Au(TS)(PEt_3)] for in vitro anticancer activity against the cisplatin-sensitive cell line A2780 and the cisplatin-resistant line A2780cis was performed using previously established procedures and cisplatin as the reference drug.[5] Its IC_{50} values (Table 2) show [Au(TS)(PEt_3)] to be more effective than cisplatin against both cell lines, A2780cis especially. Note that for gold compounds in vitro activity seems to be a necessary condition for activity in vivo, albeit not a sufficient one.[4]

In brief, we have described a one-pot reaction in which HPLRod evolves to give a 3-thiol-7-azacoumarin−gold(I) complex, the structure of which has been determined by X-ray diffractometry. This complex is weakly luminescent in the solid state but exhibits strong and complex luminescence behavior in solution. In preliminary in vitro screening experiments, it showed promising cytotoxicity against the cisplatin-resistant cell line A2780cis.

CCDC 642394 contains supplementary crystallographic data for the structures described in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

IC700861A