Studies on the interaction of gold(I) phosphines with 2-thiouracil. Related studies with silver(I) phosphines

Cameron S. W. Harker, Edward R. T. Tiekink*

Jordan Laboratories, Department of Physical and Inorganic Chemistry, University of Adelaide, Adelaide, SA 5001 (Australia)

and **Michael W. Whitehouse**

Department of Pathology, University of Adelaide, Adelaide, SA 5001 (Australia)

(Received July 19, 1990)

Abstract

The crystal structure of $Et_3PAu(2\text{-TU})$ shows that the gold atom is linearly coordinated by a P atom (2.248(2) Å) and a S atom (2.310(2) Å) derived from a 2-TU anion which functions as a thiolate ligand. Monoclinic crystals of the complex have space group $P2_1/c$ with unit cell dimensions $a = 9.161(1)$, $b = 11.233(1)$, $c = 14.049(2)$ Å, $\beta = 95.39(1)°$; final $R = 0.044$ for 2181 reflections. The anti-arthritic activity of $R_3PAu(2\text{-TU})$, R = Et and Ph, is reported. The attempted reaction between the bis chelated diphosphine complex $[Au(dppe)_2]Cl$ and the 2-TU anion yielded a complex of stoichiometry $[Au(dppe)_2][(2\text{-TU})(2\text{-TUH})]$ in which there is no interaction between the nucleobase and the Au atom. The lattice comprises discrete tetrahedral cations and 2-TU anions; the latter being associated with the neutral 2-TUH molecule via a hydrogen bond. Crystals are triclinic, $P\bar{1}$, $a = 15.407(2)$, $b = 17.251(2)$, $c = 11.526(2)$ Å, $\alpha = 109.50(1)$, $\beta = 97.81(1)$, $\gamma = 85.11(1)°$; final $R = 0.046$ for 6323 reflections. Related reactions employing silver phosphine salts and three nucleobases are also reported briefly. In no instances were mixed silver phosphine/nucleobase complexes obtained. In general, silver phosphine complexes remained intact after reaction with a nucleobase and, in all but one instance, when starting with an authentic silver nucleobase complex the phosphine ligand replaced the coordinated nucleobase yielding binary silver phosphine compounds.

Introduction

Increasing interest in the coordination chemistry of gold(I) arises as a result of the use of certain gold(I) compounds as anti-arthritic drugs [1, 2]. Polymeric gold(I) thiolates which are commercially available as drugs include gold sodium thiomalate (Myochrisine), gold thioglucose (Solganol) and gold sodium thiosulfate (Sanochrysine). The monomeric phosphinegold(I)thioglucose derivative (1-thio-β-D-gluco-pyranose 2,3,4,6-tetraacetato-*S*)(triethylphosphine)gold(I), Auranofin, also exhibits anti-arthritic activity and is in clinical use [3, 4]. More recently, gold(I) phosphine complexes have also been shown to possess anti-tumour activity [5, 6]. Auranofin itself was shown to possess limited anti-tumour activity [7] as have a number of related monomeric gold(I) compounds (e.g. ref. 8). The bis chelated diphosphine complex, $[Au(dppe)_2]^+$ (where dppe is 1,2-bis-(diphenylphosphino)ethane), has been shown to be cytotoxic against a variety of tumorous cells [9, 10]; similarly the silver(I) [11] and copper(I) [12] analogues are active in this regard.

The mechanism of action of the bis chelated compounds is unknown at present. It has been suggested however, that the role of the metal atom is to deliver the active phosphine ligands, intact, to the tumorous cells and thus the metal atom may be considered simply as a carrier [5]. Therefore, the $[Au(dppe)_2]^+$ complex might interact with biological substrates via a ring-opening mechanism which would transfer the phosphine ligand to the active site. Gold(I) is a soft metal atom and as such would be expected to react with sulfur donor atoms [13]. It was thought worthwhile to investigate the reaction of $[Au(dppe)_2]^+$ with the pyrimidine, 2-thiouracil (hereafter 2-TUH), a sulfur containing analogue of uracil which occurs naturally in transfer ribonucleic acid [14], under laboratory conditions to determine whether a mixed ligand complex containing both

*Author to whom correspondence should be addressed.

0020-1693/91/$3.50

phosphine and thiouracil could be obtained. The monomeric complex $Ph_3PAu(2\text{-TU})$ has been characterized recently by spectroscopic methods and X-ray crystallography [15], indicating that stable gold phosphine thiouracil complexes do exist. Similar studies involving $[Ag(dppe)_2]^+$, and other silver phosphines, with 2-TUH, adenine and 9-methyladenine are also reported here. The results of tests for anti-arthritic activity are included for the $R_3PAu(2\text{-TU})$, R = Et and Ph, compounds.

Experimental

Instrumentation

NMR spectra were recorded in $CDCl_3$ solution on a Bruker CXP300 (^1H at 300.13 MHz and ^{13}C at 75.47 MHz) spectrometer. IR spectra were recorded on a Perkin-Elmer 1720X FT spectrometer. Fast atom bombardment mass spectra were obtained on an VG ZAB 2HF spectrometer using 3-nitrobenzyl as the matrix, Ar as the exciting gas, a FAB gun voltage of 7.5 kV, a current of 1 mA, and an accelerating potential of 8 kV.

Starting materials

The phosphines, Et_3P (Fluka), Ph_3P (B.D.H) and dppe (Strem) were used as supplied. $HAuCl_4$ was prepared from elemental gold as per the literature method [16]. The gold complexes Et_3PAuCl, Ph_3PAuCl [17] and $[Au(dppe)_2]Cl$ [9] were each prepared by the literature method. $AgNO_3$ (Matthey Garrett) was used as supplied. The silver phosphine complexes were prepared using published methods: $[Ag(dppe)_2]NO_3$ [11] and $[Ag(PPh_3)_n]$, $n = 1$, 2, 3 and 4 [18].

Preparation of new compounds

$Et_3PAu(2\text{-TU})$

This compound was prepared from the equimolar reaction of Et_3PAuCl (200 mg), 2-TUH and NaOH in an aqueous ethanol solution as described for the Ph_3P analogue [15]. Crystals for the X-ray study were obtained from the slow evaporation of an ethanol solution of the compound; m.p. 131–132 °C. ^1H NMR ($CDCl_3$) δ 10.45, N(3)*H*; 7.65 d, H(5); 6.05 d, H(6), $J_{H(5),H(6)}$ 6.7 Hz; 1.91 dq, CH_2, $^2J_{P,H}$ 9.9 Hz; 1.24 ppm dt, CH_3, $^3J_{P,H}$ 18.6 Hz. ^{13}C NMR ($CDCl_3$) δ 169.0, C(2); 163.6, C(4); 154.6, C(6); 109.7, C(5); 17.9 d CH_2, $J_{C,H}$ 31.7 Hz, 8.93 ppm CH_3.

$[Au(dppe)_2][(2\text{-TU})(2\text{-TUH})]$

This compound was prepared from the equimolar reaction of $[Au(dppe)_2]Cl$ (150 mg), 2-TUH and NaOH in refluxing methanol solution for 4 h. Evaporation of the solution yielded colourless crystals which were suitable for X-ray analysis; m.p. 228–231 °C. ^1H NMR ($CDCl_3$) δ 8.00 d, H(5); 7.16–7.38 m, Ph; 5.75 d, H(6), $J_{H(5),H(6)}$ 6.8 Hz; 2.44 ppm br, CH_2. Limited solubility precluded a ^{13}C NMR study.

TABLE 1. Crystal data and refinement details for $Et_3PAu(2\text{-TU})$ and $[Au(dppe)_2][(2\text{-TU})(2\text{-TUH})]$

Compound	$Et_3PAu(2\text{-TU})$	$[Au(dppe)_2][(2\text{-TU})(2\text{-TUH})]$
Formula	$C_{10}H_{18}AuN_2OPS$	$C_{60}H_{55}AuN_4O_2P_4S_2$
Formula weight	442.3	1249.1
Crystal system	monoclinic	triclinic
Space group	$P2_1/c$	$P\bar{1}$
a (Å)	9.161(1)	15.407(2)
b (Å)	11.233(1)	17.251(2)
c (Å)	14.049(2)	11.526(2)
α (°)	90	109.50(1)
β (°)	95.39(1)	97.81(1)
γ (°)	90	85.11(1)
V (Å^3)	1439.3	2858.3
Z	4	2
D_c (g cm^{-3})	2.041	1.451
$F(000)$	840	1260
μ (cm^{-1})	104.03	27.6
Transmission factors (max./min.)	0.127; 0.023	0.652; 0.386
θ limits (°)	1.5 – 27.5	1.5–22.5
No. data collected	3655	7507
No. unique data	3311	7487
No. unique reflections used with $I > 2.5\sigma(I)$	2181	6323
R	0.044	0.046
g	0.0066	0.0038
R_w	0.042	0.050

Crystallography

Intensity data for $Et_3PAu(2\text{-}TU)$ and $[Au(dppe)_2][(2\text{-}TU)(2\text{-}TUH)]$ were measured at room temperature on an Enraf-Nonius CAD4F diffractometer fitted with graphite monochromatized Mo Kα radiation, $\lambda = 0.7107$ Å. The ω:2θ scan technique was employed in each case. The data sets were corrected for Lorentz and polarization effects and for absorption with the use of an analytical procedure in each case [19]. Relevant crystal data are collected in Table 1.

The structures were solved by the Patterson method and each refined by a full-matrix least-squares procedure based on F [19]. Phenyl rings were refined as hexagonal rigid groups for $[Au(dppe)_2][(2\text{-}TU)(2\text{-}TUH)]$ and the remaining non-H atoms in each structure were refined with anisotropic thermal parameters. Hydrogen atoms were included in the models at their calculated positions. After the inclusion of a weighting scheme of the form, $w = [\sigma^2(F) + g|F|^2]^{-1}$, the refinements were continued until convergence; final refinement details are listed in Table 1. The analysis of variance showed no special features in either case. Fractional atomic coordinates are listed in Tables 2 and 3 and the numbering schemes employed are shown in Figs. 1, 3 and 4 which were drawn with ORTEP [20] at 25% probability ellipsoids. Scattering factors for neutral Au (corrected for f' and f'') were from ref. 21 while those for the remaining atoms were as incorporated in the SHELX76 program [19]. Refinements were performed on a SUN4/280 computer. See also 'Supplementary material'.

Animal studies

Male Dark Agouti rats (220 ± 20 g) were injected in the tailbase with an arthritogenic freund's adjuvant on day 0 to initiate an anti-allergic polyarthritis. Test compounds were administered subcutaneously on alternate days, beginning on day 0 for a total of 9 doses (last on day 16), as dispersions in 0.02% (vol./vol.) Tween-20:0.15 M NaCl. Sodium aurothiomalate was used as the reference drug (6 mg Au/kg/dose). Arthritis was scored on days 18, 22 and 28.

Results and discussion

$Et_3PAu(2\text{-}TU)$

The facile equimolar reaction between Et_3PAuCl, 2-TUH and NaOH gave $Et_3PAu(2\text{-}TU)$ as colourless crystals. The complex was characterized by absorptions in the infrared spectrum at 1662, 1650 and 1637 cm^{-1} assigned to $\nu(C{=}O)$, and at 1522 assigned to $\nu(C{=}S)$. In accord with the $Ph_3PAu(2\text{-}TU)$ com-

TABLE 2. Fractional atomic coordinates ($\times 10^5$ for Au; $\times 10^4$ for remaining atoms) for $Et_3PAu(2\text{-}TU)$

Atom	x	y	z
Au	2364(3)	18858(3)	11877(2)
P(1)	2403(2)	932(2)	1305(2)
N(1)	−907(8)	3608(8)	−452(6)
C(2)	−2006(8)	3624(8)	79(6)
S(2)	−2048(3)	2772(2)	1092(2)
N(3)	−3181(6)	4331(6)	−138(5)
C(4)	−3329(9)	5127(8)	−887(6)
O(4)	−4422(7)	5780(6)	−1016(4)
C(5)	−2143(11)	5098(11)	−1450(8)
C(6)	−997(10)	4359(11)	−1224(8)
C(11)	3379(10)	1142(9)	243(6)
C(12)	2563(16)	747(14)	−668(7)
C(21)	2164(9)	−661(7)	1437(6)
C(22)	3548(10)	−1417(9)	1555(8)
C(31)	3705(10)	1406(9)	2281(7)
C(32)	3072(12)	1360(10)	3232(7)

TABLE 3. Fractional atomic coordinates ($\times 10^5$ for Au; $\times 10^4$ for remaining atoms) for $[Au(dppe)_2][(2\text{-}TU)(2\text{-}TUH)]$

Atom	x	y	z
Au	24179(1)	23878(1)	1067(2)
P(1)	973(1)	2601(1)	−807(2)
P(2)	2280(1)	962(1)	−1113(2)
P(3)	2901(1)	2684(1)	2270(1)
P(4)	3673(1)	3109(1)	52(2)
C(111)	834(2)	3026(3)	−2076(4)
C(112)	1556(2)	3328(3)	−2373(4)
C(113)	1463(2)	3631(3)	−3367(4)
C(114)	648(2)	3632(3)	−4063(4)
C(115)	−74(2)	3331(3)	−3766(4)
C(116)	19(2)	3028(3)	−2772(4)
C(121)	150(3)	3165(3)	196(4)
C(122)	50(3)	4014(3)	438(4)
C(123)	−502(3)	4486(3)	1302(4)
C(124)	−953(3)	4108(3)	1923(4)
C(125)	−853(3)	3259(3)	1681(4)
C(126)	−302(3)	2788(3)	817(4)
C(131)	575(4)	1561(4)	1576(6)
C(132)	1324(5)	985(4)	−2229(7)
C(211)	3136(3)	411(3)	−2034(4)
C(212)	2958(3)	−113(3)	−3249(4)
C(213)	3636(3)	−588(3)	−3875(4)
C(214)	4492(3)	−538(3)	−3285(4)
C(215)	4671(3)	−14(3)	−2070(4)
C(216)	3993(3)	460(3)	−1445(4)
C(221)	2003(3)	233(2)	−391(5)
C(222)	1464(3)	509(2)	558(5)
C(223)	1215(3)	−38(2)	1098(5)
C(224)	1506(3)	−863(2)	689(5)
C(225)	2045(3)	−1139(2)	−260(5)
C(226)	2294(3)	−591(2)	−800(5)
C(311)	2797(3)	1936(3)	3040(5)

(*continued*)

TABLE 3. (*continued*)

Atom	*x*	*y*	*z*
C(312)	2211(3)	2093(3)	3923(5)
C(313)	2068(3)	1483(3)	4414(5)
C(314)	2510(3)	717(3)	4023(5)
C(315)	3095(3)	561(3)	3140(5)
C(316)	3239(3)	1170(3)	2649(5)
C(321)	2543(2)	3663(3)	3333(4)
C(322)	3013(2)	4035(3)	4484(4)
C(323)	2720(2)	4797(3)	5255(4)
C(324)	1957(2)	5186(3)	4874(4)
C(325)	1487(2)	4814(3)	3724(4)
C(326)	1780(2)	4052(3)	2953(4)
C(331)	4086(4)	2790(4)	2301(6)
C(332)	4227(5)	3390(5)	1645(7)
C(411)	3504(3)	4096(3)	−200(5)
C(412)	3994(3)	4319(3)	−962(5)
C(413)	3828(3)	5080(3)	−1144(5)
C(414)	3170(3)	5619(3)	−562(5)
C(415)	2680(3)	5396(3)	200(5)
C(416)	2847(3)	4635(3)	381(5)
C(421)	4455(3)	2544(3)	−1003(4)
C(422)	4116(3)	2204(3)	−2242(4)
C(423)	4673(3)	1778(3)	−3127(4)
C(424)	5569(3)	1692(3)	−2772(4)
C(425)	5908(3)	2032(3)	−1533(4)
C(426)	5350(3)	2457(3)	−649(4)
S(12)	1937(1)	8414(1)	3293(2)
O(14)	−287(3)	9656(3)	6107(5)
N(11)	1775(4)	8029(3)	5306(5)
N(13)	780(3)	9028(3)	4899(5)
C(12)	1468(4)	8493(4)	4576(6)
C(14)	327(4)	9139(4)	5890(6)
C(15)	628(5)	8620(5)	6597(7)
C(16)	1363(6)	8118(5)	6294(7)
S(22)	3386(1)	6895(1)	7071(2)
O(24)	5016(4)	5152(3)	3659(5)
N(21)	3194(4)	6958(4)	4795(6)
N(23)	4236(4)	6009(3)	5161(5)
C(22)	3615(4)	6615(4)	5604(6)
C(24)	4455(5)	5729(4)	3981(7)
C(25)	4003(5)	6126(5)	3143(7)
C(26)	3401(6)	6704(6)	3581(8)

plex [15], the spectrum was consistent with coordination to the Au gold via the S atom.

The molecular structure of $Et_3PAu(2\text{-TU})$ is shown in Fig. 1 and selected interatomic parameters are given in Table 4. The Au atom exists in the expected linear geometry defined by the P atom, Au–P 2.248(2) Å, of the Et_3P ligand and the S atom, Au–S 2.310(2) Å, of the deprotonated thiouracil ligand. The P–Au–S angle is 176.9(1)°; the small deviation from the ideal linear geometry may be due in part to a weak intramolecular Au...N interaction of 3.113(2) Å, a distance that is less than the sum of the van der Waals radii of the Au and N atoms of 3.25 Å [22]. The lengthening of the C(2)–S(2) bond distance

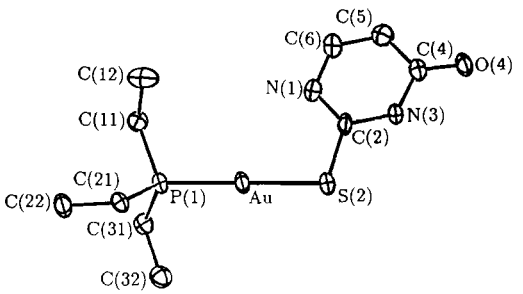


Fig. 1. Molecular structure and crystallographic numbering scheme employed for $Et_3PAu(2\text{-TU})$.

TABLE 4. Selected bond distances (Å) and angles (°) for $Et_3PAu(2\text{-TU})$

Au–P(1)	2.248(2)	Au–S(2)	2.310(2)
C(2)–S(2)	1.719(9)	C(2)–N(1)	1.31(1)
N(1)–C(6)	1.37(1)	C(2)–N(3)	1.349(9)
N(3)–C(4)	1.38(1)	C(4)–O(4)	1.24(1)
C(4)–C(5)	1.40(1)	C(5)–C(6)	1.35(2)
P(1)–Au–S(2)	176.9(1)	Au–P(1)–C(11)	112.1(3)
Au–P(1)–C(21)	111.3(3)	Au–P(1)–C(31)	115.4(3)
C(11)–P(1)–C(21)	106.5(4)	C(11)–P(1)–C(31)	104.0(5)
C(21)–P(1)–C(31)	106.9(4)	Au–S(2)–C(2)	101.4(3)
S(2)–C(2)–N(1)	122.9(6)	S(2)–C(2)–N(3)	115.8(6)
N(1)–C(2)–N(3)	121.3(8)	C(2)–N(1)–C(6)	116.8(8)
C(2)–N(3)–C(4)	125.0(7)		

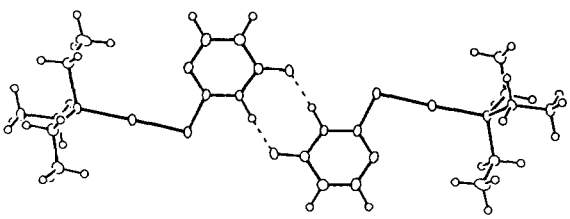


Fig. 2. Hydrogen bonding interactions in $Et_3PAu(2\text{-TU})$.

(1.719(9) Å cf. 1.683(3) Å) and concomitant shortening of the N(1)–C(2) bond (1.31(1) Å cf. 1.338(4) Å) in the $Et_3PAu(2\text{-TU})$ complex compared to that found in the free ligand [23] (without substantial changes being observed for the remaining interatomic parameters defining the 2-TU ligand) indicates that the 2-TU anion coordinates the Au atom as a thiolate ligand rather than as a thione, again consistent with the Ph_3P analogue [15]. In the crystal lattice there are significant hydrogen bonding contacts, as illustrated in Fig. 2, between centrosymmetrically related molecules. These involve the O(4) atom and the H atom residing on N(3) such that the O(4)...H(3)′ separation is 1.88 Å and the O(4)...H(3)′–(N3)′ angle is 169°.

The geometric parameters found in $Et_3PAu(2\text{-TU})$ are equal within experimental error to the comparable parameters found in the Ph_3P analogue [15]. In

related studies of phosphinegold/nucleobase interactions, the effect on the electronic structure of the coordinated nucleobase when either Et_3P or Ph_3P is present has been investigated [24, 25]; these results are summarized in Table 5. The results of the present investigation support previous conclusions namely, that in the absence of any obvious crystal packing or steric effects (as in the case of the 1-methylthyminate compounds [25]) the nature of the phosphine does not affect the site of metallation nor impinge greatly on the geometric parameters defining the nucleobase.

Anti-arthritic activity of $Et_3PAu(2\text{-}TU)$ and $Ph_3PAu(2\text{-}TU)$

The $R_3PAu(2\text{-}TU)$, R = Et and Ph, compounds were assayed for their potential anti-arthritic activity in a gold-sensitive rat strain [28, 29]. Only the Ph_3P compound was an effective prophylactic, almost completely preventing rearpaw swelling (only 5% controls) on day 18 given at a dose of 12 mg Au/kg (given 9 times, see 'Experimental'). After a further 10 days without treatment, the rearpaw swelling was still only 65% that of untreated controls. Sodium aurothiomalate (6 mg Au/kg) inhibited rearpaw swelling by only 54% on day 18. By contrast, animals treated with the same dosage (12 mg Au/kg) of the Et_3P compound suffered arthritis more severe than that of the untreated controls (rearpaw swelling = 127% on day 18).

$[Au(dppe)_2][(2\text{-}TU)(2\text{-}TUH)]$

The anti-tumour active compound $[Au(dppe)_2]^+$, as its chloride salt, was reacted with 2-TUH in order to see whether a mixed phosphine/nucleobase compound of gold could be obtained. Initially a 1:1 reaction between the gold complex and 2-TUH was attempted in refluxing methanol solution. An analysis of the crystalline products after work-up revealed that the original starting materials had been recovered. Repeating the reaction in the presence of one molar equivalent of NaOH resulted in the isolation of well-formed, colourless crystals with spectroscopic properties different from those of either starting materials. In the infrared spectrum, absorptions were observed at 1656 and 1633 cm^{-1} characteristic of $\nu(C{=}O)$ and at 1234 cm^{-1} assigned to $\nu(C{=}S)$. In the FAB mass spectrum of the compound no evidence was found for a molecular ion containing both Au and 2-thiouracil although a molecular ion corresponding to $[Au(dppe)_2]^+$ was observed. In order to resolve these ambiguous spectroscopic results an X-ray analysis was performed.

The results of the crystal structure determination are given in Figs. 3 and 4 and Table 6. The unit cell was found to contain $[Au(dppe)_2]^+$ cations, 2-TU anions and neutral 2-TUH molecules in the ratio 1:1:1. In effect, the chloride ion of the parent complex has been replaced by a 2-TU anion there being no interaction between the gold atom and the nucleobase.

TABLE 5. Selected parameters (Å) for R_3PAu(nucleobase) structures; R = Et, Ph

	R = Et	R = Ph
R_3PAu(adeninate)		
Au–P	2.238(2) [24]	2.240(1) [26]
Au–N(9)	2.057(6)	2.038(4)
R_3PAu(1-methylthyminate)		
Au–P	2.223(6) [25]	2.240(5) [27]
Au–N(3)	2.06(2)	2.20(1)
R_3PAu(thiouracilate)		
Au–P	2.248(2)	2.248(2), 2.248(2)[a] [15]
Au–S(2)	2.310(2)	2.296(2), 2.300(2)

[a]Two molecules in crystallographic asymmetric unit.

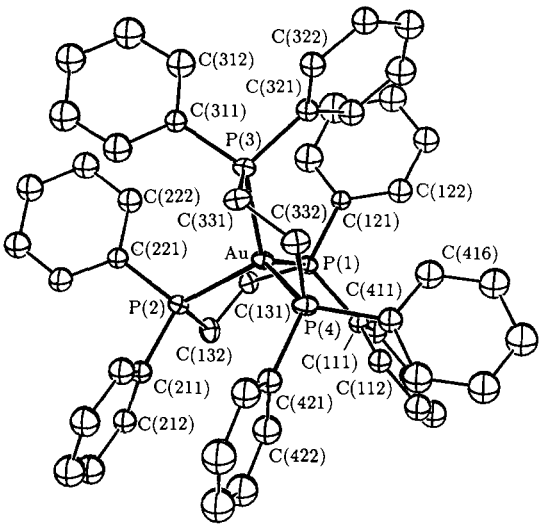


Fig. 3. Molecular structure and crystallographic numbering scheme employed for $[Au(dppe)_2][(2\text{-}TU)(2\text{-}TUH)]$.

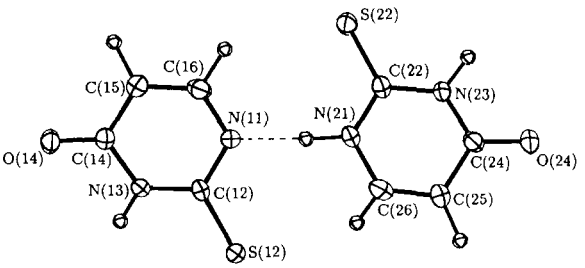


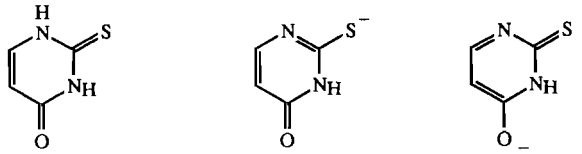
Fig. 4. The association between the 2-TU and 2-TUH molecules and crystallographic numbering scheme employed for $[Au(dppe)_2][(2\text{-}TU)(2\text{-}TUH)]$.

TABLE 6. Selected bond distances (Å) and angles (°) for [Au(dppe)$_2$][(2-TU)(2-TUH)]

Au–P(1)	2.384(2)	Au–P(2)	2.402(2)
Au–P(3)	2.397(2)	Au–P(4)	2.406(2)
P(1)–C(111)	1.825(4)	P(1)–C(121)	1.824(5)
P(1)–C(131)	1.832(6)	P(2)–C(123)	1.827(7)
P(2)–C(211)	1.807(5)	P(2)–C(221)	1.830(5)
P(3)–C(311)	1.821(5)	P(3)–C(321)	1.817(4)
P(3)–C(331)	1.844(6)	P(4)–C(332)	1.840(7)
P(4)–C(411)	1.813(5)	P(4)–C(421)	1.812(5)
C(131)–C(132)	1.56(1)	C(331)–C(332)	1.52(1)
N(11)–C(12)	1.361(8)	N(11)–C(16)	1.34(1)
C(12)–S(12)	1.693(7)	C(12)–N(13)	1.351(8)
N(13)–C(14)	1.369(9)	C(14)–O(14)	1.235(8)
C(14)–C(15)	1.41(1)	C(15)–C(16)	1.38(1)
N(21)–C(22)	1.334(9)	N(21)–C(26)	1.39(1)
N(21)–H(21)	1.02(-)	C(22)–S(22)	1.675(7)
C(22)–N(23)	1.369(9)	N(23)–C(24)	1.362(9)
C(24)–O(24)	1.253(9)	C(24)–C(25)	1.44(1)
C(25)–C(26)	1.32(1)	H(21)...N(11′)	1.74(-)
P(1)–Au–P(2)	86.4(1)	P(1)–Au–P(3)	127.0(1)
P(1)–Au–P(4)	124.6(1)	P(2)–Au–P(3)	116.7(1)
P(2)–Au–P(4)	120.2(1)	P(3)–Au–P(4)	85.9(1)
Au–P(1)–C(111)	118.9(1)	Au–P(1)–C(121)	119.0(2)
Au–P(1)–C(131)	104.3(2)	C(111)–P(1)–C(121)	104.4(2)
C(111)–P(1)–C(131)	102.1(3)	C(121)–P(1)–C(131)	106.1(3)
Au–P(2)–C(132)	102.9(2)	Au–P(2)–C(211)	120.4(2)
Au–P(2)–C(221)	119.5(2)	C(132)–P(2)–C(211)	105.3(3)
C(132)–P(2)–C(221)	103.7(3)	C(211)–P(2)–C(221)	103.1(2)
Au–P(3)–C(311)	120.8(2)	Au–P(3)–C(321)	117.9(1)
Au–P(3)–C(331)	101.1(2)	C(311)–P(3)–C(321)	104.8(2)
C(311)–P(3)–C(331)	106.6(3)	C(321)–P(3)–C(331)	103.8(3)
Au–P(4)–C(332)	104.1(2)	Au–P(4)–C(411)	119.0(2)
Au–P(4)–C(421)	116.9(2)	C(332)–P(4)–C(411)	102.4(3)
C(332)–P(4)–C(421)	108.7(3)	C(411)–P(4)–C(421)	104.5(2)
P(1)–C(131)–C(132)	109.5(4)	P(2)–C(132)–C(131)	110.7(5)
P(3)–C(331)–C(332)	109.8(5)	P(4)–C(332)–C(331)	113.1(5)
C(12)–N(11)–C(16)	117.7(6)	C(22)–N(21)–C(26)	120.3(6)
N(11)–C(12)–S(12)	121.2(5)	N(21)–C(22)–S(22)	122.0(5)
N(13)–C(12)–S(12)	120.2(5)	N(23)–C(22)–S(22)	121.8(5)
N(11)–C(12)–N(13)	118.6(6)	N(21)–C(22)–N(23)	116.2(6)
C(12)–N(13)–C(14)	126.2(5)	C(22)–N(23)–C(24)	126.0(5)
N(21)–H(21)...N(11′)	165(-)		

The Au atom in the $[Au(dppe)_2]^+$ cation exists in a distorted tetrahedral geometry, the distortion arising from the restricted bite distances of the dppe ligands which subtend angles at the Au atom of 86.4(1) and 85.9(1)°, respectively. As a consequence the remaining P–Au–P angles are opened up from the ideal tetrahedral angle to compensate for this strain imposed by the diphosphine ligands. The Au–P bond distances lie in the narrow range 2.384(2)–2.406(2) Å; the remaining geometric parameters describing the cation are as expected. In all respects the $[Au(dppe)_2]^+$ geometry is virtually identical to those found in the $[Au(dppe)_2]Cl \cdot H_2O$ [30] and $[Au(dppe)_2][SbF_6] \cdot$ acetone [31] complexes determined previously. Of more interest in the structure is the presence of the thiouracil molecules in the crystal lattice.

The counter ion in the complex is a 2-TU anion, deprotonated at the N(1) position, which is connected via a hydrogen bond to a neutral 2-thiouracil molecule as shown in Fig. 4. The N(21)–H(21) bond distance is 1.02 Å and the H(21)...N(11)′ separation is 1.74 Å with a N(21)–H(21)...N(11)′ angle of 165°. The geometric parameters defining the neutral 2-TUH molecule are equal within experimental error to those found for the 'free' ligand which was found to exist in the lactam-thione form in the solid state, i.e. resonance form **A** in Fig. 5 [23]. The 2-TU anion shows an interesting reorganization of electron density however. When the 2-TU ligand coordinates a



A B C

Fig. 5. Resonance forms for the 2-thiouracil ligand and anion.

metal centre via the S atom (i.e. as a thiolate), the C–S bond is elongated somewhat and there is a concomitant decrease in the N(1)–C(2) bond distance; the remaining bond distances within the nucleobase do not change significantly and thus resonance form **B** is a good representation of the 2-TU anion in these complexes; see Fig. 5. However, in the 2-TU anion in $[Au(dppe)_2][(2\text{-TU})(2\text{-TUH})]$, the C=S bond is not significantly longer than it is in the free ligand, i.e. C(2)=S(2) 1.693(7) cf. 1.683(3) Å. There are other systematic changes in bond distances within the heterocyclic ring which suggest that resonance form **C** is an important resonance structure for the anion. These changes include the lengthening of the N(1)–C(2), C(4)–O(4) and C(5)–C(6) bond distances compared to the free ligand and the shortening of the N(1)–C(6) and C(4)–C(5) bond distances. In solution it was not possible to distinguish between the two thiouracil molecules indicating rapid exchange of the acidic proton between the molecules.

Silver phosphine/nucleobase interactions

Similar reactions as described above for $[Au(dppe)_2]^+$ and 2-thiouracil were attempted using $[Ag(dppe)_2]^+$ which is also known to exhibit cytotoxic properties [11]. A recent crystal structure determination of $[Ag(dppe)_2]NO_3$ [32] shows a distorted tetrahedral geometry about the silver atom, as described for the gold analogue. It was therefore envisaged that the chelate ring structure of the bidentate phosphine would be disruptured enabling the coordination of a nucleobase. The reaction mechanism, distinct from that of the gold species, may involve a concerted process in which a five-coordinate intermediate may exist [5]. Silver(I) being a 'hard' metal [13] would be expected to react preferentially with a N-donor (over a S atom for example). Therefore two additional nucleobases were employed in this study, namely adenine and 9-methyladenine, in addition to 2-thiouracil.

$[Ag(dppe)_2]NO_3$ was refluxed in methanol solution with each of three nucleobases in turn for 1 h in both the presence and absence of an equimolar amount of NaOH. Each of the six solutions was evaporated to dryness and in each instance only starting materials were recovered according to melting point, IR and FAB-MS analysis. Similar reactions were also attempted with excess nucleobase (up to 4:1) however, the same results were obtained. As the nucleobases chosen were found not to coordinate the silver atom in $[Ag(dppe)_2]^+$ an alternative approach was attempted.

A reverse pathway involving the preparation of the silver/nucleobase complexes and then reacting these with phosphines was attempted. The polymeric nucleobase compounds $[Ag(2\text{-TUH})]NO_3$ and $[Ag(adenH)]NO_3$ [33] were first prepared. The silver nucleobase complexes of silver were each suspended in $CHCl_3$ solution and refluxed with 1 equivalent, and later 2 equivalents, of dppe (with the exclusion of light) for 4 h. The resultant solution was filtered and allowed to stand until a crystalline product precipitated. The reaction involving the adenine complex yielded $[Ag(dppe)_2]NO_3$ (m.p., IR and FAB-MS analysis) indicating complete displacement of the nucleobase. In contrast, the $[Ag(2\text{-TUH})]NO_3$ complex remained intact.

Similar reactions were then attempted using the monodentate phosphine, PPh_3. The ratio of complex to PPh_3 was 1:2, the $CHCl_3$ solution was refluxed for 4 h and the resultant solution allowed to stand until a product precipitated as described above. The product isolated from the reaction with $[Ag(adenH)]NO_3$ was recrystallized from benzene solution to yield colourless crystals. These crystals had an IR spectrum very similar to that of $[Ag(PPh_2)_2]NO_3$ but a different melting point and unit cell characteristics, when compared to an authentic sample [18]. A subsequent crystal structure analysis showed that the compound was in fact $[Ag(PPh_3)_2]NO_3$ isolated as a benzene (1/1) solvate [34]. The reaction between $[Ag(2\text{-TUH})]NO_3$ and two equivalents of PPh_3 was also attempted. In contrast to the reaction with dppe, the PPh_3 ligand displaced the 2-thiouracil ligand to form $[Ag(PPh_3)_3]NO_3$ (m.p., IR, FAB-MS and unit cell data [18]).

In conclusion, the work on the gold and silver complexes shows that these metal centres have a distinct preference for phosphine ligands over the nucleobases chosen, under the reaction conditions employed in this study.

Supplementary material

Crystallographic details comprising thermal parameters, hydrogen atom parameters, all bond distances and angles, and tables of observed and calculated structure factors are available from author E.R.T.T.

Acknowledgements

The Australian Research Council (crystallographic facility) and The National Heath and Medical Research Council (animal studies) are thanked for support.

References

1 R. V. Parish and S. M. Cottrill, *Gold Bull., 20* (1987) 3.
2 D. R. Haynes and M. W. Whitehouse, in K. D. Rainsford and G. P. Velo (eds.), *New Developments in Antirheumatic Therapy*, Kluwer, Dordrecht, 1989, Ch. 8, p. 207.
3 B. M. Sutton, E. McGusty, D. T. Walz and M. J. DiMartino, *J. Med. Chem., 15* (1972) 1095.
4 B. M. Sutton, *Gold Bull., 19* (1986) 15.
5 S. J. Berners-Price and P. J. Sadler, *Chem. Br., 23* (1987) 541.
6 S. J. Berners-Price and P. J. Sadler, *Struct. Bonding (Berlin), 70* (1988) 27.
7 T. M. Simon, D. H. Kunishima, G. J. Vibert and A. Lorber, *Cancer (Philadelphia), 44* (1979) 1965.
8 C. K. Mirabelli, R. K. Johnson, C.-M. Sung, L. F. Faucette, K. Muirhead and S. T. Crooke, *Cancer. Res., 45* (1985) 32.
9 S. J. Berners-Price, C. K. Mirabelli, R. K. Johnson, M. R. Mattern, F. L. McCabe, L. F. Faucette, C.-M. Sung, S.-M. Mong, P. J. Sadler and S. T. Crooke, *Cancer. Res., 46* (1986) 5686.
10 C. K. Mirabelli, D. T. Hill, L. F. Faucette, F. L. McCabe, G. R. Girard, D. B. Bryan, B. M. Sutton, J. O'Leary Bartus, S. T. Crooke and R. K. Johnson, *J. Med. Chem., 30* (1987) 2181.
11 S. J. Berners-Price, R. K. Johnson, A. J. Giovenella, L. F. Faucette, C. K. Mirabelli and P. J. Sadler, *J. Bioinorg. Chem., 33* (1988) 285.
12 S. J. Berners-Price, R. K. Johnson, C. K. Mirabelli, L. F. Faucette, F. L. McCabe and P. J. Sadler, *Inorg. Chem., 26* (1987) 3383.
13 J. E. Huheey, *Inorganic Chemistry*, Harper and Row, New York, 3rd edn., 1983, p. 312.
14 M. Yaniv and W. R. Folk, *J. Biol. Chem., 250* (1975) 3243.
15 B. F. Hoskins, L. Zhenrong and E. R. T. Tiekink, *Inorg. Chim. Acta, 158* (1989) 7.
16 W. H. Baddley, F. Basolo, H. B. Gray, C. Nölting and A. J. Poë, *Inorg. Chem., 2* (1963) 921.
17 A. K. Al-Saády, C. A. McAuliffe, R. V. Parish and J. A. Sandbank, *Inorg. Synth., 23* (1985) 191.
18 P. F. Barron, J. C. Dyason, P. C. Healy, L. M. Engelhardt, B. W. Skelton and A. H. White, *J. Chem. Soc., Dalton Trans.*, (1986) 1965.
19 G. M. Sheldrick, *SHELX76*, program for crystal structure determination, Cambridge University, U.K., 1976.
20 C. K. Johnson, *ORTEP-II, Rep. ORNL-2794*, Oak Ridge National Laboratory, TN, U.S.A., 1971.
21 *International Tables for X-ray Crystallography*, Vol. IV, Kynoch Press, Birmingham, U.K., 1974, pp. 99, 149.
22 A. Bondi, *J. Phys. Chem., 68* (1964) 441.
23 E. R. T. Tiekink, *Z. Kristallogr., 187* (1989) 79.
24 E. R. T. Tiekink, T. Kurucsev and B. F. Hoskins, *J. Crystallogr. Spectrosc. Res., 19* (1989) 823.
25 E. R. T. Tiekink, *J. Crystallogr. Spectrosc. Res., 20* (1990) 371.
26 Y. Rosopulos, U. Nagel and W. Beck, *Chem. Ber., 118* (1985) 931.
27 R. Faggiani, H. E. Howard-Lock, C. J. L. Lock and M. A. Turner, *Can. J. Chem., 65* (1987) 1568.
28 I. R. Garrett, M. W. Whitehouse, B. Vernon-Roberts and P. M. Brooks, *J. Rheumatol., 12* (1985) 1079.
29 M. W. Whitehouse, A. H. Horewood and B. Vernon-Roberts, *Agents Actions, Suppl., 24* (1988) 184.
30 P. A. Bates and J. M. Waters, *Inorg. Chim. Acta, 81* (1984) 151.
31 S. J. Berners-Price, M. A. Mazid and P. J. Sadler, *J. Chem. Soc., Dalton Trans.*, (1984) 969.
32 C. W. S. Harker and E. R. T. Tiekink, *J. Coord. Chem., 21* (1990) 287.
33 E. R. T. Tiekink, unpublished results.
34 C. W. S. Harker and E. R. T. Tiekink, *Acta Crystallogr., Sect. C, 45* (1989) 1815.