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In Vitro Cytotoxic Properties of Gold(I) and Platinum(II) Compounds containing Asymmetric [2-(Methylsulfinyl) ethyl]diphenylarsine and Its Phosphorus Analogue.

Simon Y.M. Chooi, Pak-Hing Leung*, K.Y. Sim,

Department of Chemistry, National University of Singapore, Singapore 0511.

K.S. Tan, O.L. Kon*

Department of Biochemistry, National University of Singapore, Singapore 0511.

Abstract: The preparation of novel gold(I) compounds [ClAu($Ph_2ECH_2CH_2S(O)Me$] (**1** for E = As, **2** for E = P) containing the optically active and racemic forms of asymmetric $Ph_2ECH_2CH_2S(O)Me$ ligands is described. In both solid state and solution, the ligands behave as monodentates that coordinate to gold via arsenic or phosphorus. In vitro cytotoxicity evaluation in three human tumour models (Molt 4, Raji and CEM) showed the optically active and racemic forms of **2** to be remarkably potent. With the exception of the CEM tumour cells, (*R*)- and (*S*)-**2** displayed much higher potency than the corresponding gold-arsine analogues. In contrast, the optically active dichloro-platinum(II) compounds [$Cl_2Pt(Ph_2ECH_2CH_2S(O)Me$] (**3** for E = As, **4** for E = P) displayed negligible activities.

Ever since the antiarthritic drug Auranofin was reported to have antitumour activity,[1] there has been increasing interest in the potential of gold-phosphine complexes in the treatment of neoplastic diseases.[2] A diverse spectrum of phosphine ligands was evaluated and maximal activity was eventually reaped from bis(phosphines) bridged by cis-ethylene or ethane viz. 1,2-bis(diphenylphosphino)ethane (dppe).[3] However the linear gold compound [ClAu(dppe)AuCl] readily underwent ring closure to form the four-coordinate tetrahedral [$Au(dppe)_2$]Cl in the presence of thiols and blood plasma.[4] The bis-chelated complex, subsequently synthesised directly,[5] was found to display *in vivo* activity against several serial transplantable murine tumour models.[6] Meanwhile, the role of sulfoxides in antitumour research cannot be overlooked. Indeed, besides being a good solvent for hydrophobic anticancer drugs,[7] dimethyl sulfoxide (DMSO) is known to affect the biochemical functions of HL-60 leukemia cells[8] and reduce the nephrotoxicity of cisplatin.[9] In addition, sulfoxide complexes like [$Rh(S\text{-}Me_2SO)(pyridine)_2Cl_3$][10] and [PtCl(diam)(S-R'R"SO)]NO_3[11] (where diam is a bidentate diamine and R'R"SO is a substituted sulfoxide) have been reported to be active against KB carcinoma, P388 and L1210 leukemia. Collectively, these observations suggest that a gold compound containing an ethane disubstituted ligand incorporating both phosphine and sulfoxide donors may possess potent antitumour activity.

One ligand having the mentioned structural features is the novel $Ph_2PCH_2CH_2S(O)Me$. The coordination chemistry of this hetero bidentate ligand is enriched by the dual presence of a soft pi-acid (phosphine) and polar ambidentate function (sulfoxide). Along with its arsine counterpart, both $Ph_2ECH_2CH_2S(O)Me$ (E = As, P) ligands are good sequesters of Pd(II) and Pt(II) ions, and an E-S bonding

mode has already been documented in the series of $[Cl_2M(Ph_2ECH_2CH_2S(O)Me]$ (M = Pd, Pt) complexes.[12] Recently, *en route* to a successful optical resolution of the ligands, an unexpected E-O coordination was observed under the influence of stereoelectronic factors.[13] The availability of enantiomers of both ligands may have a bearing on the mechanistic aspect of the present work in view of the reported effect of chirality of sulfoxide ligands on antitumour activity.[11]

We report herein the synthesis and characterisation of new gold(I) compounds containing $Ph_2ECH_2CH_2S(O)Me$, and their *in vitro* cytotoxicities in several human tumour cell lines including Molt 4 (T-cell leukemia), Raji (B-cell lymphoma), CEM (T-lymphoblastoid), HeLa (cervical cancer) and MCF 7 (breast cancer).

Results and Discussion

Synthesis of Gold(I) Compounds. The $[ClAu(Ph_2ECH_2CH_2S(O)Me]$ compounds, **1** (E = As) and **2** (E = P) (Figure 1), were synthesised in optically active or racemic form by addition of one mole of (*R*)-, (*S*)- or (±)-$Ph_2ECH_2CH_2S(O)Me$ ligand to an aqueous acetone solution of freshly prepared chloro(thiodiglycol)gold ($[HO(CH_2)_2]_2SAuCl$) at room temperature. The latter was obtained by reducing sodium tetrachloroaurate(III) with excess thiodiglycol. The sulfinyl-substituted tertiary arsine or phosphine then displaces the thiodiglycol, forming an insoluble chlorogold(I) compound that is easily isolated by filtration. Crystallisation from dichloromethane-diethyl ether afforded white crystals in ca. 85% yield. These neutral compounds are air-stable and are soluble in a wide range of solvents like acetone, acetonitrile, chloroform, DMF, DMSO and ethanol.

In the solid state, the $Ph_2ECH_2CH_2S(O)Me$ ligands in these novel compounds were found to coordinate to gold via only their E donors. From the IR spectra, the absence of significant shift in ν(S=O) from that of the free ligand precludes any bonding of the sulfoxide group to gold.[14] In contrast, a shift from 1053 to 1198 cm^{-1} was previously reported for Au-S coordination in $[Au(S\text{-}Me_2SO)Cl_3]$.[15] Additionally, the two-coordinate geometry of the compounds was confirmed by the Au-Cl stretching at 315 and 328 cm^{-1}.[16] The monodentate behaviour was also evident in solution from ^1H NMR studies. In $CDCl_3$, each of the six compounds exhibited one sharp SMe singlet at ca. δ 2.60 which is very close to δ 2.53 registered by both the free ligands. Furthermore, in the $[ClAu(Ph_2PCH_2CH_2S(O)Me]$ compounds, a sharp singlet at δ 29.4 in the proton decoupled ^{31}P NMR is diagnostic of monodentate phosphine-coordinated chlorogold(I) compounds.[17]

At present, the inability of the sulfoxide to coordinate needs to be addressed. While the poor nucleophilicity at the sulfur stereocentre may not necessarily be the sole reason, the small bite angle of the $Ph_2ECH_2CH_2S(O)Me$ ligands will render them ineffective in meeting the requirements demanded by a three-coordinate compound. Interestingly, the former reason could be invoked to explain the failure to obtain the bridging compound $[(ClAu)_2(Ph_2ECH_2CH_2S(O)Me]$ using a ligand:Au(I) ratio of 1:2; in this case, only **1** or **2** was isolated.

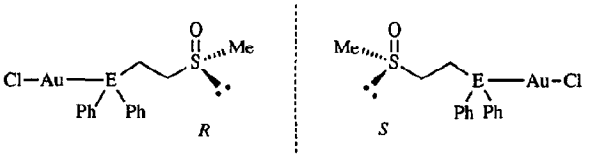

Figure 1. Enantiomers of $[ClAu(Ph_2ECH_2CH_2S(O)Me]$ (E = As, P)

Biological Activity. The biological tests indicate clearly that changes in the donor atom within the ligand coordinated to gold atom as well as in the metal itself can profoundly alter the *in vitro* cytotoxicities of the compounds. The cytotoxicity assay used measures the conversion of 3(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide to a blue compound by mitochondrial dehydrogenase. The intensity of absorbance values at 570 nm (A_{570}) reflects normal mitochondrial and cellular function. Low A_{570} values correlate with decreased viable cell numbers i.e. with cytotoxic effects. The results are depicted first in Figure 2 where the optically active gold-phosphine analogues (*R*)-**2** (IC_{50} 3.3 X 10^{-6} M) and (*S*)-**2** (IC_{50} 3.5 X 10^{-6} M) were more cytotoxic in Molt 4 cells than (*R*)-**1** ($IC_{50} > 10^{-5}$ M) and (*S*)-1 (IC_{50} 7.1 X 10^{-6} M) while the platinum(II) derivatives (*R*)-**3**, (*S*)-**3**, (*R*)-**4** and (*S*)-**4** had little or no cytotoxic activity in the same cell line (Figure 3). Interestingly, the cytotoxic effects of (*R*)-**1**, (*S*)-**1**, (*R*)-**2** and (*S*)-**2** appeared to be specific for certain tumour cell lines in that these compounds, while active in Molt 4 cells, had only slight effects on HeLa and MCF 7 cells (as shown in Table 1).

Table 1. Effect of compounds on three human tumour cell lines.

	Molt 4		HeLa		MCF 7	
	A_{570} (S.D.)[a]	$\%C_S$[b]	A_{570} (S.D.)	$\%C_S$	A_{570} (S.D.)	$\%C_S$
C_G[c]	0.24 (0.02)		0.49 (0.01)		0.41 (0.02)	
C_{S1}[d]	0.26 (0.01)	100.0	0.54 (0.03)	100.0	0.40 (0.01)	100.0
(*R*)-**1**[e]	0.15 (0.01)	57.7	0.51 (0.02)	94.4	0.38 (0.03)	95.0
(*S*)-**1**[e]	0.17 (0.05)	65.4	0.48 (0.03)	88.9	0.38 (0.02)	95.0
(*R*)-**2**[e]	0.00 (0)	0.0	0.47 (0.03)	87.0	0.39 (0.01)	97.5
(*S*)-**2**[e]	0.01 (<0.01)	3.8	0.50 (0.03)	92.6	0.42 (0.02)	105.0
C_{S2}[f]	0.25 (0.02)	100.0	0.50 (0.03)	100.0	0.38 (0.01)	100.0
(*R*)-**3**[g]	0.19 (0.02)	76.0	0.48 (0.02)	96.0	0.37 (0.03)	97.4
(*S*)-**3**[g]	0.19 (<0.01)	76.0	0.46 (0.02)	92.0	0.36 (0.03)	94.7
(*R*)-**4**[g]	0.19 (<0.01)	76.0	0.52 (0.01)	104.0	0.38 (0.03)	100.0
(*S*)-**4**[g]	0.20 (0.02)	80.0	0.49 (0.02)	98.0	0.39 (<0.01)	103.0

[a] mean absorbance at 570 nm (standard deviation). [b] mean absorbance in the presence of test compound expressed as a percentage of solvent control. [c] growth control. [d] contained 1.2% (v/v) ethanol. [e] tested at 1.25 X 10^{-5}M. [f] contained 1.25% (v/v) DMSO. [g] tested at 1.25 X 10^{-4}M.

Table 2 illustrates the effects of the same series of compounds on Raji and CEM cell lines. Raji cells resembled Molt 4 cells in their responses: (*R*)-**2** and (*S*)-**2** were more cytotoxic than (*R*)-**1** and (*S*)-**1**. However, CEM cells showed a pronounced cytotoxic response to all four optically active compounds. While the true biological significance of this observation is uncertain, it is consistent with bioselective effects of this series.

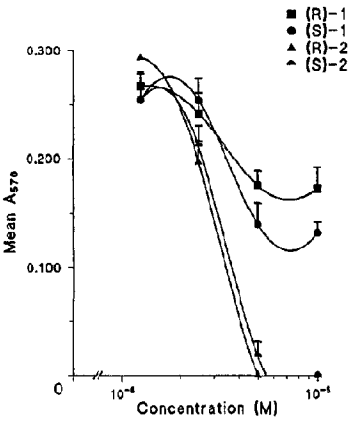

Figure 2. Cytotoxicity of optically active gold(I) compounds on Molt 4 cells

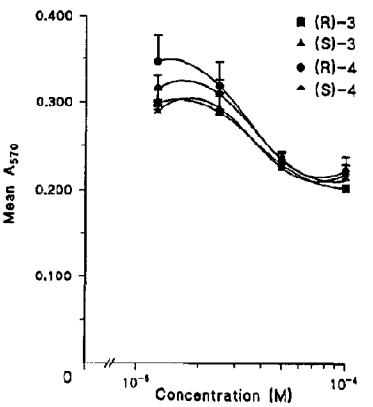

Figure 3. Cytotoxicity of optically active platinum(II) compounds on Molt 4 cells

Table 2. Effect of compounds on Raji and CEM cells.

	Raji		CEM	
	A_{570} (S.D.)[a]	%C_S[b]	A_{570} (S.D.)	%C_S
C_G[c]	0.34 (0.02)		0.27 (0.01)	
C_S[d]	0.33 (0.01)	100.0	0.24 (0.01)	100.0
(*R*)-1[e]	0.29 (0.02)	87.9	0.03 (0.01)	12.5
(*S*)-1[e]	0.24 (0.02)	72.7	0.01 (< 0.01)	4.2
(*R*)-2[e]	0.01 (0.01)	3.0	0.00 (0)	0.0
(*S*)-2[e]	0.01 (< 0.01)	3.0	0.00 (0)	0.0
(*R*)-3[f]	0.35 (0.01)	106.1	0.21 (0.02)	87.5
(*S*)-3[f]	0.35 (0.01)	106.1	0.22 (< 0.01)	91.7
(*R*)-4[f]	0.34 (< 0.01)	103.0	0.23 (0.01)	95.8
(*S*)-4[f]	0.33 (0.01)	100.0	0.22 (0.01)	91.7
(±)-2[e]	0.03 (0.02)	9.1	0.00 (0)	0.0
Standard[e,g]	0.00 (0)	0.0	0.01 (< 0.01)	4.2

[a] mean absorbance at 570 nm (standard deviation). [b] mean absorbance in the presence of test compound expressed as a percentage of solvent control. [c] growth control. [d] contained 1.25% (v/v) DMSO. [e] tested at 1.25 X 10^{-5}M. [f] tested at 1.25 X 10^{-4}M. [g] $[Au(dppe)_2]Cl$.

The biological data (Tables 2 and 3) also revealed that the *in vitro* cytotoxicity of the optically active [ClAu($Ph_2PCH_2CH_2S(O)Me$] compounds in the Molt 4, Raji and CEM tumour models are as potent as the [Au(dppe)$_2$]Cl complex which was included in these experiments as a standard. This augurs well for the potential of the former compounds for *in vivo* evaluation although the mechanism of the *in vitro* activity remains speculative. However, it is unlikely to be similar to that of [Au(dppe)$_2$]Cl which involves cross-linking of proteins to DNA,[18] but may resemble that of [ClAuPEt$_3$][19] with the polarity of the sulfoxide possibly aiding the transport of the largely lipophilic compound in aqueous medium. This notion comes in the wake of the observation that the racemic form of [ClAu($Ph_2PCH_2CH_2S(O)Me$] is as active as each individual enantiomer, thereby relegating the importance of the role of chirality in the sulfoxide function.

Table 3. Comparison of (±)-2 and standard compound with (*R*)-1, (*S*)-1, (*R*)-2 and (*S*)-2 in the Molt 4 tumour cell line.

	A_{570}[a]	S.D.[b]	$\%C_S$[c]
C_G[d]	0.201	0.01	
C_S[e]	0.180	0.01	100.0
(*R*)-1[f]	0.047	0.01	26.1
(*S*)-1[f]	0.012	0.01	6.7
(*R*)-2[f]	0.006	0.01	3.3
(*S*)-2[f]	0.009	0.01	5.0
(±)-2[g]	0.012	<0.01	6.7
Standard[g,h]	0.009	<0.01	5.0

[a] mean absorbance at 570 nm. [b] standard deviation. [c] mean absorbance in the presence of test compound expressed as a percentage of solvent control. [d] growth control. [e] contained 1.2% (v/v) ethanol. [f] tested at 1.25 X 10^{-5}M. [g] tested at 1.25 X 10^{-4}M. [h] [Au(dppe)$_2$]Cl.

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Experimental

General. ^{1}H and ^{31}P NMR spectra were recorded at 25°C on a Bruker ACF 300 spectrometer. IR spectra were obtained from a Perkin Elmer 598 spectrometer. Optical rotations were measured on the specified solutions in a 1-dm cell at 25°C with a Perkin Elmer 241 polarimeter. Melting points were determined on an Electrothermal IA 9200 apparatus. Elemental analyses were performed on a Perkin Elmer 2400 elemental analyser by the Microanalytical Laboratory staff of the Department of Chemistry. Sodium tetrachloroaurate(III) (Aldrich Chemical) and thiodiglycol (Merck) were commercially available. (±)-$Ph_2ECH_2CH_2S(O)Me$ and their optically active enantiomers,[13] the optically active **3** and **4**,[13] and $[Au(dppe)_2]Cl_5$ were obtained according to procedures in the literature.

(±)-Chloro[[2-(methylsulfinyl)ethyl]diphenylarsine-As]gold(I) ((±)-1). Thiodiglycol (0.15 mL, 1.56 mmol) was first added to a stirring aqueous acetone (1:1, 15 mL) solution containing $Na[AuCl_4].2H_2O$ (0.31 g, 0.78 mmol). When the solution became colourless, (±)-$Ph_2AsCH_2CH_2S(O)Me$ (0.25 g, 0.78 mmol) was added. After 1 h, the reaction mixture was concentrated, and the white precipitate was filtered, washed with water, dried and crystallised from dichloromethane-diethyl ether as white needles (0.38 g, 87%), mp 148-149°C (dec.). Found: C, 32.5; H, 3.0. $C_{15}H_{17}AsAuClOS$ requires C, 32.6; H, 3.1%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (s, 3H, SMe), 2.79-3.07 (m, 4H, CH_2CH_2), 7.48-7.66 (m, 10H, aromatics); IR (CsI) 315 (Au-Cl), 1036 (S=O) cm^{-1}.

(*R*)-Chloro[[2-(methylsulfinyl)ethyl]diphenylarsine-As]gold(I) ((*R*)-1). The compound was similarly prepared using (*R*)-$Ph_2AsCH_2CH_2S(O)Me$ (0.15 g, 0.47 mmol): white microcrystals (0.21 g, 81%), mp 139-140°C (dec.). $[\alpha]_D$ -38.4 (c = 1.0, CH_2Cl_2). IR (CsI) and ^{1}H NMR (300 MHz, $CDCl_3$) spectra are identical to the racemic compound.

(*S*)-Chloro[[2-(methylsulfinyl)ethyl]diphenylarsine-As]gold(I) ((*S*)-1). The (*S*)-compound was isolated as white microcrystals in 84% yield, mp 139-140°C (dec.). $[\alpha]_D$ +38.2 (c = 1.0, CH_2Cl_2).

(±)-Chloro[[2-(methylsulfinyl)ethyl]diphenylphosphine-P]gold(I) ((±)-2). Following the procedure as described for the arsine analogue, and using (±)-$Ph_2PCH_2CH_2S(O)Me$ (0.58 g, 2.10 mmol) as ligand, the racemic gold(I) compound was obtained as white needles from dichloromethane-diethyl ether in 85% yield (0.87 g), mp 146-147°C (dec.). Found: C, 35.1; H, 3.3. $C_{15}H_{17}AuClOPS$ requires C, 35.4; H, 3.4%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (s, 3H, SMe), 2.76-3.07 (m, 4H, CH_2CH_2), 7.49-7.75 (m, 10H, aromatics); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 29.39 (s); IR (CsI) 328 (Au-Cl), 1038 (S=O) cm^{-1}.

(*R*)-Chloro[[2-(methylsulfinyl)ethyl]diphenylphosphine-P]gold(I) ((R)-2). The optically active compound was synthesised likewise using (*R*)-$Ph_2PCH_2CH_2S(O)Me$: white prisms (0.15 g, 82%), mp 138-139°C (dec.). $[\alpha]_D$ -29.7 (c = 1.0, CH_2Cl_2). IR (CsI) and ^{1}H NMR (300 MHz, $CDCl_3$) spectra are similar to the racemic compound.

(*S*)-Chloro[[2-(methylsulfinyl)ethyl]diphenylphosphine-P]gold(I) ((S)-2). Likewise, the (*S*)-compound was obtained as white prisms in 83% yield, mp 138-139°C (dec.). $[\alpha]_D$ +29.5 (c = 1.0, CH_2Cl_2). IR (CsI) and ^{1}H NMR (300 MHz, $CDCl_3$) spectra are similar to the racemic compound.

Biological Assays.

(a) **Cell lines.** The following human tumour cell lines were cultured at 37°C and 5% carbon dioxide in RPMI 1640 medium containing 10% fetal calf serum: Molt 4 (T-cell leukemia), Raji (B-cell lymphoma) CEM

(T-lymphoblastoid). HeLa (cervical cancer) and MCF 7 (breast cancer) were cultured in RPMI 1640 medium containing 5% newborn calf serum. Cells were subcultured at 2-3 day intervals at a density of 250,000 cells/mL (for suspension cultures) or split at 1:4 to 1:6 ratios (for monolayer cultures). Cytotoxic assays were set up in 96-well plates at a density of 30,000 cells/well (suspension cultures), 50,000 cells/well (HeLa) and 45,000 cells/well (MCF 7).

(b) Cytotoxic assay. Compounds were tested against the above panel of human tumour cell lines using the tetrazolium salt, (3[4,5-dimethylthiazol-2-yl]2,5-diphenyltetrazolium bromide) (MTT) as previously described[20] except that the tumour cells were dispensed in aliquots of 70 μL/well and test compounds were added in a volume of 10 μL. Stock solutions of test compounds [10^{-3}M for compounds (*R*)-**1**, (*S*)-**1**, (*R*)-**2** and (*S*)-**2** in 95% (v/v) ethanol; 10^{-2}M for compounds (*R*)-**3**, (*S*)-**3**, (*R*)-**4** and (*S*)-**4** in dimethyl sulfoxide] were prepared. Dilutions from stocks were made with serum-supplemented RPMI 1640 medium such that the final concentrations of ethanol and DMSO were 1.2% (v/v) and 1.25% (v/v) respectively.

Three different controls were initially set up in every assay. Firstly, growth controls (abbreviated C_G in Tables 1-3) were in serum-supplemented RPMI 1640 medium without either test compound or solvent. Solvent controls (C_S) received an identical concentration of either 1.2% (v/v) ethanol or 1.25% (v/v) DMSO in place of test compounds, while drug controls consisted of 70 μL of serum-supplemented RPMI 1640 medium and 10 μL of a test compound. Growth control wells reflected proliferation and growth of cells in the absence of any treatment or solvent. Solvent control wells reflected the extent to which solvent alone affected cell viability and proliferation. Drug control wells were intended to correct for colour development in the MTT assay method due to the interfering presence of the drug alone. Drug controls were omitted from the later assays because all compounds produced negligible background absorbance at 570 nm (A_{570}) in the absence of cells. Compounds were tested for cytotoxic activity either at a single concentration (1.25×10^{-5}M) or over a dose range between approximately 10^{-7}M and 10^{-5}M. Growth controls, solvent controls and test wells were set up in triplicate. Treatment was implemented for 14h-16h. Results are presented as mean A_{570} (± standard deviation) of triplicate wells.

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