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# Organogold(III) metallacyclic chemistry. Part 4[1]. Synthesis, characterisation, and biological activity of gold(III)-thiosalicylate and -salicylate complexes

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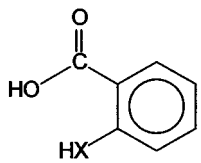
**Abstract**

The silver(I) oxide mediated reactions of the gold(III) dichloride complex [{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}$AuCl_2$] **2a** with thiosalicylic or salicylic acid gives the respective complexes [{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Au{$XC_6H_4(COO)$-2}] **3a** (X = S) or **6b** (X = O), containing chelating thiosalicylate or salicylate dianion ligands. X-ray studies show that for the thiosalicylate system, the thiosalicylate sulfur atom is *trans* to the *N*,*N*-dimethylamino group, whereas in the structure of the salicylate complex, it is the carboxylate group that is *trans* to $NMe_2$. Both complexes show puckered metallacycles in the solid state. Electrospray mass spectrometry (ESMS) shows strong $[M + H]^+$ and $[2M + H]^+$ ions for both the gold-thiosalicylate and -salicylate complexes, and these ions possess a high stability towards cone voltage-induced fragmentation. ESMS was also used to identify a minor impurity, the bis(cyclo-aurated) cationic complex $[Au\{C_6H_3(CH_2NMe_2)$-2-(OMe)-5$\}2]^+$ in the starting dihalide complex **2a** and in the product **3a**. This complex can be formed by reaction of $Me_4N[AuCl_4]$ with 2 equivalents of the organomercury precursor [Hg{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Cl]. The biological (antitumour, antimicrobial and antiviral) activities are also reported, and these reveal the complexes have moderate to high anti-tumour, antibacterial and antifungal activity. © 1998 Elsevier Science S.A. All rights reserved.

*Keywords:* Gold; Thiosalicylate; Salicylate; Metallacycle; Crystal structure; Electrospray

## 1. Introduction

Gold complexes with thiolate ligands are an important class of coordination complex, finding various applications, including drugs for the treatment of rheumatoid arthritis [1–6] and nanotechnologies [7] among others. Thiosalicylic acid (2-sulfanylbenzoic acid) is a heterodifunctional thiol ligand capable of bonding to a range of metal centres as either a monoanion or a dianion, and is capable of coordinating in a range of bonding modes. The strong propensity of gold(I) to form stable thiolate complexes is well-known [8–13], and several gold(I)-thiosalicylate complexes have been described. Schmidbaur and co-workers have recently reported a number of gold(I) complexes of thiosalicylic




**1a X = S**

**1b X = O**

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[1] For parts 1–3 see references [23–25], respectively.


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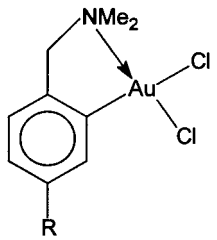
acid (and other mercapto-carboxylic acids), including the sulfonium salt [14] $[(Ph_3PAu)_2\{SC_6H_4(COOH)\text{-}2\}]^+BF_4^-$ and the isocyanide complexes [15] $[Au\{SC_6H_4(COOH)\text{-}2\}(RNC)]$ (R = *tert*-butyl or mesityl). The related phosphine complex $[Au\{SC_6H_4(COOH)\text{-}2\}(Ph_3P)]$ has also been described, and its structure determined [16]. Compounds of this type are of interest for their hydrogen-bonding as well as Au…Au interactions in the solid-state. A gold(I) bis(thiosalicylate) complex $Na_3[Au\{SC_6H_4(COO)\text{-}2\}_2]\cdot 5H_2O$ has recently been synthesised and characterised [17]. Oligomeric and polymeric silver(I)-thiosalicylate complexes, with a 1:1 silver:thiosalicylate ratio, have also been described and found to display effective antimicrobial properties for yeast, bacteria and mold [18]. Gold-thiosalicylate complexes have been studied as model complexes for the interaction of gold with sulfur donor groups in humic acid in natural systems [19]. The gold salt of $[Hg\{SC_6H_4(COO)\text{-}2\}_2]^{2-}$ has been described [20], and a gravimetric method using thiosalicylic acid for the determination of gold has also been reported [21].

In this contribution we report the synthesis of some organo-gold(III) complexes containing the chelating thiosalicylate and salicylate dianion ligands. Complexes containing cycloaurated *N*,*N*-dimethylbenzylamine or related [22] ligands together with two *cis*-chlorides are attractive starting materials for the study of gold(III) metallacyclic chemistry, and we recently reported the synthesis of Au–C–S(O)$_2$–C, Au–C–C(O)–C [23] and Au–N–C(O)–N [24] ring systems as well as novel gold(III)–sulfido–silver(I)–halide aggregates [25], the latter from reactions with thioureas. The new gold(III)-thiosalicylate complexes reported herein allow comparisons to be made with the isoelectronic platinum(II) thiosalicylate complexes, which we have recently described [26]. Since the chelating binding mode of the thiosalicylate ligand in these gold(III) complexes is very different to the previously characterised gold(I) complexes, such complexes might display different biological activities, which could be of interest given the medical importance of gold-thiolate complexes.

## 2. Results and discussion

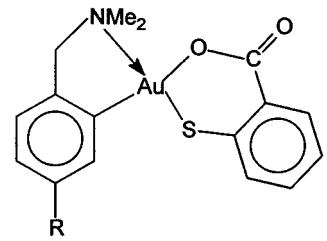
Reactions of the cycloaurated *N*,*N*-dimethylbenzylamine complexes **2a** and **2b**




**2a** R = OMe

**2b** R = H

with one molar equivalent of thiosalicylic acid and excess silver(I) oxide in refluxing dichloromethane gives the respective gold(III) thiosalicylate complexes **3a** and **3b.**




**3a** R = OMe

**3b** R = H

Both complexes are air- and reasonably light-stable, bright yellow solids, with the methoxy-functionalised derivative **3a** showing a significantly higher solubility in organic solvents than the unsubstituted complex **3b**. The reactions proceed in high yield, and NMR spectra of the crude reaction products (after removal of the silver salts and evaporation of the solvent) indicated that a single, pure product was formed in each case. However, unambiguous identification of the actual isomer formed was not possible using NMR spectroscopy, despite an attempt at correlating the chemical shifts of the methylene and *N*,*N*-dimethylamino protons and carbons with the nature of the other groups coordinated to the gold(III) centre. Correlation and NOE experiments could also not distinguish between the two possible isomers, since the thiosalicylate ligand is too far removed from NMR active nuclei in the *N*,*N*-dimethylbenzylamine group. The unsubstituted complex **3b** gave crystals of suitable quality for an X-ray structure determination on recrystallisation from dichloromethane-diethyl ether, and the analysis was carried out in order to unequivocally determine which isomer had been formed.

### 2.1. Discussion of the structure *3b*

The molecular structure is shown in Fig. 1, showing the atom numbering scheme. The data set was unfortunately of poor quality (*R* factor 0.156) which was primarily attributed to twinning present in the crystal, together with significant disorder. However, the overall connectivity and conformation of the compound is unambiguous, and the internal check provided by the presence of two independent molecules in the asymmetric unit lends some additional credibility to the results of the study.

The structure confirms the presence of the chelating dianionic thiosalicylate ligand, which is coordinated with the thiolate sulfur *trans* to the *N*,*N*-dimethylamino group of the cycloaurated benzylamine ligand. As a result, the two soft, strong $\sigma$-donor ligands (the aryl and thiolate moieties) are *cis* to each other. This effect, *anti*-symbiosis, is well known in gold(III) chemistry

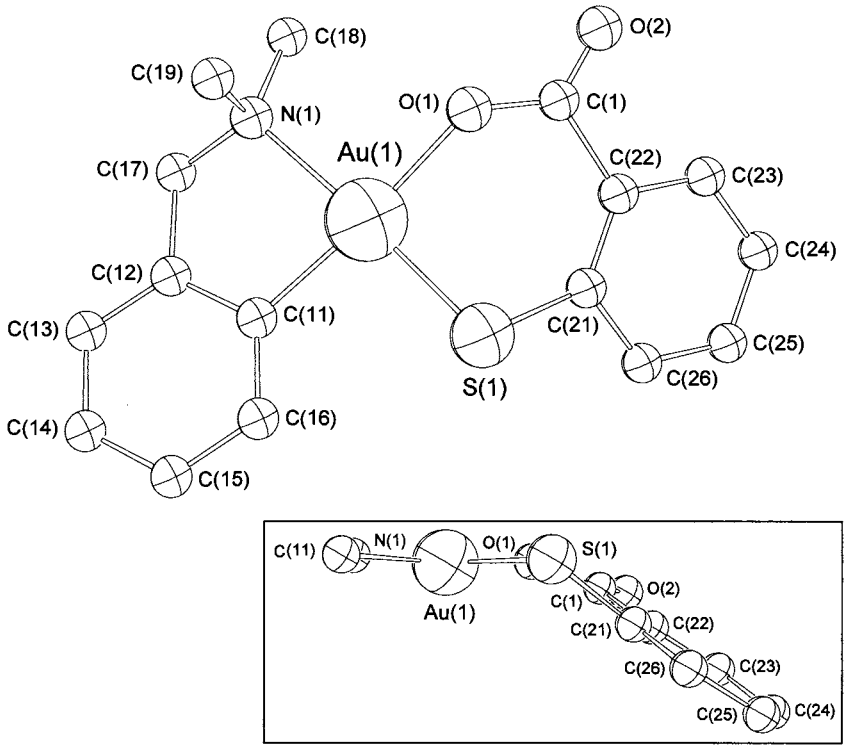
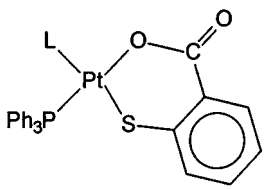



Fig. 1. PLUTO representation of the molecular structure of the gold(III) thiosalicylate complex [{$C_6H_4(CH_2NMe_2)$-2}Au{$SC_6H_4(COO)$-2}] **3b** (Molecule 1) showing the atom numbering scheme. The inset shows a side-on view demonstrating the non-planarity of the gold-thiosalicylate moiety.

[27,28], and X-ray structures of the bis(cyclometallated)gold(III) complexes [{$C_6H_4(CH_2NMe_2)$-2}Au{$C_6H_4(N{=}NPh)$-2}] $ClO_4$ [29] and [Au{$C_6H_4(N{=}NPh)$-2}$_2$]$^+$ [30] both show the high *trans*-influence aryl ligands in mutually *cis* positions. The platinum(II) thiosalicylate complex [Pt{$SC_6H_4(COO)$-2}($PPh_3$)(py)] **4a** [31] (py = pyridine) shows the same effect, with the poorer donor ligand (pyridine) *trans* to the sulfur atom.

The most striking feature of the structures is that the gold-thiosalicylate moiety is markedly non-planar, with fold angles of 30.1(8)° and 37.8(6)° for molecules 1 and 2, between the planes defined by S(1), Au(1), O(1) and S(1), C(21), C(22), O(1), C(1) for molecule 1, and S(2), Au(2), O(3) and S(2), C(41), C(42), O(3), C(2) for molecule 2. These are significantly greater than that observed for the isoelectronic platinum(II) complex **4a**




**4a** L = py

**4b** L = $PPh_3$

[10.3(4)°] [31], but considerably less than that of [Pt{$SC_6H_4(COO)$-2}($PPh_3$)$_2$] **4b** [26] [45.9°]. The reason for the different fold angles for **4a** and **4b** is not clear, although presumably the conformation is readily influenced by crystal-packing forces. This notion is tentatively supported by the different fold angles measured for the independent molecules 1 and 2 in **3b**. The related nickel(II) complex [Ni{$SC_6H_4(COO)$-2}(dppp)] [dppp = $Ph_2P(CH_2)_3PPh_2$] was also found to be bent, with a fold angle of 9.4° [26]. In the case of the complex **3b**, steric factors are likely to play only a minor part in the puckering of the thiosalicylate ligand. We suggested previously that the puckering of the platinum(II) thiosalicylate moiety in **4b** compared to that in nickel(II) complex might be due to the bite of the thiosalicylate ligand which is better suited towards coordination of the smaller nickel(II), although in light of the structural evidence from **4a** and from the salicylate systems (see later) this interpretation is possibly oversimplified. Clearly more structure determinations are required for a more definitive picture to emerge.

The structure bears a close resemblance to the recently reported gold complex involving the thiomalate ligand, [{$C_6H_4(CH_2NMe_2)$-2}Au{$SCH(COO)CH_2$-COOH}] **5** [32],

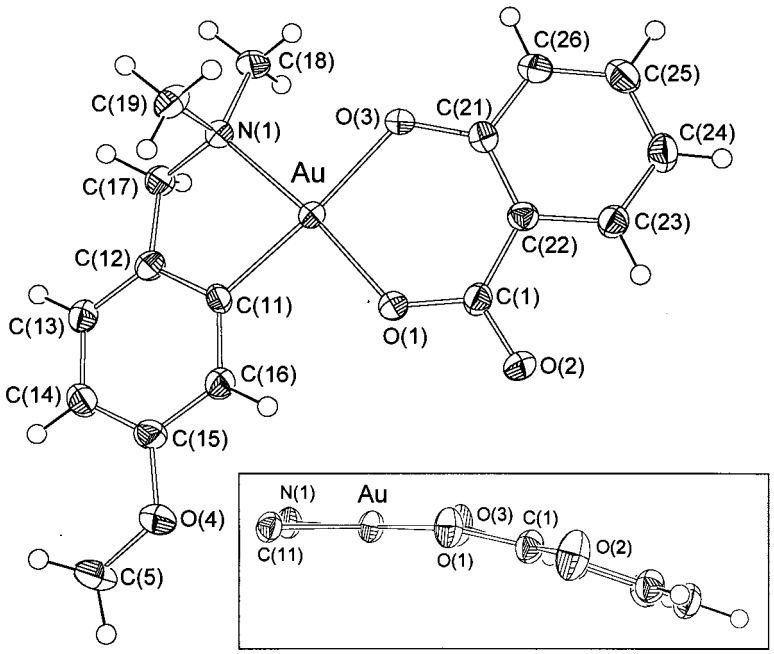
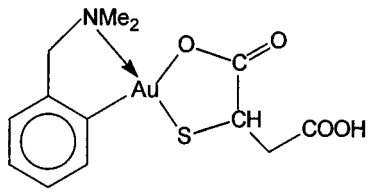



Fig. 2. ORTEP representation of the molecular structure of the gold(III) salicylate complex [{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Au{$OC_6H_4(COO)$-2}] **6b** showing the atom numbering scheme. The inset shows a side-on view demonstrating the non-planarity of the gold-salicylate metallacycle. The thermal ellipsoids are shown at the 50% probability level.

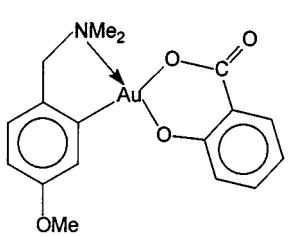



**5**

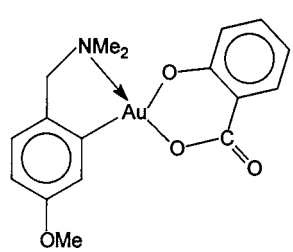
although the five-membered Au–S–C–C–O ring for this complex was planar. The quality of the data does not warrant discussion of the remaining structural features, and comparisons of bond lengths and angles with those of **5**, **6b** (see later) or the platinum and nickel thiosalicylate complexes can not be made with confidence.

### 2.2. Gold(III) salicylate complex

Given the high regioselectivity of the reactions of the gold(III) halide complexes with thiosalicylic acid, it was of interest to see whether the same selectivity also existed in the reaction with salicylic acid, where the two donor groups are now both relatively low *trans*- influence oxygen atoms. The reaction of complex **2a** with salicylic acid **1b** was carried out in refluxing dichloromethane with silver(I) oxide, and NMR ($^1H$ and $^{13}C$) analysis of the crude reaction product indicated the expected mixture of isomers of the gold(III) salicylate complexes [{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Au{$OC_6H_4(COO)$-2}] **6a** and **6b** in an approximately 3:1 ratio. Confirmation of reaction completion was provided by ESMS which gave $[M + H]^+$ and $[2M + H]^+$ ions, obviously indistinguishable for **6a** and **6b**.




**6a**




**6b**

Upon standing the mixture of isomers in $CDCl_3$ overnight, complete conversion to a single isomer was effected. Light yellow crystals were obtained from the crude yellow solution by layering diethyl ether and pentane onto a solution of the complex in a dichloromethane-chloroform mixture.

The initially formed, kinetically favoured isomer, is tentatively assigned as the same isomer as for the gold(III) thiosalicylate complexes, i.e. with the phenolate group *trans* to the *N*,*N*-dimethylamino group. The phenolate group has a slightly higher *trans*-influence than the carboxylate group, as shown by values of $^1J(^{195}Pt-^{31}P)$ of 3549 and 3929 Hz for the triphenylphosphine ligands trans to O and $O_2C$ moieties, respectively, in the platinum-salicylate complex [Pt{$OC_6H_4(COO)$-2}$(PPh_3)_2$] [26]. The corresponding $^1J(^{195}Pt-^{31}P)$ values for $PPh_3$ ligands *trans* to S and $O_2C$ in [Pt{$SC_6H_4(COO)$-2}$(PPh_3)_2$] **4b** are 2884 and 3899 Hz.

Table 1
Selected bond lengths (Å) and angles (°) for **6b** with estimated standard deviations in parentheses

| Bond | Length | Bonds | Angle |
|---|---|---|---|
| Au–O(3) | 2.037(3) | O(3)–Au–O(1) | 82.41(13) |
| Au–O(1) | 1.985(3) | N(1)–Au–C(11) | 92.45(11) |
| Au–N(1) | 2.057(3) | N(1)–Au–O(3) | 91.24(13) |
| Au–C(11) | 2.001(3) | O(1)–Au–C(11) | 122.0(2) |
| | | Au–O(3)–C(21) | 126.1(2) |
| | | Au–O(1)–C(1) | |
| Salicylate ligand | | | |
| O(3)–C(21) | 1.329(5) | O(3)–C(21)–C(22) | 125.8(3) |
| C(1)–O(1) | 1.315(4) | C(21)–C(22)–C(1) | 126.2(3) |
| C(1)–O(2) | 1.222(5) | C(22)–C(1)–O(2) | 120.2(3) |
| C(1)–C(22) | 1.497(5) | C(22)–C(1)–O(1) | 122.6(3) |
| | | O(2)–C(1)–O(1) | 117.3(3) |

A single-crystal X-ray diffraction study was carried out on the salicylate complex **6b** in order to confirm the isomer assignment from NMR spectroscopy, and to compare the binding requirements of the gold-salicylate moiety with the gold and platinum thiosalicylate moieties. Additionally there is a paucity of structure determinations of salicylate complexes with platinum group metals and gold, so little is known about the detailed binding of the salicylate ligand towards these metals.

### 2.3. Discussion of the structure *6b*

The molecular structure is shown in Fig. 2, together with the atom numbering scheme, while selected bond lengths and angles are given in Table 1. The complex is the opposite isomer to that observed for the analogous thiosalicylate complex **3b**, in having the carboxylate group *trans* to the *N*,*N*-dimethylamino moiety. It appears that the geometric requirements of the salicylate ligand are a good match for the gold(III) centre; the four donor atoms around the gold atom form a very regular square plane, with the maximum deviation from the least-squares plane defined by atoms Au, N(1), C(11), O(1), and O(2) being only 0.013(1) Å above the plane for atom N(1) and 0.012(1) Å below for Au. Additionally, the bite angle of the salicylate ligand at gold, O(1)–Au–O(2) at 93.9(1)°, is close to the idealised 90°, and almost identical to that of the thiosalicylate complex **3b** [average 91.9(4)°].

As found in the thiosalicylate-gold system, the salicylate ligand is also non-planar with the gold square-plane, though the degree of puckering [17.9(2)°] is considerably less than for the thiosalicylate complex **3b**. Unfortunately, no X-ray structure determinations of platinum(II) salicylate complexes exist to enable a comparison to be made. Indeed, an examination of the Cambridge X-ray Crystal Structure Database, surprisingly revealed this to be only the second reported structure of a third row transition-metal mononuclear complex containing a chelating salicylate dianion. A number of mononuclear salicylate dianion complexes derived from Mn(III) [33–35], Mn(IV) [36], Fe(III) [37], Co(III) [38,39], Cu(II) [40,41], Mo(VI) [42–44] and Os(VI) [45] have been structurally characterised previously. The first row transition metal salicylate complexes show essentially no puckering of the salicylate ring, whereas the molybdenum and osmium examples show significant puckering with fold angles of 24 and 12° for the two coordinated salicylate ligands in a molybdenum derivative [43], and 14.9° for the osmium system [45]. The former lends further evidence of the flexible nature of the salicylate ligand, since both ligands are bound to the same metal centre.

### 2.4. NMR and IR spectroscopic characterisation

Proton and carbon NMR spectra for the complexes **3a**, **3b** and **6b** have been fully assigned in conjunction with the use of COSY, HMBC and HSQC experiments, while **6a** was assigned by analogy with **6b**. The aromatic region of the proton NMR spectrum for complex **3b** is shown

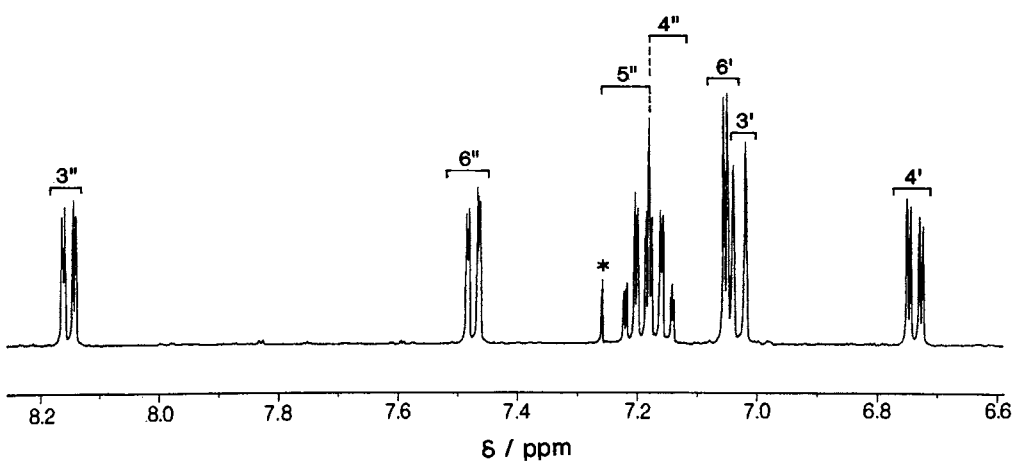


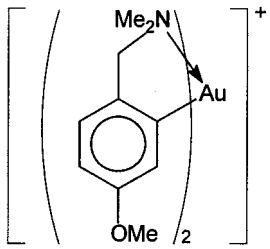

Fig. 3. $^1$H-NMR spectrum (400 MHz) of the aromatic region of complex **3a** in $CDCl_3$ with proton assignments (refer also Section 3). The peak marked with an asterisk is due to $CHCl_3$ from the solvent.

in Fig. 3, together with the numbering scheme. For this complex the presence of the methoxy substituent markedly simplifies the $^1$H spectrum compared to that of **3b**, by substantially reducing the number of $^3J$ and $^4J$ couplings on the aurated aromatic ring. Thus in **3b** the isolated proton 6′ appears as a simple doublet due to $^4J$ coupling to proton 4′. Proton 4′ gives a doublet of doublets due to $^4J$ and $^3J$ couplings (to 6′ and 3′, respectively). Proton 3′ appears as a slightly broadened doublet, possibly showing unresolved $^4J$ coupling to the methylene protons. The thiosalicylate protons 3″ and 6″ give doublets of doublets, while the central protons 4″ and 5″ give the expected pseudo-doublets of triplets, which were partially overlapping. The $^1$H-NMR spectrum is completed by $CH_2$, OMe and $NMe_2$ singlet resonances at 4.16, 3.81 and 3.06 ppm, respectively. The presence of 2 equivalent NMe resonances indicates that in solution the gold-thiosalicylate moiety is either planar or undergoing rapid inversion, equilibrating the two *N*-bonded methyl groups which are inequivalent in the solid state. The salicylate derivative **6b**, shows similar $^1$H- and $^{13}$C-NMR spectroscopic features to **3a**, with only minor changes in resonance positions for the cycloaurated benzylamine ligand.

### 2.5. Electrospray mass spectrometry

Positive-ion ESMS spectra of the complexes **3a**, **3b** and **6b** recorded in 1:1 MeCN-$H_2O$ solution, yield the protonated $[M + H]^+$ ions as the base peaks, though the aggregate ions $[2M + H]^+$ were also of almost equal intensity in the spectra recorded at cone voltages of 20 V. As suggested for the related platinum, palladium and nickel complexes [26], the carbonyl group is the sole site for protonation for **3b** in the absence of other basic groups in the molecule. However, for the methoxy-substituted complexes, the MeO group is also expected to play a significant role in the ionisation of the complex, as is the phenoxy O present in **6b**. The $[M + H]^+$ ions show exceptional stability when subjected to exceedingly high cone voltages (up to 200 V), which typically induces extensive fragmentation of parent ions. Undoubtedly, this stability is due to the presence of two chelate rings in the complexes, together with the absence of a facile decomposition pathway, such as cyclometallation of a phosphine ligand. We have noted previously that complexes containing phosphine ligands which do not readily undergo cyclometallation reactions [e.g. dppe and PTA (phosphatriaza-adamantane)] also show pronounced stability towards fragmentation at high cone voltages in ESMS experiments [26]. Thus, for the complexes **3a**, **3b** and **6b** at the maximum cone voltage possible for the instrument used (200 V), the $[M + H]^+$ ions remained the base peaks. This compares with the complex $[Pt\{SC_6H_4(COO)\text{-}2\}(PTA)_2]$ which also showed a comparable stability towards cone voltage-induced fragmentation [26].

The ESMS spectrum of the crude reaction product of complex **3a** indicated an additional species at $m/z$ 525, which was removed on recrystallisation. ESMS analysis of the starting dichloride complex **2a** revealed the same impurity species. This species was tentatively assigned as the cationic complex **7**




**7**

containing two cycloaurated dimethylbenzylamine ligands. Due to the cationic nature of **7** it is likely to have a very high ESMS ionisation efficiency. Other charged species such as metal complex cations and phosphonium salts typically yield very intense parent ions [46]. In comparison, the complex **2a** ionises by loss of a chloride ligand, and, depending on the cone voltage, coordinates a molecule of the solvent, similar to the ionisation observed for a range of other transition-metal halide and related complexes [47]. This ionisation process is likely to be far less efficient, resulting in detection of the cation **7** in ESMS, but not in the NMR spectra. Upon addition of pyridine to the solution of **2a** in MeCN/$H_2O$, the species $[\mathbf{2a}\text{-Cl} + py]^+$ is the major ion observed, and **7** was not observed in this experiment, suggesting that the added pyridine is more effective at forming positive ions than with the MeCN–$H_2O$ solvent alone [47]. The cationic pyridine derivative of **2b**, $[Au\{C_6H_4(CH_2NMe_2)\text{-}2\}(py)Cl]^+$, has been isolated as its perchlorate salt [48].

Modification of the synthesis of complex **2a**, by reaction of $Me_4N[AuCl_4]$ with 2 mol equivalents of the organomercury precursor $[Hg\{C_6H_3(CH_2NMe_2)\text{-}2\text{-}(OMe\text{-}5\}Cl]$ in refluxing MeCN gave a very pale yellow solution, ESMS analysis of which revealed only the cation **7** at $m/z$ 525. Addition of pyridine to the ESMS solution of **7** yielded no pyridine adducts, consistent with it being a bis(cyclometallated) species. Attempted isolation of complex **7** has not been successful, since it appears to be very light and/or air sensitive, decomposing even in the refrigerator; the nature of the anion remains unknown. The complex **7** does not appear to have been described previously. The reaction of $H[AuCl_4]$, $Na[AuCl_4]$ or $[AuLCl_2]$ with excess $[\{HgLCl\}_n]$ (HL = 2-phenylpyridine) was unsuccessful in giving such a bis(cyclometallated) gold(III) cation [49]. However, several bis[(2-phenylazo)phenyl]gold(III) cationic complexes containing $[Au\{C_6H_4(N{=}NPh)\text{-}2\}_2]^+$ have been synthesised [30] by reaction of $[Hg(C_6H_4(N{=}NPh)\text{-}2)_2]$ with $Me_4N[AuCl_4]$ followed by $AgClO_4$, and the mixed cyclometallated ligand cation $[\{C_6H_4(CH_2NMe_2)\text{-}2\}Au\{C_6H_4(N{=}NPh)\text{-}2\}]^+$, has been synthesised [29] by reaction of **2b** with $[Hg(C_6H_4(N{=}NPh)\text{-}2)_2]$.

Table 2
(a) Antitumour (P-388) and antiviral/cytotoxicity assay results and (b) antimicrobial/antifungal[e] activities[f] of **3a**, **3b** and **6b** (2 μg loaded on disc).

| (a) Compound | $IC_{50}^{a}$ | Cyt[b] |
|---|---|---|
| **3a** | 301 | 3+[c] |
| **3b** | 1937 | 4+[d] |
| **6b** | 5056 | 4+ |

| (b) | Ec | Bs | Pa | Ca | Tm | Cr |
|---|---|---|---|---|---|---|
| **3a** | 2 | 6 | 3 | 5 | 4 | 7 |
| **3b** | 4 | 10 | 4 | 6 | 12 | 4 |
| **6b** | 8 | 12 | 7 | 8 | 13 | 1 |

[a] The concentration of sample in ng/ml required to reduce the cell growth of the P-388 leukemia cell line (ATCC CCL 46) by 50%.
[b] Cytotoxicity to BSC cells.
[c] 3+ denotes antiviral or cytotoxic zone 4–6 mm excess radius form the disc (75% zone).
[d] 4+ denotes antiviral or cytotoxic zone over whole well (100% zone).
[e] Ec, *Escherichia coli*; Bs, *Bacillus subtilis*; Pa, *Pseudomonas aeruginosa*; Ca, *Candida albicans*; Tm, *Trichophyton mentagrophytes*; Cr, *Cladosporium resinae*.
[f] Inhibition zone as excess radius (mm) from a 6 mm (diameter) disc containing 2 μg of sample.

### 2.6. Biological activity of the gold(III) thiosalicylate and salicylate complexes *3a*, *3b* and *6b*

The cyclometallated gold(III) complex $[Au\{C_6H_4(CH_2NMe_2)\text{-}2\}(OOCMe)_2]$ **8**, containing water-solubilising acetate ligands has generated interest since it shows both antibacterial activity, and activity against Chinese hamster ovary cells comparable to that of the well-established drug cisplatin [50]. The dichloride complex **2a** also possesses activity against human breast tumour cells [51]. Studies of the interaction of **8** with the thiol-containing compounds L-cysteine and glutathione indicated that cyclic thiolate complexes were formed [50]. We have therefore tested the biological activity of the complexes **3a**, **3b** and **6b**, and all three show wide-spectrum biological activity, the results of which are summarised in Table 2a and b.

Against P388 leukaemia cells, the complex **3a** gave an $IC_{50}$ value (the amount required to inhibit 50% of cell growth) of 301 ng $ml^{-1}$, which can be interpreted as having very high anti-tumour activity. Complex **3b** also showed significant activity ($IC_{50}$ 1937 ng $ml^{-1}$), although considerably less than that of **3a**. This is possibly the result of poorer solubility in biological media, with the absence of the solubilising methoxy group. The salicylate derivative **6b** showed only moderate anti-tumour activity ($IC_{50}$ 5056 ng $ml^{-1}$).

For the antimicrobial assay, the complex **3a** showed moderate activity against the tested bacteria *Escherichia coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa*, and the fungi *Candida albicans*, *Trichophyton mentagropytes* and *Cladosporium resinae*. Surprisingly **3b** and **6b** showed significantly higher activity against the microbes tested, and the reason for this is not obvious. The compounds show effectively no antiviral activity, since their high cytotoxicity killed the majority (or all) of the BSC-1 cell line used for test.

### 2.7. Attempted reaction of *3a* with mercury(II) iodide

We have previously reported reactions of several cyclic platinum(II) thiolate complexes, including the thiosalicylate complex **4b** with excess mercury(II) iodide, which results in the formation of tetrametallic thiolate-bridged complexes with the thiolate sulfur atoms of the platinum complexes coordinated to the two mercury atoms of a $IHg(\mu\text{-}I)_2HgI$ unit [52,53]. These reactions are readily monitored by NMR spectroscopy, whereupon coordination of the thiolate sulfur induces chemical shift and coupling constant changes in the metalloligand. We have therefore investigated the reaction of one of the new gold(III) thiosalicylate complexes to see if the same general reaction holds.

Addition of excess red $HgI_2$ to a $CDCl_3$ solution of **3a** rather surprisingly results in no interaction; the $^1$H-NMR spectrum of **3a** is completely unchanged, and no colour change was observed. The complexes **3a** and **3b** contain sterically unhindered sulfur atoms, and the reluctance of **3a** to undergo coordination to mercury(II) is possibly related to the greater electronegativity of gold(III) compared to platinum(II), withdrawing electron-density away from the thiolate sulfur.

### 2.8. Conclusions

We have synthesised the first gold(III) complexes containing the thiosalicylate and salicylate dianion ligands, and the structure of the thiosalicylate derivative **3b** bears resemblance to the isoelectronic platinum(II) complex **4b** structurally characterised previously, with both complexes containing markedly puckered metal-thiosalicylate systems. Electrospray mass spectrometry reveals that the gold-thiosalicylate complexes are stable towards cone-voltage induced fragmentation. The compounds all displayed moderate to high biological activity, suggesting that further study of analogues of this class of compound could be useful.

## 3. Experimental

Dichloromethane and diethyl ether were freshly distilled from calcium hydride and sodium-benzophenone respectively, under nitrogen. Reactions were carried out under nitrogen, in flasks which were protected

from light. Once reactions were complete, no precautions were undertaken to exclude light, and products were isolated in air. The complexes **2a** [48] and **2b** [51] were prepared by the literature procedures by transmetallation of the respective organomercury precursors [Hg{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Cl] [54] and [Hg{$C_6H_3(CH_2NMe_2)$-2}Cl] [55] with $Me_4N[AuCl_4]$, and were stored in the refrigerator. Thiosalicylic acid, salicylic acid and red mercury(II) iodide were obtained from BDH and used as supplied. Silver(I) oxide was prepared from sodium hydroxide and silver(I) nitrate.

All $^1$H- and $^{13}$C-NMR spectra were recorded at 400.13 and 100.61 MHz, respectively, on a Bruker DRX400 instrument, with the exception of that of **6a** for which $^1$H and $^{13}$C spectra were recorded at 300.13 and 75.47 MHz on a Bruker AC300. Deuterated chloroform was used as the solvent in all cases. Melting points were recorded on a Reichert Thermovar apparatus and are uncorrected, while FTIR spectra were recorded as KBr disks on a BioRad FTS40 instrument. Positive-ion electrospray mass spectra were obtained in 1:1 MeCN-$H_2O$ solution on a VG Platform II instrument, with nitrogen as both the nebulising and drying gas. Cone voltages were varied up to the maximum possible (200 V) in order to investigate the stability of the gold complexes. Comparison of observed and calculated [56] isotope distribution patterns was carried out as an aid to species identification, but is of limited use due to the mono-isotopic nature of gold. However, the presence of heavier isotopomers (arising from contributions from $^2$H, $^{13}$C etc.) at integral mass unit separation confirms the unipositive charge on all the observed major ions.

Elemental analyses were obtained by the University of Otago Campbell Microanalytical Laboratory, and biological testing was carried out by the Marine Chemistry Group, University of Canterbury, New Zealand.

### 3.1. Preparation of *3a*

To a Schlenk flask containing dichloromethane (25 ml), was added [Au{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}$Cl_2$] **2a** (0.050 g, 0.116 mmol), thiosalicylic acid (0.018 g, 0.117 mmol) and silver(I) oxide (0.081 g, excess) and the mixture refluxed under nitrogen for 2 h. Without further exclusion of air, the silver salts were filtered off, and the solvent evaporated under reduced pressure, to give a bright yellow oil which resisted crystallisation. However, rapid addition of hexane to a dichloromethane solution yielded **3a** as a yellow micro-crystalline powder (0.045 g, 76%).

M.p. 176–179°C (melted with decomposition).

Found: C, 39.1; H, 4.0; N, 2.8%; $C_{17}H_{18}NO_3SAu$ requires: C, 39.8; H, 3.5; N, 2.7%.

IR: $\nu$(CO region) 1624 (s), 1598 (vs).

ESMS: (Cone voltage = 20 V) $m/z$ 1027 ($[2M+H]^+$, 94%), 514 ($[MH]^+$, 100%). (Cone voltage = 200 V) $m/z$ 1027 ($[2M+H]^+$, 33%), 514 ($[MH]^+$, 100%).

$^1$H-NMR: $\delta$ 8.15 (1H, dd, $^3J_{3'',4''} = 7.22$ Hz, $^4J_{3'',5''} = 2.18$ Hz, H-3″), 7.47 (1H, dd, $^3J_{6'',5''} = 7.63$ Hz, $^4J_{6'',4''} = 1.92$ Hz, H-6″), 7.19 (1H, td, $^3J_{5'',4''/6''} = 7.91$ Hz, $^4J_{5'',3''} = 2.43$ Hz, H-5″), 7.16 (1H, td, $^3J_{4'',3''/5''} = 7.64$ Hz, $^4J_{4'',6''} = 2.02$ Hz, H-4″), 7.05 (1H, d, Hz, $^4J_{6',4'} = 2.46$ HzH-6′), 7.03 (1H, d, $^3J_{3',4'} = 8.29$ Hz, H-3′), 6.74 (1H, dd, $^3J_{4',3'} = 8.29$ Hz, $^4J_{4',6'} = 2.46$ Hz, H-4′), 4.16 (2H, s, C$\underline{H}_2$), 3.81 (3H, s, OC$\underline{H}_3$), 3.06 (6H, s, NC$\underline{H}_3$). $^{13}$C-NMR: $\delta$ 168.8 (s, C=O), 158.0 (s, C-5′), 137.3 (s, C-2′), 136.5 (s, C-1′), 134.9 (s, C-1″), 134.9 (s, C-2″), 133.3 (d, C-3″), 130.1 (d, C-5″), 129.7 (d, C-6″), 125.3 (d, C-4″), 124.7 (d, C-3′), 115.6 (d, C-6′), 114.0 (d, C-4′), 71.4 (t, $\underline{C}H_2$), 55.6 (q, O$\underline{C}H_3$), 50.0 (q, N$\underline{C}H_3$).

### 3.2. Preparation of *3b*

Similarly, [Au{$C_6H_4(CH_2NMe_2)$-2}$Cl_2$] **2b** (0.051 g, 0.127 mmol), thiosalicylic acid (0.020 g, 0.130 mmol) and silver(I) oxide (0.083 g, excess). The mixture was refluxed under nitrogen for 2 h, during which time the solution changed from almost colourless to bright yellow. Workup gave a bright yellow solid residue which could readily be recrystallised from dichloromethane-ether to yield yellow crystals of **3b** (0.048 g, 79%).

M.p. 165–170°C (decomposed without melting).

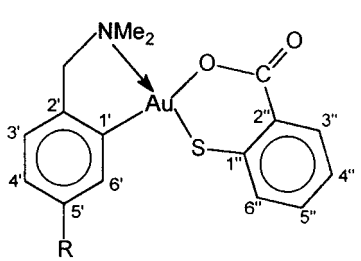
Found: C, 39.5; H, 3.4; N, 2.9%; $C_{16}H_{16}NO_2SAu$ requires: C, 39.8; H, 3.3; N, 2.9%.

IR: $\nu$(CO region) 1621 (vs), 1604 (m), 1582 (m).

ESMS: (Cone voltage = 20 V) $m/z$ 967 ($[2M+H]^+$, 97%), 484 ($[MH]^+$, 100%). (Cone voltage = 200 V) $m/z$ 967 ($[2M+H]^+$, 48%), 484 ($[MH]^+$, 100%).

$^1$H-NMR: $\delta$ 8.17 (1H, dd, $^3J_{3'',4''} = 7.50$ Hz, $^4J_{3'',5''} = 1.91$ Hz, H-3″), 7.50 (1H, dd, $^3J_{6',5'} = 7.88$ Hz, $^4J_{6',4'} = 1.06$ Hz, H-6′), 7.42 (1H, dd, $^3J_{6'',5''} = 7.49$ Hz, $^4J_{6'',4''} = 1.60$ Hz, H-6″), 7.22 (1H, td, $^3J_{5',4'/6'} = 7.36$ Hz, $^4J_{5',3'} = 1.18$ Hz, H-5′), 7.21 (1H, td, $^3J_{5'',4''/6''} = 7.22$ Hz, $^4J_{5'',3''} = 1.84$ Hz, H-5″), 7.17 (1H, td, $^3J_{4'',3''/5''} = 7.36$ Hz, $^4J_{4'',6''} = 1.18$ Hz, H-4″), 7.15 (1H, t, $^3J_{4',3'/5'} = 7.66$ Hz, H-4′), 7.12 (1H, d, $^3J_{3',4'} = 7.47$ Hz, H-3′), 4.23 (2H, s, C$\underline{H}_2$), 3.11 (6H, s, NC$\underline{H}_3$). $^{13}$C-NMR: $\delta$ 168.8 (s, C=O), 145.4 (s, C-1′), 135.9 (s, C-2′), 134.9 (s, C-1″), 134.9 (s, C-2″), 133.3 (d, C-3″), 130.4 (d, C-6′), 130.1 (d, C-5″), 129.7 (d, C-6″), 128.6 (d, C-5′), 127.9 (d, C-4′), 125.3 (d, C-4″), 124.1 (d, C-3′), 71.9 (t, $\underline{C}H_2$), 50.2 (q, N$\underline{C}H_3$).

Atom numbering scheme for **3a** (R = OMe) and **3b** (R = H):



### 3.3. Preparation of **6a** and **6b**

Similarly, [Au{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}$Cl_2$] **2a** (0.050 g, 0.116 mmol), salicylic acid (0.016 g, 0.116 mmol) and silver(I) oxide (0.087 g, excess) were refluxed under nitrogen for 4 h. Workup gave a pale yellow residue, which was revealed to be a mixture of the isomers **6a** and **6b** by preliminary $^1$H and $^{13}$C-NMR spectroscopy, in a 1:3 ratio. However, standing a solution of the mixture for 24 h at r.t. gave a pure product, this being the minor isomer initially. The almost pure residue crystallised readily by liquid–liquid diffusion of ether into a dichloromethane solution to give **6b** as yellow needles (0.040 g, 70%).

M.p. 132–135°C.

Found: C, 39.6; H, 3.8; N, 2.6%; $C_{17}H_{18}NO_4Au$ requires: C, 41.0; H, 3.7; N, 2.8%.

IR: $\nu$(CO region) 1599(s), 1576(vs).

ESMS: (Cone voltage = 20 V) $m/z$ 1017 ([2M + Na]$^+$, 32%), 995 ([2M + H]$^+$, 92%), 498 ([MH]$^+$, 100%). (Cone voltage = 200 V) $m/z$ 1017 ([2M + Na]$^+$, 28%), 995 ([2M + H]$^+$, 60%), 498 ([MH]$^+$, 100%).

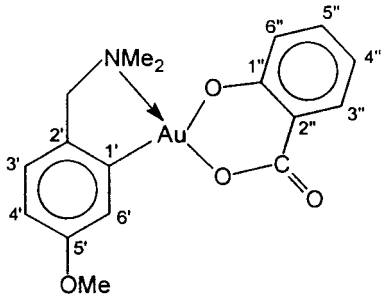
### 3.4. Final isomer **6b**

$^1$H-NMR: $\delta$ 8.10 (1H, dd, $^3J_{3'',4''} = 7.91$ Hz, $^4J_{3'',5''} = 1.58$ Hz, H-3″), 7.22 (1H, td, $^3J_{5'',4''/6''} = 7.61$ Hz, $^4J_{5'',3''} = 1.75$ Hz, H-5″), 7.05 (1H, d, $^4J_{6',4'} = 2.37$ Hz, H-6′), 6.99 (1H, d, $^3J_{6'',5''} = 8.26$ Hz, H-6″), 6.94 (1H, d, $^3J_{3',4'} = 8.32$ Hz, H-3′), 6.82 (1H, t, $^3J_{4'',3''/5''} = 7.69$ Hz, H-4″), 6.80 (1H, td, $^3J_{4',3'} = 8.29$ Hz, $^4J_{4',6'} = 2.42$ Hz, H-4′), 4.20 (2H, s, C$\underline{H}_2$), 3.85 (3H, s, OC$\underline{H}_3$), 3.14 (6H, s, NC$\underline{H}_3$). $^{13}$C-NMR: (100.61 MHz) $\delta$ 167.8 (s, C=O), 163.3 (s, C-1″), 157.2 (s, C-5′), 138.6 (s, C-1′), 135.7 (s, C-2′), 133.3 (d, C-3″), 132.4 (d, C-5″), 123.5 (d, C-3′), 121.4 (s, C-2″), 120.0 (d, C-6″), 118.7 (d, C-4″), 114.8 (d, C-4′), 111.8 (d, C-6′), 74.0 (t, $\underline{C}H_2$), 55.5 (q, O$\underline{C}H_3$), 52.3 (q, N$\underline{C}H_3$).

### 3.5. Initial isomer **6a**

$^1$H-NMR: $\delta$ 7.98 (1H, dd, $^3J_{3'',4''} = 8.00$ Hz, $^4J_{3'',5''} = 1.70$ Hz, H-3″), 7.22 (1H, td, $^3J_{5'',4''/6''} = 7.64$ Hz, $^4J_{5'',3''} = 1.86$ Hz, H-5″), 6.97 (1H, d, $^4J_{6',4'} = 2.14$ Hz, H-6′), 6.86 (1H, d, $^3J_{3',4'} = 8.32$ Hz, H-3′), 6.71 (1H, d, $^3J_{6'',5''} = 7.97$ Hz, H-6″), 6.68 (1H, t, $^3J_{4'',3''/5''} = 7.49$ Hz, H-4″), 6.59 (1H, td, $^3J_{4',3'} = 8.31$ Hz, $^4J_{4',6'} = 2.40$ Hz, H-4′), 4.23 (2H, s, C$\underline{H}_2$), 3.74 (3H, s, OC$\underline{H}_3$), 3.11 (6H, s, NC$\underline{H}_3$). $^{13}$C-NMR: $\delta$ 166.9 (s, C=O), 165.9 (s, C-1″), 157.3 (s, C-5′), 140.5 (s, C-1′), 135.6 (s, C-2′), 133.8 (d, C-3″), 133.3 (d, C-5″), 123.5 (d, C-3′), 121.4 (d, C-6″), 118.5 (s, C-2″), 116.7 (d, C-4″), 114.5 (d, C-4′), 112.2 (d, C-6′), 74.8 (t, $\underline{C}H_2$), 55.8 (q, O$\underline{C}H_3$), 52.6 (q, N$\underline{C}H_3$).

Atom numbering scheme for **6b** (**6a** is analogous):




### 3.6. Preparation of **7**

The orthomercurated complex [Hg{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Cl] (0.101 g, 0.267 mmol), $Me_4N[AuCl_4]$ (0.054 g, 0.131 mmol) and tetramethylammonium chloride (0.032 g, 0.292 mmol) were dissolved in acetonitrile (30 ml) which had been previously been degassed and purged with nitrogen. The yellow solution was refluxed for 1 h, during which time the mixture became almost colourless. The solvent was evaporated under vacuum, and the residue dissolved in dichloromethane. The insoluble material was filtered off, and the solvent removed from the supern atant, to give a white powder characterised by ESMS as containing cation **7**. Efforts at further purification and analysis were unsuccessful and resulted in rapid decomposition to gold metal, since the material is very air and/or light sensitive.

ESMS: (Cone voltage = 20 V) $m/z$ 525 ([M]$^+$, 100%), 200 (unidentified, 57%). (Cone voltage = 50 V) $m/z$ 525 ([M]$^+$, 100%), 164 ([$C_6H_3(CH_2NMe_2)$-2]$^+$, 72%).

### 3.7. X-ray structure determination of complex **3b**

Unit cell dimensions and intensity data were obtained on a Siemens CCD detector mounted on a P4 diffractometer at the University of Canterbury. A crystal of dimensions $0.35 \times 0.30 \times 0.09$ mm was used for the study and a total of 16271 reflections (of which 5161 were unique) in the range $1.29 < \theta < 24.99°$ were collected at 203(2) K, with monochromatic Mo–$K_\alpha$ X-rays ($\lambda = 0.71073$ Å). The data collection nominally covered over a hemisphere of reciprocal space, by a combination of two sets of exposures. In the first each exposure covered 0.3° for a total of 52° in $\omega$. The second run covered 360° in $\phi$ (the mounting axis) also using 0.3° increments between frames. The crystal to detector distance was 4.0 cm. The data set was corrected empirically for absorption using SADABS [57] ($T_{max.,\ min.} = 1.00, 0.50$).

Crystal data: $C_{16}H_{16}NO_2SAu$, $M_r = 483.34$, monoclinic, space group $P2_1/c$, $a = 17.560(1)$, $b = 12.418(1)$, $c = 15.608(1)$ Å, $\beta = 116.07(1)°$, $U = 3057.3(1)$ Å$^3$, $D_{calc} = 2.100$ g cm$^{-3}$, $Z = 8$, $F(000) = 1840$, $\mu$(Mo–$K_\alpha$) = 9.76 mm$^{-1}$.

Solution and refinement: The structure was solved by the Patterson methods option of SHELXS-96 [58], and the gold positions determined. All further non-hydrogen atoms were located routinely (SHELXL-96 [59]). Building a model that successfully accounted for the observed electron density was thwarted by apparent twinning and/or disorder present in the crystals. This persisted despite two independent data collections on two different crystals. Significant electron density remained which could not be sensibly modelled in chemically sensible positions. The best refinement led only to an $R_1$ of 0.1555, therefore the determination can only be taken to indicate atom connectivity and overall conformation, and so no numerical data are presented for this structure analysis.

### 3.8. X-ray structure determination of complex **6b**

Unit cell dimensions and intensity data were obtained on a Siemens CCD SMART diffractometer at the University of Auckland. A crystal of dimensions $0.52 \times 0.19 \times 0.11$ mm was used for the study and a total of 9026 reflections (of which 4159 were unique) in the range $1.99 < \theta < 28.26°$ were collected at 203(2) K, with monochromatic Mo–$K_\alpha$ X-rays ($\lambda = 0.71073$ Å). The data collection nominally covered over a hemisphere of reciprocal space, by a combination of three sets of exposures; each set had a different f angle for the crystal and each exposure covered 0.3° in $\omega$. The crystal to detector distance was 5.0 cm. The data set was corrected empirically for absorption using SADABS57 ($T_{\max.,\min.} = 0.54,\ 0.34$).

Crystal data: $C_{17}H_{18}NO_4Au \cdot CH_2Cl_2$, $M_r = 582.22$, triclinic, space group $P\bar{1}$ (no. 2), $a = 9.4172(2)$, $b = 9.9906(2)$, $c = 11.5903(2)$ Å, $\alpha = 67.993(1)$, $\beta = 69.561(1)$, $\gamma = 79.844(1)°$, $U = 946.06(3)$ Å$^3$, $D_{calc} = 2.044$ g cm$^{-3}$, $Z = 2$, $F(000) = 560$, $\mu$(Mo–$K_\alpha$) = 8.081 mm$^{-1}$.

Solution and refinement: The structure was solved by the Patterson methods option of SHELXS-96 [58], and the gold position determined. All further non-hydrogen atoms were located routinely (SHELXL-96 [59]). In the final cycle of the full-matrix least-squares refinement based on $F^2$, all non-hydrogen atoms were assigned anisotropic temperature factors, and all hydrogen atom positions determined by calculation. The refinement converged with $R_1 = 0.0223$ for 3960 data with $I \geq 2\sigma(I)$, 0.0237 for all data; $wR_2 = 0.0534$ $\{w = 1/[\sigma^2(F_o^2) + (0.0161P)^2 + 2.2576P]$ where $P = (F_o^2 + 2F_c^2)/3\}$, and Goodness-of-Fit = 1.079. No parameter shifted in the final cycle. The final difference map showed no peaks or troughs of electron density greater than $+0.86$ and $-1.90$ e Å$^{-3}$, respectively, both adjacent to the gold atom.

Further details of both structure investigations, together with lists of final atomic coordinates, thermal parameters, and complete bond distances and angles, and structure factors may be obtained from the Cambridge Crystallographic Data Centre, or from the authors on request.

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