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Organogold(III) metallacyclic chemistry. Part 2. Synthesis and characterisation of the first gold(III) ureylene complexes. Crystal structures of [{$C_6H_3(CH_2NMe_2)-2-(OMe)-5$}Au{RNC(O)NR}] (R = Ph and C(O)Me

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Abstract

The reactions of the cyclometallated gold complex [Au{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Cl_2] **3a** with *N*,*N*'-diphenylurea or *N*,*N*'-diacetylurea using an excess of silver(I) oxide in refluxing dichloromethane gave the aura-ureylene complexes [{$C_6H_3(CH_2NMe_2)-2-(OMe)-5$}Au{NRC(O)NR}] R = Ph **6a** and R = Ac [Ac = C(O)Me] **6b** respectively, containing the Au–N–C(O)–N four-membered ring. This ring system has not been reported for gold previously, but is known for other metals e.g. Pt, Pd, Rh, Ir, Ru, Os and Re. The complex **6a** was also successfully synthesised by reaction of **3a**, *N*,*N*'-diphenylurea and sodium hydride in THF at room temperature. The complexes have been fully characterised by ^{1}H- and ^{13}C-NMR and IR spectroscopies, electrospray mass spectrometry, and single crystal X-ray structures are reported for both complexes. The latter shows the aura-ureylene rings of both complexes are planar. Reaction of **6a** with phenyl isocyanate gave the expected six-membered ring insertion product [{$C_6H_3(CH2NMe_2)-2-(OMe)-5$}Au{NPhC(O)NPhC(O)NPh}] **11**, although dimethyl acetylenedicarboxylate proved unreactive. Pure samples of **11** readily deinsert phenyl isocyanate in solution, to regenerate **6a**. This is also clearly observed in electrospray mass spectrometry studies. The biological properties of **6b** have been assessed and the compound possesses high cytotoxicity and moderate antitumour activity.

Keywords: Gold; Metallacycle; Crystal Structure; Ureylene

1. Introduction

Ureylene complexes of transition metals incorporating the M–N–C(O)–N ureylene ring system are well known. Examples of ruthenium, palladium, platinum, rhodium, iridium, rhenium and osmium complexes have been synthesised by a variety of methods. These include reactions of low-valent metal complexes with various isocyanates or organic azides [1–4], by the oxidative addition of *N*,*N*'-di-*p*-toluene-sulfonylurea [2,3,5] and by reaction of [$Pd(OAc)_2$(phen)] (phen = *o*-phenanthroline) with the dilithio salt of *N*,*N*'-diphenylurea [3]. Dinuclear iron complexes [6] and tri- and tetra-nuclear palladium complexes [7], containing bridging urea dianions have also been prepared.

We recently reported that a range of platinum(II) ureylene complexes **1a–1h** (summarised in Scheme 1) can also be synthesised, in good yield, by reaction of platinum(II) chloride complexes with the appropriate parent urea in the presence of silver(I) oxide [8]. The presence of one sufficiently acidic urea hydrogen atom appeared to be essential, with no reaction occurring between [$PtCl_2$(COD)] (COD = cyclo-octa-1,5-diene) and *N*,*N*'-dimethylurea. However, if *N*-phenyl-*N*'-methyl urea or *N*-acetyl-*N*'-methyl urea were used, high

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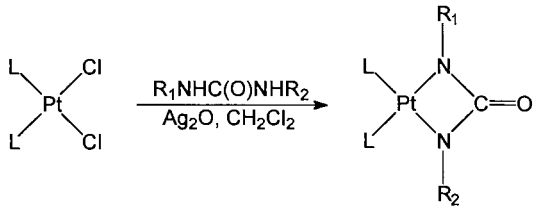


	L or L-L	R_1	R_2
1a	COD	Ph	Ph
1b	PPh_3	Ph	Ph
1c	COD	Ph	2-Py
1d	COD	Ph	1-Ad
1e	COD	Ph	Me
1f	COD	Ac	Me
1g	PPh_3	Ph	H
1h	PPh_3	H	H
2	COD	Ac	Ac

COD = cyclo-octa-1,5-diene, Py = pyridyl, Ad = adamantyl.

Scheme 1.

yields of [Pt{NPhC(O)NMe}(COD)] **1e** or [Pt{NAcC(O)NMe}(COD)] **1f** respectively could be obtained.

Ureylene complexes have also been inadvertently synthesised by reaction of $[PtCl_2(COD)]$ with *N*,*N*′,*N*″-triacetylguanidine in the presence of silver(I) oxide, during our studies into the synthesis of guanidine dianion complexes [9], which are isoelectronic with ureylene systems. Apparently the guanidine hydrolysed under the reaction conditions used, to give the ureylene complex 2, which was isolated as the sole product. The ureylene complexes were also spectroscopically observed, although in smaller amounts, for the iridium and osmium systems studied. When analogous ruthenium and rhodium compounds were used, the expected guanidine complex was the only reaction product. Direct synthesis of the ureylene complexes was readily achieved in near quantitative yields by reaction of the appropriate metal precursor, *N*,*N*′-diacetylurea and silver(I) oxide.

Recently we have begun to focus our attention on the metallacyclic chemistry of gold(III), which despite being isoelectronic with platinum(II) has been largely neglected in this important area of chemistry. The cyclometallated gold precursors [Au{$C_6H_3(CH_2NMe_2)$-2-R-5}Cl_2] R = OMe **3a** [10] or R = H **3b** [11] have proven to be good analogues of platinum(II), and to date appear to mimic many silver(I) oxide reactions undergone by L_2PtCl_2 complexes. For example, reaction of **3a** with diphenacyl sulfone or dimethyl 1,3-acetonedicarboxylate in refluxing dichloromethane in the presence of silver(I) oxide afforded in high yields the complexes **4** and **5** [12], respectively, analogous to the platinum(II) systems [13,14]. Additionally, recent publications [15–17] regarding the biological activity of gold(III) compounds, which often rival those of platinum, have further enhanced gold(III) organometallic complexes as lucrative systems, demanding closer investigation.

Gold(I) amide complexes are relatively sparse in the literature, but compounds derived for example from barbituric acid [18], succinimide [19], purines [20], and phthalimide [21] have been reported. Fewer still have been reported for gold(III) [15,22], despite the ability of amide ligands to stabilise high oxidation states [e.g. copper(III) [23,24].

Here we report our studies on the silver(I) oxide and sodium hydride mediated syntheses of the first gold ureylene complexes, and their reactivity toward dimethyl acetylenedicarboxylate (DMAD) and phenyl isocyanate. The biological activity of one derivative is also reported.

2. Results and discussion

The silver(I) oxide mediated reactions of [Au{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Cl_2 **3a** with either *N*,*N*′-diphenylurea or *N*,*N*′-diacetylurea in refluxing dichloromethane for 2 h, afford in good yields the ureylene complexes **6a** and **6b**, respectively. These reactions proceed markedly faster than for the synthesis of platinum ureylene complexes, where typically a reaction time of 24 h was required for completion. The compound **6a** forms bright orange needles, whereas **6b** is isolated as cream-coloured blocks. This striking colour difference can be attributed to the conjugation imparted by the phenyl rings of the ureylene ligand present in **6a**, and was also noted for the analogous platinum ureylene systems [8]. The synthesis of **6a** was also achieved using sodium hydride as the base in THF at room temperature.

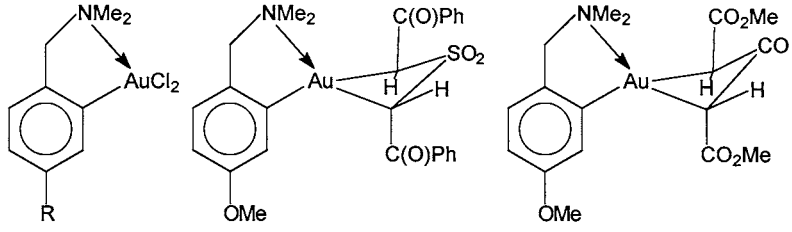
The complexes **6a** and **6b** were unambiguously characterised on the basis of elemental microanalysis, NMR spectroscopy, electrospray mass spectrometry, and single crystal X-ray crystallographic studies.

The crystal structures of both complexes were carried out in order to fully characterise the reaction product of both *N*,*N*′-diphenylurea and *N*,*N*′-diacetylurea dianions with **3a**, the geometry of the compounds, and for comparison with the ureylene structures determined for platinum and palladium. Additionally, complex **6b** showed a very strong $[2M + H]^+$ ion in the electrospray

mass spectrum (see Section 2.3), and a possible dimerisation of the complex was considered. It has been shown in our laboratory that the reaction of $NCCH_2C(O)NHC(O)OEt$ with **3a** gives initially the monomer complex **7**, but eventually crystallises as the poorly soluble dimer **8**, thus forming an eight-membered ring [25]. Diagnostic distinction between monomer or dimer systems is not readily achievable by spectroscopic methods. Also, the determination of the structures of both **6a** and **6b** allows direct comparison of two electronically different ureylene substituents.

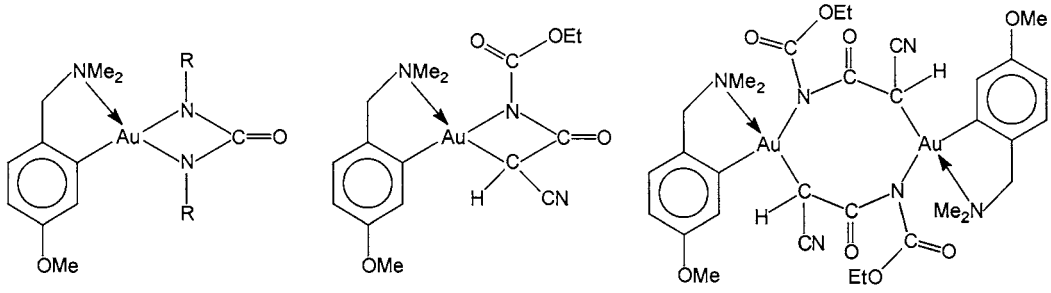
*2.1. Discussion of the structures of **6a** and **6b***

The structures confirm the expected monomeric reaction products analogous to ureylene complexes reported previously for platinum [3,8] and palladium(II) [4]. Selected bond lengths and angles are presented in Tables 1 and 2, respectively, with ORTEP perspective views of **6a** and **6b** shown in Figs. 1 and 2 together with the atom numbering schemes. The equivalent bond lengths and angles for **6a** and **6b** are remarkably similar, with the majority being identical within two stan-



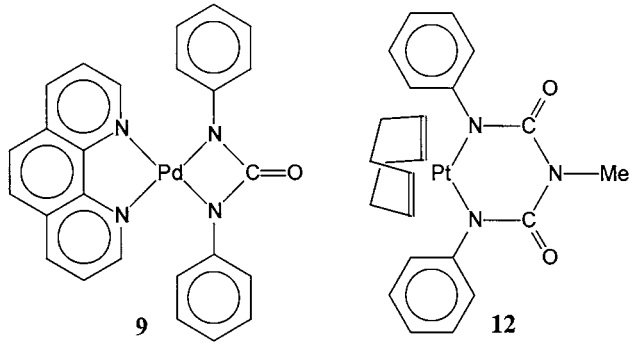
3a R = OMe **4** **5**

3b R = H



6a R = Ph **7** **8**

6b R = Ac



dard deviations. This shows that the complexes formed by the *N*,*N*′-diphenylurea and the *N*,*N*′-diacetylurea dianions, despite being somewhat electronically different, nonetheless give extremely similar structures.

The geometry about the gold atom of complex **6a** is, as expected, planar with no atom deviating from a least-squares plane defined by N(1), N(2), Au, N(3) and C(31) by more than 0.065(3) Å, for N(1). Similarly, for **6b** the analogous plane drawn through N(1), N(2), Au, N(3) and C(11) has no atom deviating by more than 0.120(3) Å, for N(2). The four-membered ureylene rings formed by Au, N(1), N(2) and C(1) are also planar, with the largest deviation being 0.014(4) and 0.031(4) Å [for C(1)] for **6a** and **6b**, respectively. The carbonyl groups also lie in this plane, as expected. Thus the gold ureylene structures, as for platinum, closely resemble the isoelectronic cabonato complexes [26], rather than the puckered ring system reported previously for the aurathietane-3,3-dioxide complex **4** [12]. The major distortion from a regular square-planar arrangement is the N(1)–Au–N(2) bite angle, which is 64.3(2)° for **6a** and 64.1(2)° for **6b**, a geometrical constraint imposed by the ureylene ligand. These are comparable to those previously reported for the platinum and palladium(II) complexes **1d** [8] and [Pd{NPhC(O)NPh}(phen)] **9** [4], which have bite angles of 64.7(3) and 65.6(1)°, respectively for the ureylene ligands.

Due to the non-symmetrical nature of the five-membered cyclometallated ring, the bond lengths from the gold atom to the ureylene nitrogen atoms, N(1) and N(2), are not equal. Since the *ortho*-carbon on the cyclometallated ring has a higher *trans* influence [27] than co-ordinated nitrogen, the Au–N(2) distances are significantly longer [2.092(6) Å for both **6a** and **6b**] than Au–N(1) [2.003(6) Å for **6a** and 2.014(6) Å for **6b**]. Comparing these lengths to the closest related platinum(II) ureylene complex that has had its structure determined **1d**, which has Pt–N distances of 2.048(8) Å for Pt–NAd and 2.021(8) Å for Pt–NPh, it is clear the average Au–NPh lengths for **6a** and **6b** [ca. 2.05(1) Å] are very much consistent with the platinum ureylene system.

It is evident from Figs. 1 and 2 that the OMe groups for **6a** and **6b** point in opposite directions, with the Me group orientated towards the ureylene ligand for **6a** and away for **6b**. The water of crystallisation [O(5)] in **6b** [which is hydrogen-bonded to O(3) (O···O distance 2.813(9) Å)] is 3.627(9) and 4.424(9) Å from O(2) and O(4) (in adjacent molecules), respectively, so the orientation of the OMe group is probably not directed by hydrogen-bonding interactions. Additionally, the phenyl group in **6a** is bulkier than the C(O)Me in **6b**, so steric effects are also unlikely.

Table 1
Selected interatomic bond lengths (Å) for **6a** and **6b**·$\frac{1}{2}H_2O$ with estimated standard deviations in parentheses

6a		**6b**·$\frac{1}{2}H_2O$	
Bond	Length	Bond	Length
Au–N(1)	2.003(6)	Au–N(1)	2.014(5)
Au–N(2)	2.092(6)	Au–N(2)	2.092(6)
Au–N(3)	2.088(6)	Au–N(3)	2.090(5)
Au–C(31)	2.025(7)	Au–C(11)	2.021(6)
Au.C(1)	2.584(8)	Au···C(1)	2.622(7)
PhNC(O)NPh Ligand		AcNC(O)NAc Ligand	
C(1)–O(1)	1.219(8)	C(1)–O(1)	1.222(9)
C(1)–N(1)	1.387(10)	C(1)–N(1)	1.415(8)
C(1)–N(2)	1.383(9)	C(1)–N(2)	1.392(9)
N(1)–C(11)	1.404(9)	N(1)–C(2)	1.390(9)
N(2)–C(21)	1.421(9)	N(2)–C(4)	1.371(8)
		C(2)–O(2)	1.230(8)
		C(4)–O(3)	1.218(9)

For these reasons the most probable explanation for the observation is crystal-packing forces. The two carbonyl groups C(2)–O(2) and C(4)–O(3) both point towards the cyclometallated ligand, thus minimising steric interactions of the bulkier methyl groups, C(3) and C(5). The torsion angles of the ureylene phenyl rings of **6a** are 39.1(2) and 49.2(2)° for C(26)–C(21)–N(2)–C(1) and C(16)–C(11)–N(1)–C(1), respectively. For **6b** the torsion angles are 11.4(2) and 22.3(2)° for C(5)–C(4)–N(2)–C(1) and C(3)–C(2)–N(1)–C(1).

Table 2
Selected bond angles (°) for **6a** and **6b**·$\frac{1}{2}H_2O$ with estimated standard deviations in parentheses

6a		**6b**·$\frac{1}{2}H_2O$	
Bonds	Angle	Bonds	Angle
N(1)–Au–N(2)	64.3(2)	N(1)–Au–N(2)	64.1(2)
N(2)–Au–N(3)	108.6(2)	N(2)–Au–N(3)	108.9(2)
N(1)–Au–C(31)	106.3(3)	N(1)–Au–C(11)	107.0(2)
N(3)–Au–C(31)	80.9(3)	N(3)–Au–C(11)	80.7(2)
PhNC(O)NPh ligand		AcNC(O)NAc ligand	
Au–N(1)–C(1)	97.7(5)	Au–N(1)–C(1)	98.2(4)
Au–N(2)–C(1)	93.9(5)	Au–N(2)–C(1)	95.6(4)
Au–N(1)–C(11)	137.3(5)	Au–N(1)–C(2)	133.8(4)
Au–N(2)–C(21)	143.1(5)	Au–N(2)–C(4)	133.4(5)
N(1)–C(1)–N(2)	103.9(6)	N(1)–C(1)–N(2)	102.0(6)
N(1)–C(1)–O(1)	127.1(7)	N(1)–C(1)–O(1)	128.8(6)
N(2)–C(1)–O(1)	128.9(8)	N(2)–C(1)–O(1)	129.1(7)
C(1)–N(1)–C(11)	124.6(6)	C(1)–N(1)–C(2)	125.2(6)
C(1)–N(2)–C(21)	122.5(6)	C(1)–N(2)–C(4)	127.1(6)
		N(1)–C(2)–O(2)	119.7(6)
		N(2)–C(4)–O(3)	121.4(7)

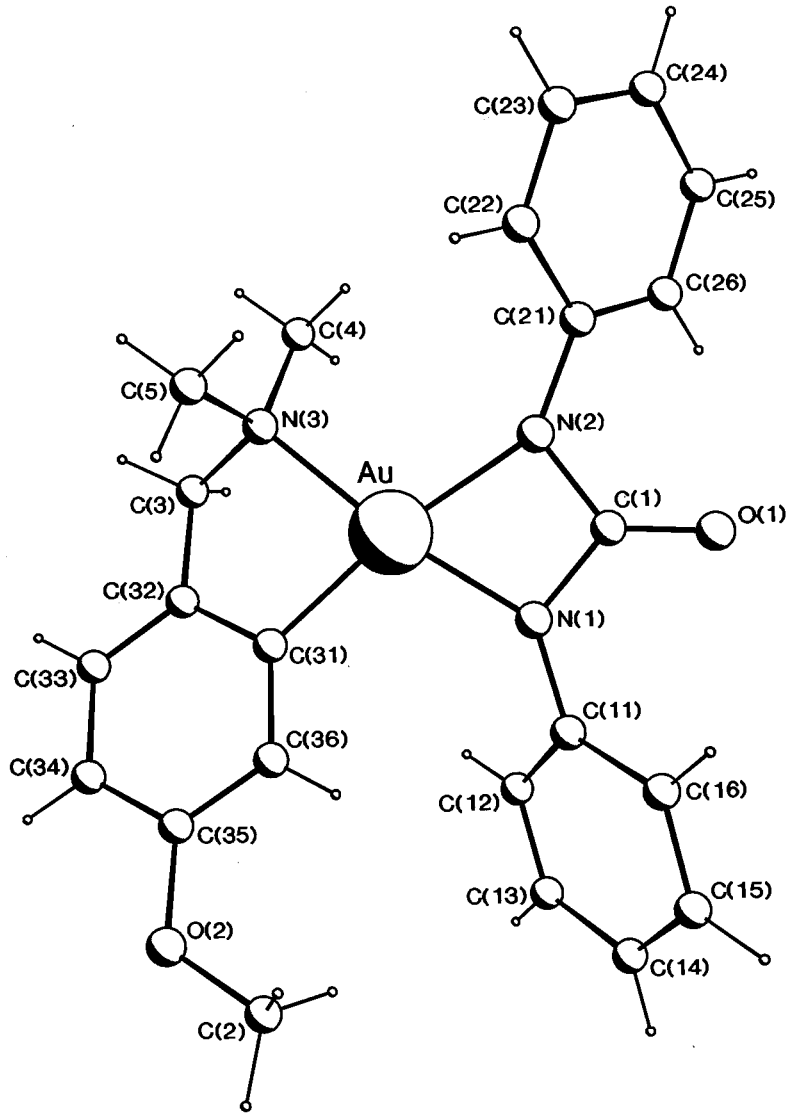


Fig. 1. Molecular structure of [{$C_6H_3(CH_2NMe_2)-2-(OMe)-5$}Au{NPhC(O)NPh}] **6a**, showing the atom numbering scheme.

2.2. Spectroscopic characterisation

A combination of 2D experiments (HSQC, HMBC, COSY and NOESY) were used to unambiguously assign the ^{1}H- and ^{13}C-NMR spectra of **6a** and **6b**. Due to the differing *trans*-influence groups on the orthometallated ligand, the ureylene ligand, despite being symmetrical itself, gives two sets of resonances for its substituents. These could be readily assigned by 1D NOE difference or 2D NOESY experiments, which show clear through space correlation to either the *para*-methoxy group, or the NMe groups. Table 3 shows a comparison of the relevant ^{13}C chemical shifts of starting materials and products.

A large downfield shift of the central carbonyl resonance is observed upon co-ordination. This is undoubtedly due to the deshielding of this moiety by the electronegative metal centre [the electronegativity of gold(III) is quite high [28]. The same effect is noted, but to a lesser extent, for the remaining N–C groups, and those *trans* to the higher *trans*-influence C, are deshielded to a greater extent than those *trans* to N, as expected. This information can be used to unambiguously assign signals in these positions.

The IR spectrum (in the 1580–1700 cm^{-1} region) of the diphenyl ureylene complex **6a**, bears a remarkable similarity to the platinum ureylene complexes **1a–1h**, in showing two bands at 1650 and 1592 cm^{-1}. This compares with values recorded for **1a** [8] of 1648 and 1594 cm^{-1}. The spectrum recorded for **6b** is complicated by the presence of two additional carbonyl moieties and is consequently of little diagnostic value.

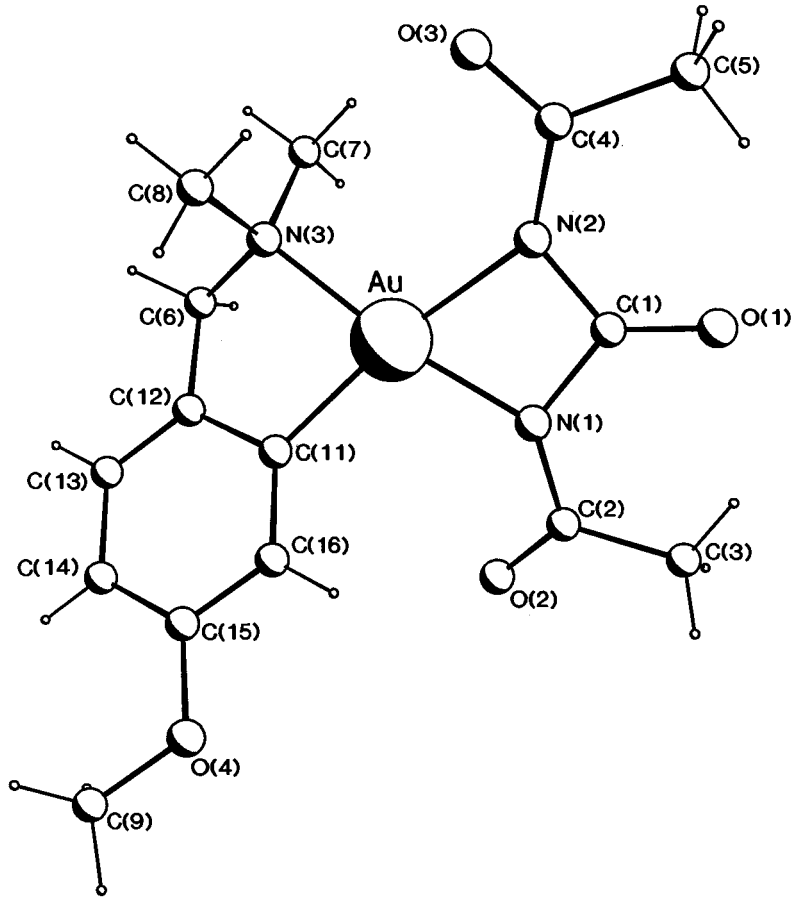


Fig. 2. Molecular structure of $[C_6H_3(\overline{CH_2NMe_2})-2-(OMe)-5\}\overline{Au\{NAcC(O)NAc}\}]\cdot\frac{1}{2}H_2O$ **6b**$\cdot\frac{1}{2}H_2O$, showing the atom numbering scheme. The water of crystallisation has been omitted.

2.3. Electrospray mass spectrometry

Electrospray mass spectrometry (ESMS) continues to provide excellent utility for the analysis of inorganic and organometallic compounds [29]. As expected for complexes containing oxygen and nitrogen atoms [in OMe, C=O, and NC(O)N groups] capable of association with protons, the complexes **6a** and **6b** give strong parent ions $[M+H]^+$, with no observable fragmentation at low cone voltages (<20 V). The complexes exhibit appreciable stability even at high cone voltages (ca. 100 V), as evidenced by the persistence of significant parent ions. This contrasts with the platinum ureylene complexes **1a–1h**, which show only fragmentation ions at high voltages. This is consistent with the notion of the extra stability imparted by two ring systems reported for complexes **4** and **5**, and has also been observed previously for platinum(II) complexes with two ring systems [30].

Table 3
Comparison of ^{13}C chemical shifts of **6a** and **6b** compared to the respective urea starting materials

$\delta^{13}C$ (ppm)				
Group	**6a**	N,N′-diphenylurea[a]	**6b**	N,N′-diacetylurea[b]
Ring C=O	169.4	152.6	163.1	151.0
N–C *trans* C	144.2	139.7	176.5	171.8
N–C *trans* N	141.7	139.7	172.8	171.8
Au–C	145.0	—	143.0	—

[a] Recorded in $(CD_3)_2SO$.
[b] Recorded in $CDCl_3$.

Fragmentation for **6a** and **6b** (cone voltage >80 V), appears to proceed via different mechanisms. For **6a**, loss of both the gold and ureylene moieties is observed giving rise to a strong peak at m/z 164, assigned as $[C_6H_3(CH_2NMe_2)$-2-(OMe)-5$]^+$. In contrast, **6b** shows loss of AcNCO to give $[Au\{\overline{C_6H_3(CH_2NMe_2}\}$-2-(OMe)-5$\}NHAc]^+$, analogous to the fragmentation of **1a** [8], which showed loss of phenyl isocyanate to give an ion assigned as $[Pt\{NHPh\}(COD)]^+$.

Also noteworthy is the propensity of **6b** to give very strong reproducible $[2M+H]^+$ ions, initially tentatively interpreted as solid state dimer formation. The reason for this is not fully clear, and was not observed for **6a**, but is most likely due to the presence of three carbonyl groups in **6b**.

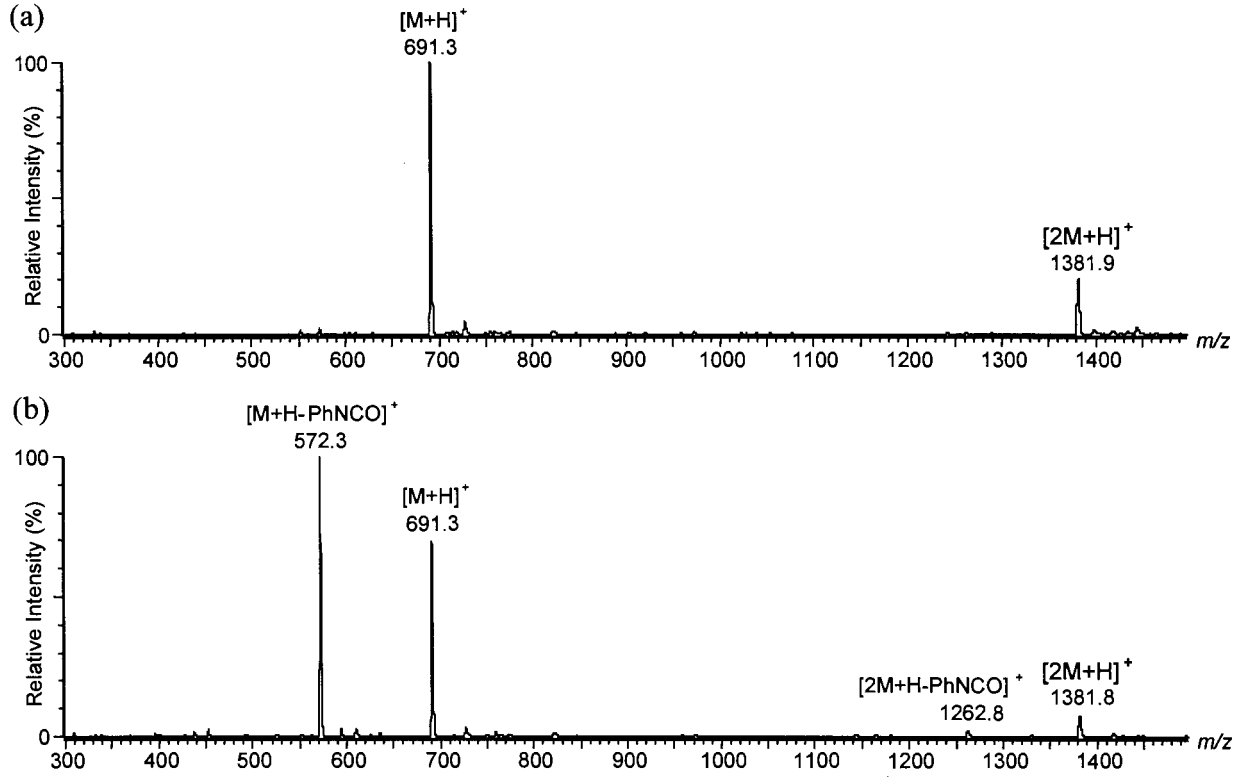


Fig. 3. Positive-ion electrospray mass spectra of [{$C_6H_3(CH_2NMe_2)-2-(OMe)-5$}Au{NPhC(O)NPhC(O)NPh}] **11** (= M), showing peak assignments. (a) Cone voltage 20 V; (b) Cone voltage 50 V.

*2.4. Reaction of **6a** with phenyl isocyanate and dimethyl acetylenedicarboxylate*

The insertion of phenyl isocyanate into the four-membered Pd–N–C(O)–N ring of the diphenylureylene palladium complex [Pd{NPhC(O)NPh}(phen)] **9** has been reported to give in high yield the triphenylbiureto derivative [Pd{NPC(O)NPhC(O)NPh}(phen) **10** [4].Similarly, some platinum ureylene complexes also appear to have a high reactivity toward unsaturated molecules, such as phenyl isocyanate, dimethyl acetylenedicarboxylate (DMAD), and carbon disulfide, which rapidly insert into the four membered ureylene metallacycles to give the expected six-membered ring insertion products [31].

We have investigated the insertion chemistry of **6a** with both DMAD and phenyl isocyanate. When DMAD is added to a stirred dichloromethane solution of **6a**, no reaction occurred, even when refluxed for 5 h. Lack of reactivity towards DMAD insertion has also been noted for **1a** [31]. However when phenyl isocyanate was added to a solution of **6a**, a rapid colour change from bright orange to bright yellow was observed. The product was characterised as the expected insertion complex [{$C_6H_3(CH_2NMe_2)-2-(OMe)-5$}Au{NPhC(O)NPhC(O)NPh}] **11** on the basis of elemental microanalysis, detailed NMR studies, and ESMS. The isolated crystalline compound is stable, but when dissolved in dichloromethane or chloroform, readily deinserts phenyl isocyanate to regenerate the starting material **6a**. For this reason NMR spectra of **11** were obtained in the presence of excess phenyl isocyanate.

Since complex **11** contains four inequivalent aromatic rings, the proton NMR contains many overlapping signals. For this reason the HOHAHA (Homonuclear Hartman–Hahn transfer) experiment was utilised. This unambiguously verified the expected presence of three phenyl rings, and one trisubstituted aromatic ring. Coupled with the NOESY experiment, this allowed complete assignment of the ^{1}H-NMR spectrum of **11** (detailed in Section 3).

The complex **11** displays very broad NMe_2 and NCH_2 ^{1}H-NMR signals, and lack of $^4J_{H,H}$ coupling on any of the three biureto phenyl rings, despite well resolved $^4J_{H,H}$ coupling observed on the orthometallated benzylamine ring. Additionally, the ^{13}C-NMR spectrum shows four resolved signals corresponding to only two inequivalent C=O groups. We believe this is the result of room temperature fluxionality, and is probably due the slow inversion of a non-planar six-membered Au–N–C(O)–N–C(O)–N ring system present in **11**. Evidence in support of this fluxionality was determined by the acquisition of a high temperature (55°C) ^{1}H-NMR spectrum, which showed marked

sharpening of the NMe_2 and NCH_2 resonances. Unfortunately the carbonyl signals could not be resolved in the high temperature ^{13}C-NMR spectrum in the timescale of the experiment, but could be expected to coalesce into two signals. The broadening and additional resonances are unlikely to be caused by rapid insertion/deinsertion of phenyl isocyanate, since no signal corresponding to the deinserted product **6a** is observed in the ESMS spectrum at low cone voltages. Indeed ESMS analysis of **11** shows solely strong parent ions ($[M+H]^+$ and $[2M+H]^+$) at cone voltage = 20 V (Fig. 3(a)), with the loss of phenyl isocyanate becoming the dominant ion only with higher voltages (Fig. 3(b)). The facile loss of phenyl isocyanate has been previously observed in the ESMS analysis of [Pt{NPhC(O)NMeC(O)NMeC(O)NPh}(COD)] **12**, the reaction product of **1e** and phenyl isocyanate [31].

2.5. Biological activity

Assays for antimicrobial, antiviral and antitumour activities were determined for **6a**. The results are summarised in Table 4. The compound showed high cytotoxicity towards the bacteria and fungi tested, and completely killed the BSC-1 cell line used for antiviral testing. Antitumour activity was moderate, requiring 7377 ng ml^{-1} to inhibit 50% of cell growth in P-388 tumour cells.

2.6. Conclusions

The gold(III) ureylene complexes reported here are analogous to those previously prepared for platinum(II), and the cyclometalled gold(III) compound **3a** continues to provide an excellent platinum(II) analogue. Although the silver(I) oxide mediated reactions used to prepare the ureylene complexes seem to proceed much more rapidly for the gold(III) system, reactivity toward insertion of phenyl isocyanate and DMAD is comparable to the platinum(II) ureylene complexes. Further studies of gold(III) metallacyclic chemistry will be described in subsequent papers.

Table 4

(a) Antitumour (P-388) and antiviral/cytotoxicity assay results

IC50[a]	HSV1[b]	PV1[c]	Cyt[d]
7377	—	—	4+[e]

(b)Antimicrobial/antifungal[f] activities[g] of **6b** (2 μg loaded on disc)

Ec	Bs	Pa	Ca	Tm	Cr
9	14	9	8	10	6

[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] Herpes simplex type I virus (strain F, ATCC VR 733) grown on the BSC cell line (ATCC CCL 26)
[c] Polio type I virus (Pfiser vaccine strain) grown on the BSC cell line.
[d] Cytotoxicity to BSC cells.
[e] 4+ denotes antiviral or cytotoxic zone over whole well (100% zone).
[f] Ec, *Escherichia coli*; Bs, *Bacillus subtilis*; Pa, *Pseudomonas aeruginosa*; Ca, *Candida albicans*; Tm, *Trichophyton mentagrophytes*; Cr, *Cladosporium resinae*.
[g] Inhibition zone as excess radius (mm) from a 6 mm (diameter) disc containing 2 μg of **6b**.

3. Experimental

Melting points were measured in air on a Reichert hotstage apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on a BioRad FTS-40 spectrophotometer. Electrospray mass spectra were recorded in positive-ion mode on a VG Platform II instrument, using a 1:1 mixture of $MeCN/H_2O$ as the mobile phase. Elemental analyses were performed by the Campbell Microanalytical Laboratory, University of Otago.

Proton and all inverse 2D-NMR experiments (HSQC, Heteronuclear Single Quantum Coherence; HMBC, Heteronuclear Multiple Bond Correlation; NOESY; and HOHAHA, Homonuclear Hartmann–Hahn transfer) were recorded on a Bruker DRX 400 spectrometer at 400.13 and 100.61 MHz for the proton and carbon channels respectively, with $SiMe_4$ (δ 0.0) as the external standard. The ^{13}C-$\{^1H\}$-NMR spectra were recorded on either the instrument above, or on a Bruker AC300 spectrometer at 75.47 MHz. All NMR analyses were carried out in $CDCl_3$, with the exception of the ^{13}C-NMR spectrum of *N*,*N*′-diphenylurea which was acquired in D_6-DMSO.

All syntheses were carried out under a dry, oxygen-free, nitrogen atmosphere, using solvents which were dried and freshly distilled prior to use. The compound [Au{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Cl_2] **3a** [10] was prepared as reported, by transmetallation of the orthomercurated complex [Hg{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Cl] [32] with Me_4NAuCl_4. Dimethyl acetylenedicarboxylate (Aldrich) and phenyl isocyanate (BDH) were obtained from commercial sources, and used as received. The sodium hydride (Koch-Light) used was oil-free and freshly powdered. *N*,*N*′-diphenylurea was prepared by the condensation of phenyl isocyanate and aniline in diethyl ether, m.p. 239–240° (lit. [33] 238°). *N*,*N*′-diacetylurea was synthesised by reacting excess acetyl chloride with urea in refluxing benzene, m.p. 155–157° (lit. [33] 154–155°).

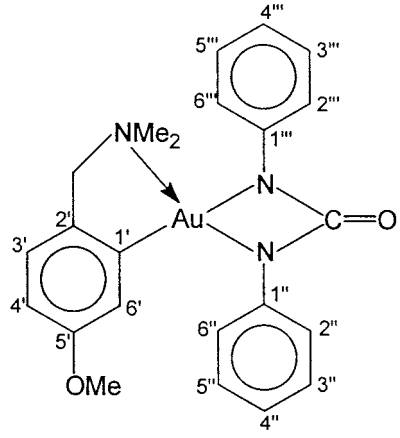
3.1. Preparation of *6a*

To a Schlenk flask containing degassed dichloromethane (25 ml) was added [Au{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Cl_2] **3a** (0.050 g, 0.116 mmol), *N*,*N*′-diphenylurea (0.025 g, 0.118 mmol) and silver(I) oxide (0.092 g, excess). The mixture was

refluxed under nitrogen for 2 h. The silver salts were filtered off and the solvent removed under reduced pressure giving a bright orange oil. This was recrystallised by vapour diffusion of ether into a dichloromethane solution, to give bright orange needles of **6a** (0.034 g, 51%).

Alternatively, complex **3a** (0.050 g, 0.116 mmol), *N*,*N*′-diphenylurea (0.025 g, 0.118 mmol) and sodium hydride (0.5 g, excess) were added to a Schlenk flask containing freshly distilled degassed THF (25 ml), and stirred under nitrogen for 1 h. The resulting bright orange solution was filtered, and the THF removed under reduced pressure. The residue was dissolved in dichloromethane and filtered again. Crystallisation by slow addition of diethyl ether gave **6a** (0.040 g, 60%).

M.p. 185–190°C. Found: C, 48.0; H, 4.4; N, 7.2%; $C_{23}H_{24}N_3O_2Au$ requires: C, 48.3; H, 4.2; N, 7.4%. IR: ν(CO region) 1650 (vs), 1592 (m) cm^{-1}. ESMS: (Cone voltage = 5 V) m/z 588 ($[MNH_4]^+$, 30%), 572 ($[MH]^+$, 100%). (Cone voltage = 50 V) m/z 588 ($[MNH_4]^+$, 25%), 572 ($[MH]^+$, 100%), 164 ($[C_6H_3(CH_2NMe_2)$-2-(OMe)-5$]^+$, 17%). (Cone voltage = 100 V) m/z 572 ($[MH]^+$, 35%), 164 ($[C_6H_3(CH_2NMe_2)$-2-(OMe)-5$]^+$, 100%). ^{1}H-NMR: (400.13 MHz) δ 7.38 (2H, dd, $^3J_{2'',3''} = 8.09$ Hz, $^4J_{2'',4''} = 1.37$ Hz, H-2″,6″), 7.33–7.25 (6H, m, H-3″,5″,2‴,6‴,3‴,5‴), 7.13 (1H, tt, $^3J_{4'',3''/5''} = 7.23$ Hz, $^4J_{4'',2''/6''} = 0.60$ Hz, H-4″), 7.03 (1H, d, $^3J_{3',4'} = 8.16$ Hz, H-3′), 7.02 (1H, t, $^3J_{4''',3'''/5'''} = 8.49$ Hz, H-4‴), 6.68 (1H, dd, $^3J_{4',3'} = 8.26$ Hz, $^4J_{4',6'} = 2.50$ Hz, H-4′), 6.14 (1H, d, $^4J_{6',4'} = 2.48$ Hz, H-6′), 4.11 (2H, s, C$\underline{H}_2$), 3.34 (3H, *s*, OC$\underline{H}_3$), 2.95 (6H, s, NC$\underline{H}_3$). ^{13}C-NMR: (75.47 MHz) δ 169.4 (s, C=O), 157.8 (s, C-5′), 145.0 (s, C-1′), 144.2 (s, C-1‴), 141.7 (s, C-1″), 136.5 (s, C-2′), 129.0 (d, C-3″,5″), 128.7 (d, C-3‴,5‴), 128.5 (d, C-2″,6″), 126.7 (d, C-2‴,6‴), 124.9 (d, C-4′), 123.5 (d, C-4‴), 123.5 (d, C-3′), 115.2 (d, C-4′), 114.8 (d, C-6′), 73.9 (t, $\underline{C}H_2$), 55.2 (q, OCH_3), 52.0 (q, N$\underline{C}H_3$).



3.2. Preparation of *6b*

In a similar fashion to the synthesis of **6a**, [Au{$C_6H_3(CH_2NMe_2)$-2-(OMe)-5}Cl_2] **3a** (0.050 g, 0.116 mmol), *N*,*N*′-diacetylurea (0.017 g, 0.118 mmol) and silver(I) oxide (0.088 g, excess) were refluxed under nitrogen for 2 h. The silver salts were filtered off and the solvent removed under reduced pressure giving a pale yellow oil. This was recrystallised by slow evaporation of an ether solution at −20°C, to give cream crystals of **6b** (0.044 g, 76%).

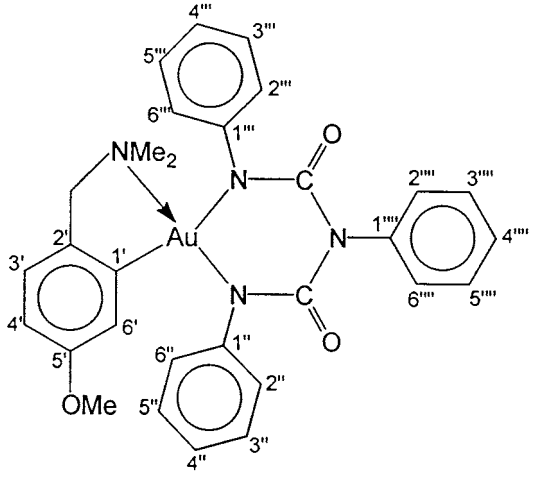
M.p. 168–171°C. Found: C, 35.9; H, 4.0; N, 8.3%; $C_{15}H_{20}N_3O_4Au$ requires: C, 35.8; H, 4.0; N, 8.4%. IR: ν(CO region) 1721 (vs), 1665 (m), 1641 (s), 1629 (s), 1596 (m) cm^{-1}. ESMS: (Cone voltage = 20 V) m/z 1007 ($[2MH]^+$, 33%), 504 ($[MH]^+$, 100%). (Cone voltage = 50 V) m/z 1007 ($[2MH]^+$, 38%), 504 ($[MH]^+$, 100%), 419 ($[MH-AcNCO]^+$, 92%). (Cone voltage = 80 V) m/z 1007 ($[2MH]^+$, 8%), 504 ($[MH]^+$, 70%), 419 ($[MH-AcNCO]^+$, 100%). ^{1}H-NMR: (400.13 MHz) δ 7.38 (1H, d, $^4J_{6',4'} = 2.49$ Hz, H-6′), 6.96 (1H, d, $^3J_{3',4'} = 8.27$ Hz, H-3′), 6.74 (1H, dd, $^3J_{4',3'} = 8.29$ Hz, $^4J_{4',6'} = 2.51$ Hz, H-4′), 4.17 (2H, s, C$\underline{H}_2$), 3.75 (3H, s, OC$\underline{H}_3$), 3.45 (6H, s, NC$\underline{H}_3$), 2.57 (3H, s, NC(O)CH_3 *trans* N), 2.49 (3H, s, NC(O)CH_3 *trans* C). ^{13}C-NMR: (100.61 MHz) δ 176.5 (s, NC(O)CH_3 *trans* C), 172.8 (s, NC(O)C$\underline{H}_3$ *trans* N), 163.1 (s, C=O), 157.2 (s, C-5′), 143.0 (s, C-1′), 138.1 (s, C-2′), 122.9 (d, C-3′), 122.1 (d, C-6′), 114.7 (d, C-4′), 75.6 (t, CH_2), 55.6 (q, OCH_3), 53.8 (q, NCH_3), 28.8 (q, NC(O)CH_3 *trans* C), 28.1 (q, NC(O)CH_3 *trans* N).

3.3. Preparation of *11*

To a stirred solution of **6a** (0.025 g, 0.044 mmol) in dichloromethane (5 ml) was added two drops of phenyl isocyanate. A marked colour change from bright orange to bright yellow occurred almost immediately. Evaporation of the solvent, and recrystallisation of the residue from dichloromethane and diethyl ether gave **11** as yellow rosettes (0.020 g, 67%). NMR studies revealed that gradual deinsertion of phenyl isocyanate to regenerate **6a** occurred over 24 h, if an excess of the isocyanate was not present.

M.p. 175–176°C. Found: C, 50.5; H, 4.1; N, 7.6%; $C_{30}H_{29}N_4O_3Au \cdot \frac{1}{2}CH_2Cl_2$ requires: C, 50.0; H, 4.1; N, 7.6%. IR: ν(CO region) 1648 (vs), 1627 (s), 1592 (m) cm^{-1}. ESMS: (Cone voltage = 20 V) m/z 1382 ($[2MH]^+$, 22%), 691 ($[MH]^+$, 100%). (Cone voltage = 50 V) m/z 1382 ($[2MH]^+$, 8%), 692 ($[MH]^+$, 69%), 572 ($[MH-PhNCO]^+$, 100%). (Cone voltage = 80 V) m/z 1382 ($[2MH]^+$, 5%), 691 ($[MH]^+$, 72%), 572 ($[MH-PhNCO]^+$, 100%). ^{1}H-NMR: (400.13 MHz) δ 8.01 (2H, d, $^3J_{2''',3'''} = 8.29$ Hz, H-2‴,6‴), 7.86 (2H, d, $^3J_{2'',3''} = 8.29$ Hz, H-2″,6″), 7.44 (2H, d, $^3J_{2'''',3''''} = 8.15$ Hz, H-2⁗,6⁗), 7.39 (2H, t, $^3J_{3'',2''/4''} = 7.80$ Hz, H-3″), 7.38 (2H, t, $^3J_{3'''',2''''/4''''} = 6.53$ Hz, H-3⁗/5⁗), 7.34 (2H, t, $^3J_{3''',2'''/4'''} = 8.08$ Hz, H-3‴/5‴), 7.31 (1H, t, $^3J_{4'''',3''''/5''''} = 8.15$ Hz, H-4⁗), 7.11 (1H, t, $^3J_{4'',3''/5''} = 7.82$ Hz, H-4″), 7.11 (1H, t, $^3J_{4''',3'''/5'''} = 8.88$ Hz, H-4‴), 6.99

(1H, t, $^3J_{3',4'} = 8.33$ Hz, H-3′), 6.69 (1H, dd, $^3J_{4',3'} = 8.30$ Hz, $^4J_{4',6'} = 2.42$ Hz, H-4′), 6.20 (1H, d, $^4J_{6',4'} = 2.40$ Hz, H-6′), 5.25 (1H, s, CH_2Cl_2 of crystallisation), 4.22 (2H, s, br, $C\underline{H}_2$), 3.33 (3H, s, $OC\underline{H}_3$), 2.79 (6H, s, br, $NC\underline{H}_3$). ^{13}C-NMR: (75.47 MHz) δ 158.0 (s, C-5′), 156.5 (s, C=O), 156.2 (s, C=O), 153.43 (s, C=O), 153.36 (s, C=O), 145.2 (s, C-1″), 144.0 (s, C-1‴), 144.0 (s, C-1′), 139.9 (s, C-1⁗), 135.9 (s, C-2′), 130.5 (d, C-2⁗,6⁗), 129.1 (d, C-3″,5″ or C-3⁗,5⁗), 128.5 (d, C-3‴,5‴), 128.3 (d, C-3″,5″ or C-3⁗,5⁗), 127.6 (d, C-4⁗), 126.9 (d, C-2‴,6‴), 125.8 (d, C-2″,6″), 124.6 (d, C-4″ or C-4‴), 124.3 (d, C-4″ or C-4‴), 123.4 (d, C-3′), 116.4 (d, C-4′), 114.7 (d, C-6′), 75.1 (t, CH_2), 55.4 (q, $OC\underline{H}_3$), 52.4 (q, $NC\underline{H}_3$).



3.4. X-ray crystal structure of **6a**

Unit cell dimensions and intensity data were obtained on a Siemens CCD SMART diffractometer at the University of Auckland. A crystal of dimensions $0.23 \times 0.09 \times 0.03$ mm was selected for the study and a total of 4909 reflections (of which 4751 were unique) in the range $1.51 < \theta < 28.14°$ were collected at 130(2) K, with monochromatic Mo–K_α 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 ϕ angle for the crystal and each exposure covered 0.3° in ω. The crystal to detector distance was 5.0 cm. The data set was corrected empirically for absorption using SADABS [34] ($T_{\text{max., min.}} = 0.86, 0.52$).

Crystal data: $C_{23}H_{24}N_3O_2Au$, Mr = 571.42, monoclinic, space group $P2_1/c$, $a = 13.5099(5)$, $b = 17.683(1)$, $c = 9.028(1)$ Å, $\beta = 92.37(1)°$, $U = 2154.7(1)$ Å^3, $D_c = 1.761$ g cm^{-3}, $Z = 4$, $F(000) = 1112$, μ(Mo–K_α) = 6.851 mm^{-1}.

Solution and refinement: The structure was solved by the Patterson methods option of SHELXS-96 [35], and the gold position determined. All further non-hydrogen atoms were located routinely (SHELXL-96 [36]). 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 $R_1 = 0.0446$ for 3233 data with $I \geq 2\sigma(I)$, 0.0882 for all data; $wR^2 = 0.0937$ $\{w = 1/[\sigma^2(F_o^2) + (0.0339P)^2 + 0.0000P]$ where $P = (F_o^2 + 2F_c^2)/3\}$, and GoF = 1.010. No parameter shifted in the final cycle. The final difference map showed no peaks or troughs of electron density greater than +1.33 and −2.02 eÅ^{-3} respectively, both adjacent to the gold atom.

3.5. X-ray crystal structure of **6b**·$\frac{1}{2}H_2O$

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 $0.60 \times 0.35 \times 0.12$ mm was used for the study and a total of 5504 reflections (of which 4068 were unique) in the range $1.89 < \theta < 30.48°$ were collected at 148(2) K, with monochromatic Mo–K_α 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 ω. The second run covered 360° in ϕ (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 SADABS34 ($T_{\text{max., min.}} = 1.00, 0.57$).

Crystal data: $C_{15}H_2ON_3O_4Au \cdot \frac{1}{2}H_2O$, $M_r = 513.32$, triclinic, space group $P\bar{1}$ (no. 2), $a = 8.890(1)$, $b = 8.983(1)$, $c = 11.201(1)$ Å, $\alpha = 74.78(1)$, $\beta = 89.77(1)$, $\gamma = 76.32(1)°$, $U = 837.1(1)$ Å^3, $D_c = 2.037$ g cm^{-3}, $Z = 2$, $F(000) = 496$, μ(Mo–K_α) = 8.814 mm^{-1}.

Solution and refinement:The structure was solved by the direct methods (TREF) option of SHELXS-96 [35], and the majority of the heavy atom positions determined. All further non-hydrogen atoms were located routinely (SHELXL-96 [36]). 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 $R_1 = 0.0396$ for 3592 data with $I \geq 2\sigma(I)$, 0.0427 for all data; $wR_2 = 0.0971$ $\{w = 1/[\sigma^2(F_o^2) + (0.0526P)^2 + 0.0000P]$ where $P = (F_o^2 + 2F_c^2)/3\}$, and GoF = 1.006. No parameter shifted in the final cycle. The final difference map showed significant peaks and troughs of electron density (maximum +3.24 and −3.94 eÅ^{-3}, respectively), adjacent to the gold atom, which can attributed to poor absorption correction beyond our control.

After elucidation of the structure, an extra peak of electron density was present in the penultimate difference map that was clearly not part of the main molecule.

This was successfully modelled as a lone oxygen atom with half occupancy, almost certainly therefore a water of crystallisation. The atom, O(5), is 2.813(8) Å from O(3), thus within hydrogen bonding distance. The associated hydrogen atoms could not be located in the final electron difference map.

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