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Synthesis and structural characterisation of linear Au(I) N-heterocyclic carbene complexes: New analogues of the Au(I) phosphine drug Auranofin

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Abstract

The synthesis and characterisation of a series of neutral Au(I) N-heterocyclic carbene complexes [(NHC)AuX] (X = Cl and 2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl-1-thiolato) are reported. The chloro complexes were synthesised either by reaction of the appropriate 1,3-dialkylimidazol-2-ylidene with [(Me_2S)AuCl] or by transmetallation between the appropriate Ag(I)–NHC complex and [(Me_2S)AuCl]. The 2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl-1-thiolato complexes were prepared from the appropriate [(NHC)Au(I)Cl] complex and 2′,3′,4′,6′-tetra-*O*-acetyl-1-thio-β-D-glucopyranose under basic conditions. A cationic Au(I)–NHC triphenylphosphine adduct was also prepared. Structural studies (X-ray diffraction) of a number of the complexes show that in each case the gold atom is (quasi-) linearly two-coordinate, having C–Au–Cl, C–Au–S or C–Au–P coordination. In one case, a new phase of [(Cy_2Im)AuCl], the molecules pack pair-wise with a close Au···Au interaction (3.1566(6) Å). Preliminary studies show this complex is luminescent in the solid state.

Keywords: N-heterocyclic carbene complexes; Gold complexes; Auranofin

1. Introduction

Various Au(I) phosphine complexes are well known for their biological activity. For example, the 2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl-1-thiolato Au(I) phosphine complex Auranofin (**1**) has been used for the treatment of severe rheumatoid arthritis for 20 years [1,2]. Auranofin and other neutral linear Au(I) complexes, including [(Et_3P)AuCl] (**2**), also exhibit modest antitumour activity, possibly by an antimitochondrial mechanism [3] involving inhibition of the mitochondrial selenoenzyme thioredoxin reductase [4,5]. Tetrahedral bis-chelated Au(I) complexes such as $[Au(dppe)_2]^+$ exhibit a broader spectrum of antitumour activity [3,6–8] and may act by an antimitochondrial mechanism that is different to that of the linear Au(I) phosphines [9].

We are exploring the possible use of N-heterocyclic carbene ligands (NHCs) as alternatives to phosphines in the synthesis of new, biologically active Au(I) compounds [9–11]. To date, all Au(I) compounds having antitumour activity contain phosphine ligands [12]. By investigating the biological activity of carbene analogues of the different classes of Au(I) antitumour compounds we aim to gain an understanding of the role of the phosphine ligands in the mechanism of action. In addition, an attractive feature of N-heterocyclic carbene chemistry is the ease with which a series of structurally similar complexes with varying lipophilicity can be synthesised,

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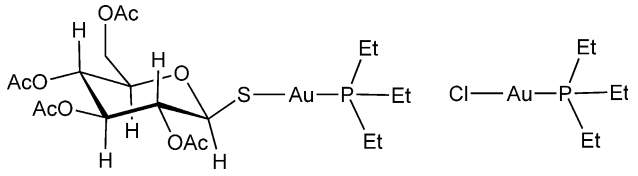
simply by changing the substituents on the imidazolium salt precursor. For bis-chelated Au(I) and Ag(I) analogues of $[Au(dppe)_2]^+$ we have shown that selectivity for tumour cells over normal cells can be achieved by fine-tuning the hydrophilic/lipophilic balance [3], but the approach is limited by the more difficult synthesis of appropriate phosphine ligands.

Here we report the synthesis and spectroscopic and structural characterisation of a series of neutral (1,3-dialkylimidazol-2-ylidine)gold complexes with chloride and 2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl-1-thiolate as ancillary ligands, as NHC-based analogues of Auranofin (**1**) and [(Et_3P)AuCl] (**2**). We also report the synthesis and characterisation of a cationic Au(I)–NHC triphenylphosphine adduct. The antitmitochondrial and other biological properties of these compounds are now being investigated and will be reported in due course.



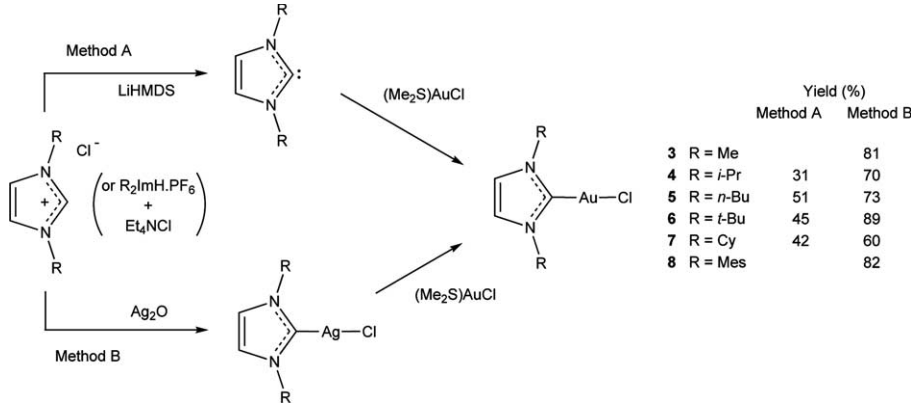
1 **2**

Several methods have been used to synthesise Au(I)–NHC complexes. Raubenheimer and co-workers have reported both cationic and neutral Au(I)–NHC complexes [13], and studied the oxidation of the cationic complexes by halogens [14] and electrochemical methods [15]. They synthesised the Au(I)–NHC complexes via a two-step process, e.g., by reaction of an Au(I) source such as [(tetrahydrothiophene)AuCl] with 2-lithio-1-methylimidazole, followed by N-methylation of the Au-bound imidazole unit [13]. Lin and co-workers have pioneered the use of Ag(I)–NHC complexes as carbene-transfer reagents [16], and have prepared cationic and neutral Au(I) complexes of imidazolium- and benzimidazolium-based NHC ligands by carbene transfer from Ag(I)–NHC complexes [17,18]. We have previously reported a family of dinuclear Au(I) complexes of bridging bidentate NHC ligands [11], which were synthesised by the reaction of bis(imidazolium) salts with Au(I) sources in the presence of a carboxylate base [11]. We have also synthesised a series of linear (pseudo)halo Au(I)–NHC complexes by using the Ag(I)–NHC transfer method to generate an Au(I)–NHC chloride complex, and subsequently using metathesis reactions to introduce other (pseudo)halide ligands in place of chloride [19]. During the course of the present study the syntheses of a variety of other related Au(I)–NHC complexes using the Ag(I)–NHC transfer method and also by direct reaction of an Au(I) source with the free NHC ligand have been reported [20].

2. Results and discussion

2.1. Synthesis of Au(I) complexes

Two synthetic procedures were investigated for the synthesis of the neutral chloro(1,3-dialkylimidazol-2-ylidine)gold [(R_2Im)AuCl] complexes **3**–**8**. The first procedure (Method A) involved treatment of a DMF solution of [(Me_2S)AuCl] with a solution containing an equimolar amount of the free NHC (formed by deprotonation of the chosen imidazolium salt with lithium bis(trimethylsilyl)azide in DMF). This procedure gave the complexes **4**–**7** in moderate yields, but often the cationic [($R_2Im)_2Au$]Cl complexes were also formed. The second procedure (Method B) involved the Ag(I)–NHC transfer method [16,19], whereby the imidazolium chloride was treated with silver oxide in CH_2Cl_2, and the resulting Ag(I)–NHC complex was allowed to react with [(Me_2S)AuCl] (Scheme 1). Where the imidazolium salt was not conveniently available as a chloride (in the syntheses of **3** and **8**), a mixture of the hexafluorophosphate salt

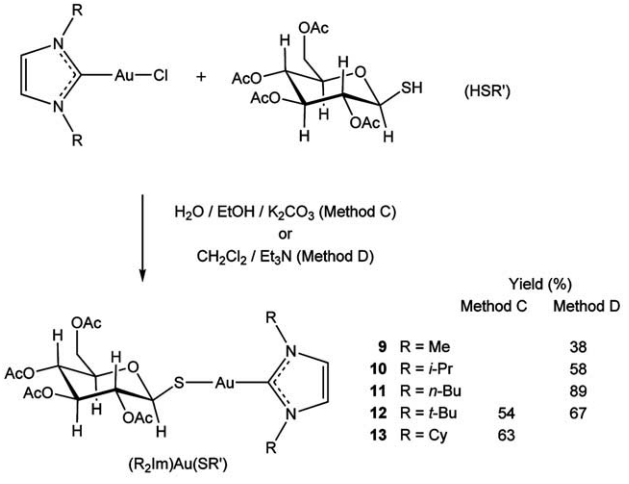


		Yield (%) Method A	Method B
3	R = Me		81
4	R = *i*-Pr	31	70
5	R = *n*-Bu	51	73
6	R = *t*-Bu	45	89
7	R = Cy	42	60
8	R = Mes		82

Scheme 1.

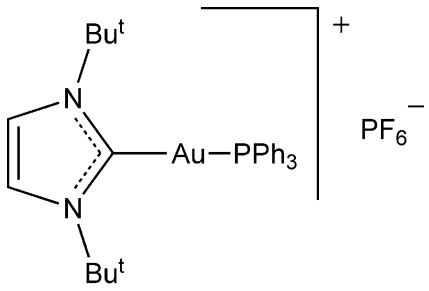
and tetraethylammonium chloride was used as the source of halide and imidazolium ions, respectively. Additional chloride is necessary to ensure sufficient chloride ions are available for formation of both [(R_2Im)AuCl] and AgCl. Not surprisingly, the use of a 1,3-dimethylimidazolium bromide in place of the corresponding chloride in an attempted synthesis of **3** give a product contaminated with [(Me_2Im)AuBr]. The syntheses of **3** [18] and **7** and **8** [20] by similar methods have been reported recently.

Modifications of two literature procedures reported for the synthesis of Auranofin **1** were investigated for the preparation of the neutral tetra-*O*-acetyl-β-D-glucopyranosyl-1-thiolato complexes [(R_2Im)Au(SR′)] **9**–**13** [21,22]. Both procedures involved treating solutions of the [(R_2Im)AuCl] complexes with tetra-*O*-acetyl-1-thio-β-D-glucopyranose (HSR′) under basic conditions (Scheme 2). The first method (Method C) used an ethanol/water solvent system and K_2CO_3 as a mild base [21]. This method, however, tended to yield oily mixtures, which in most cases could not be purified. The second procedure [22] (Method D) used CH_2Cl_2 as the solvent and triethylamine as the base and also yielded oils, but chromatography (SiO_2) followed by a recrystallisation from ethanol/water gave the desired products. The thiolato complexes are sensitive to acids. For example, dissolution of the complexes in chloroform that had not been carefully purified to remove acidic contaminants caused their decomposition. The new [(R_2Im)AuX] complexes reported here, like Auranofin, are soluble in organic solvents such as ethanol and DMSO and are poorly soluble in aqueous solutions. Auranofin is an orally administered agent, and within the body undergoes ligand dissociation reactions through displacement of the phosphine and/or the thiolato ligands to generate various different Au-based metabolites [3,23]. We are currently investigating the reactivity of the new [(R_2Im)-AuX] complexes with biologically relevant ligands and will publish the results of those studies in due course.



Scheme 2.

The cationic complex **14** was prepared from the chloro-complex **6** by displacement of the chloride by triphenylphosphine, and was conveniently isolated as its hexafluorophosphate salt **14** · PF_6.



14.PF_6

2.2. NMR spectra of complexes

The NMR spectra of the chloro complexes **3**–**8** and the phosphine complex **14** showed the number of signals expected for complexes with a symmetrical 1,3-dialkylimidazol-2-ylidine unit. For the thiolate complexes **9**–**13**, the signals expected for the 1,3-dialkylimidazol-2-ylidine unit were also detected, although the methyl and methylene groups in the isopropyl and cyclohexyl complexes **10** and **13**, respectively, were chemically inequivalent due to the chirality of the glucopyranosyl moiety. For each complex, the ^{13}C NMR spectrum showed a signal characteristic of an imidazol-2-ylidine carbene carbon. For the chlorides **3**–**8** this resonance occurs at δ 166–172 and for the thiolates **9**–**13** and the phosphine complex **14** it occurs at δ 181–185. *S*-coordination of the glucopyranosylthiolate unit was confirmed by the absence of an S–H signal in the ^1H NMR spectra of the thiolates **9**–**13** (e.g., Fig. 1).

2.3. X-ray studies

We have structurally characterised **3**, **4**, **6** [19], **7**, **8**, **12**, and **14** · PF_6. Our results for **8** are of the same form and comparable precision to those reported previously [20]. Structural studies of different forms of **3** [18] and **7** [20] have also been reported previously.

The results of our 'low'-temperature single crystal X-ray studies are consistent with the formulations [(R_2Im)AuX] · *n*(Sol) (Sol = solvent) in terms of stoichiometry and connectivity. In all cases the Au atoms are (quasi-) linearly two-coordinated by the central carbon of the NHC ligand and (in most cases) the chloride or thiolate anion. In one case, **14** · PF_6, the anion, being

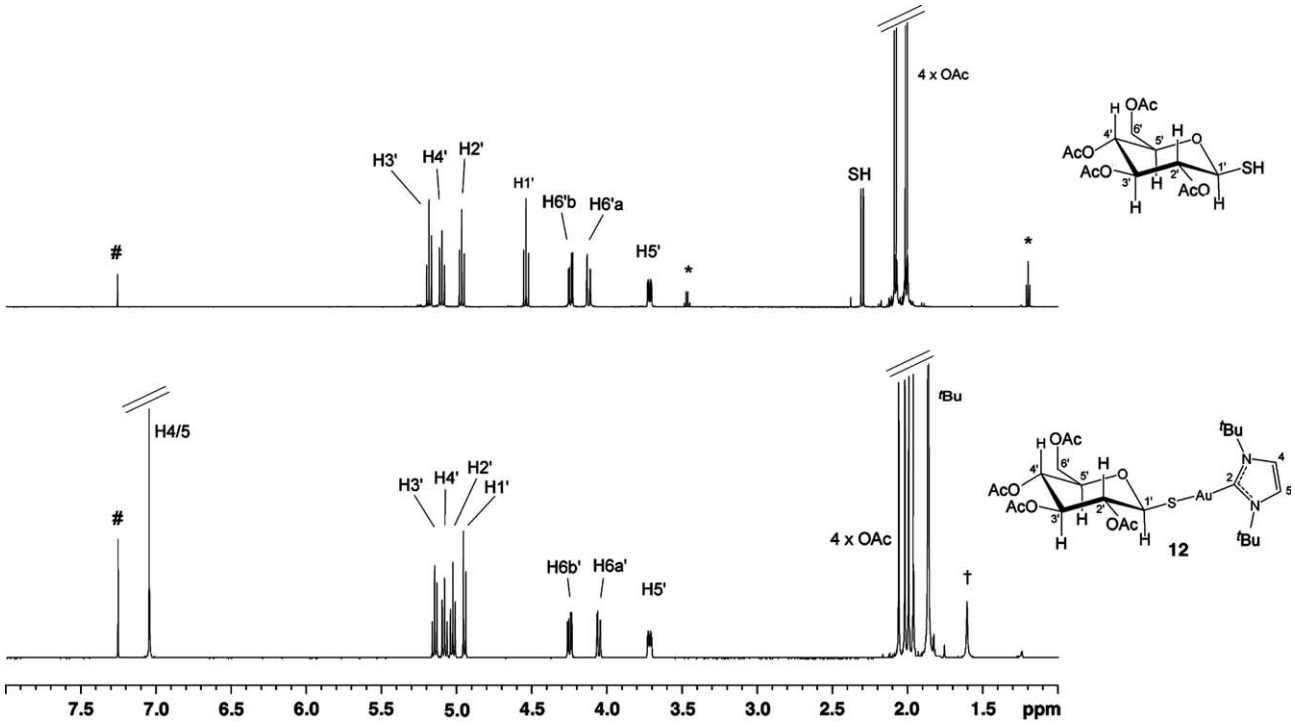


Fig. 1. ^{1}H NMR spectra (600 MHz, $CDCl_3$) for 2′,3′,4′,6′-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (upper) and complex **12** (lower). (* indicates impurity, # = residual solvent signal, † = adventitious water.)

feebly coordinating PF_6^-, is supplanted by the neutral unidentate PPh_3 donor. The constitution of the asymmetric unit throughout the various structures is diverse, ranging from three molecules devoid of crystallographic symmetry, with accompanying solvent in **3** {$[(Me_2Im)AuCl]_3 \cdot CH_2Cl_2$}, to one-half of a single molecule in [(Mes_2Im)AuCl] (**8**), wherein the molecule lies disposed on a crystallographic 2-axis [20], as is also the case in the structure of [(^{t}Bu$_2$Im)AuCl] (**6**) [19]. The determinations are of diverse degrees of precision, following variations in crystal quality; coordination geometries about the gold atoms are presented comparatively in Table 1, representations of individual species being depicted in Fig. 2. In a number of cases, the crystal packing is of interest: in the triclinic cell of [(Me_2Im)AuCl] (**3**), there is evidence of pseudo-symmetry, the three molecules of the asymmetric unit being quasi-coplanar and related by quasi-3 symmetry (Fig. 3(a/b)),

Table 1
Selected molecular geometries, [(R_2Im)AuCl]

R	Distances (Å)		Angles (°)		
	Au–X[a]	Au–C	X–Au–C	Au–C(1)–N(2,5)	N(2)–C(1)–N(5)
Me (mol 1) (**3**)	2.302(4)	1.95(2)	178.9(6)	127(1), 128(2)	105(2)
(mol 2)	2.271(5)	1.94(2)	179.1(7)	131(1), 123(1)	105(2)
(mol 3)	2.276(5)	1.93(2)	178.4(7)	127(2), 130(2)	103(2)
<>	2.28(2)	1.94(1)	178.8(4)		104(1)
^{i}Pr (**4**)	2.261(2)	1.964(6)	175.0(2)	125.2(5), 129.6(5)	105.0(5)
^{t}Bu (**6**)[b]	2.2742(7)	2.018(3)	180(–)	126.1(1) (×2)	107.8(2)
Cy (**7**)	2.294(2)	1.978(8)	176.7(2)	126.6(6), 129.2(6)	104.0(7)
Mes (**8**)[b]	2.2758(12)	1.999(5)	180(−)	126.5(2) (×2)	106.9(4)
^{t}Bu (mol 1) (**12**)	2.28(1)[c]	2.04(3)	172.9(9)	129(3), 124(2)	107(3)
(mol 2)	2.33(1)[c]	2.05(3)	177.1(9)	126(2), 130(2)	104(3)
<>	2.31(4)[c]	2.05(1)	175(3)		106(2)
^{t}Bu (mol 1) (**14**)	2.275(1)[d]	2.044(4)	177.3(1)	125.7(3), 128.2(3)	106.2(3)
(mol 2)	2.274(1)[d]	2.034(4)	177.0(1)	126.7(3), 128.0(3)	105.2(3)

[a] X = Cl^- unless otherwise indicated.
[b] Data for **6** from [19]; data for **8** from [20].
[c] X = $C_{14}H_{19}O_9S$.
[d] X = *P*Ph_3; Au–C,P here may be compared with those found in the counterpart adduct with R_2 = (5H-dibenzo[*a*,*d*]cycloheptenyl)$_2$ (2.111(7), 2.2299(2) Å; C–Au–P 173.8(2)°), see [24].

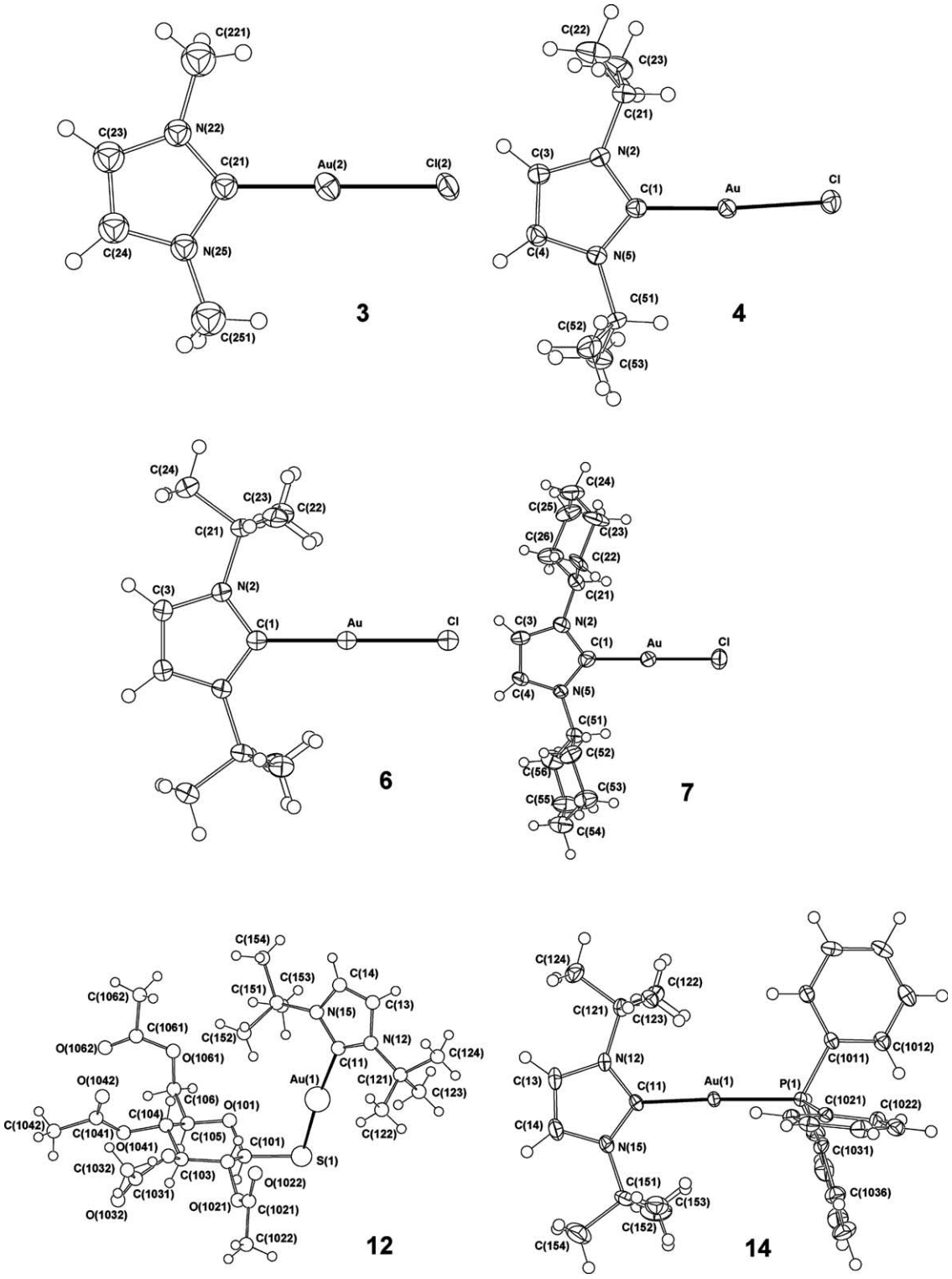


Fig. 2. Projections of individual molecules, normal to the Im C_3N_2 plane, for: [(Me_2Im)AuCl] (**3**) (molecule 2, as representative); [(^{i}Pr_2Im)AuCl] (**4**) [(^{t}Bu_2Im)AuCl] (**6**) [19]; [(Cy_2Im)AuCl] (**7**); [(^{t}Bu_2Im)Au($C_{14}H_{19}O_9S$)] (**12**); the cation [(^{t}Bu_2Im)Au(PPh_3)]$^+$ in **14**.

the closest proximity of the ordered solvent (dichloromethane) being H(1a)···Au(2)($\bar{x}$, $2-y$, $2-z$) 3.2 Å (est.). In [(^{t}Bu_2Im)AuCl] (**6**) [19], the molecules lie quasi-normal to *c* and stack in columns (Fig. 3(c)), and the Im planes, quasi-parallel to *c*, interlock in their packing. In [(Cy_2Im)AuCl] (**7**), the molecules pack in

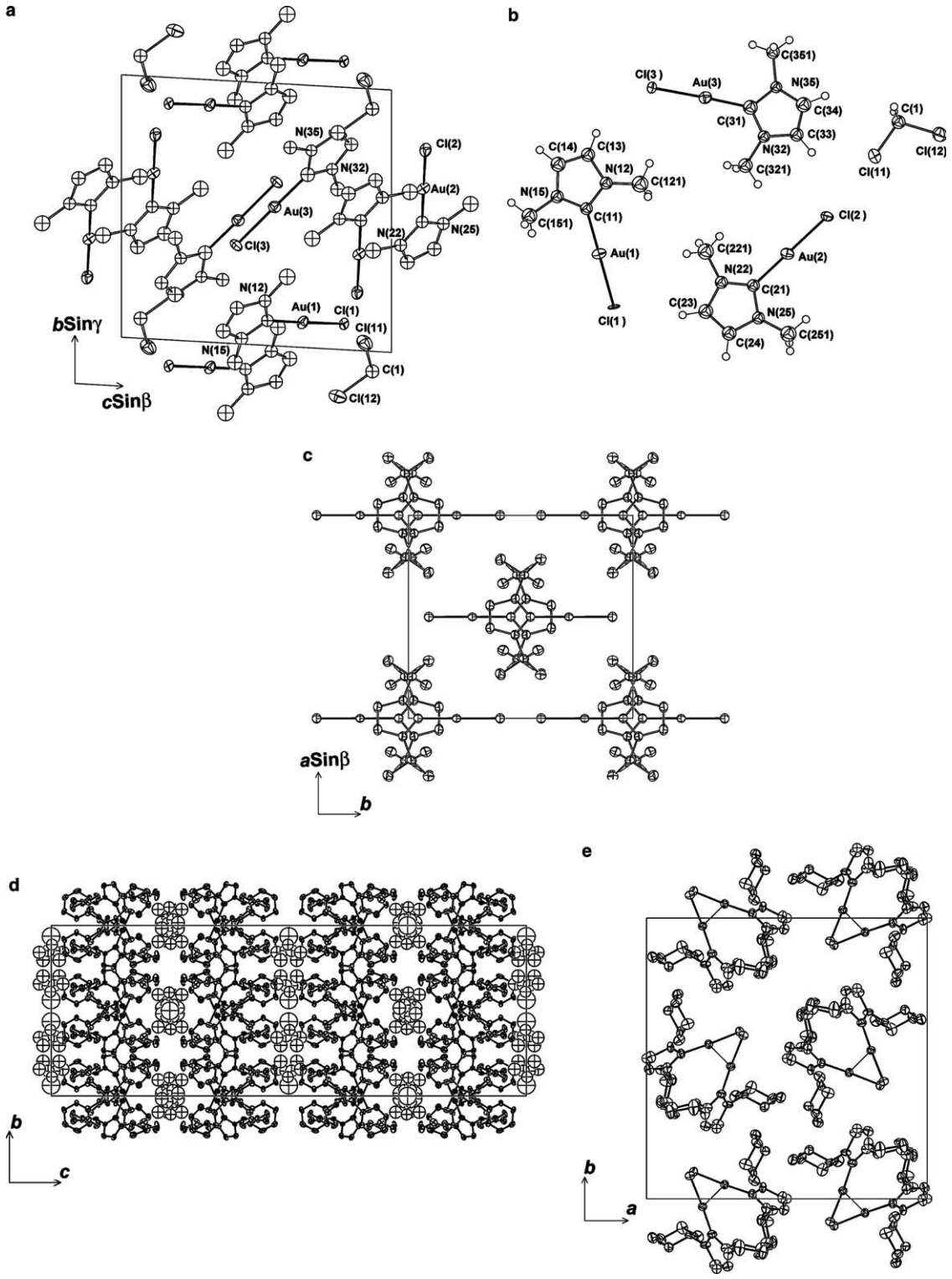


Fig. 3. (a) Unit cell contents of $[(Me_2Im)AuCl]_3 \cdot CH_2Cl_2$ (**3**) projected down *a*; (b) the asymmetric unit for **3**, projected normal to the common 'plane', and showing the quasi-3 disposition of the substrate molecules; (c) unit cell contents of $[(^tBu_2Im)AuCl]$ (**6**), projected down *c* (after [19]); (d) unit cell contents of $[(Cy_2Im)AuCl] \cdot 1/2CH_2Cl_2$ (**7**), projected down *a*, showing the layering of the structure, partitioned by solvent molecules; (e) a single layer of **7** (about $z = 1/8$) showing the pairing of the molecules within the layer.

layers normal to *c*, interleaved by planes of solvent molecules about $z = 0$, etc. (Fig. 3(d)). Within the layers, the molecules pack pair-wise with close Au···Au ($y - 1/4$, $x + 1/4$, $1/4 - z$) approaches (3.1566(6) Å), Fig. 3(e). There are no counterpart approaches in $[(Pr^i_2Im)AuCl]$ (**4**), wherein the disposition of the substituents creates

an intramolecular ambience about the molecular core (Fig. 2) essentially identical to that of **7** (the α-hydrogens of the substituents essentially in plane and directed towards Au) but contrasting to that of **6** (wherein a pair of methyl groups of each ^{t}Bu substituent straddle the coordination plane, either side of Au). Among the other compounds, there are no Au···Au approaches <4 Å. Interestingly, although colourless under ambient light, crystals of [(Cy_2Im)AuCl] (**7**) displayed orange luminescence when irradiated with ultraviolet light (~260 nm). The other compounds, which do not exhibit aurophilic interactions in the solid state, are not luminescent.

Despite the diversity in precision of the determinations, there is sufficient detail of adequate definition in Table 1 to note some possible diversity in Au–C distances, reflecting the nature of R, perhaps correlating with variations in the N–C–N angle. Attempted correlations with variations in Au–Cl are insecure, and in the broader context of the data of the additional species reported in [20] (Table 1), the variations carry little meaning. In the ^{i}Pr$_2$Im and Cy_2Im adducts **4** and **7**, angles C(1)–N(n)–C(n1) are slightly diminished relative to C(3,4)–N(n)–C(n1). It is of further interest that the complexes **3** and **7**, cosynchronously studied as reported in [18,20], here have been shown to crystallise in different (solvated) phases. The results are essentially harmonious with those of [18,20] insofar as the intramolecular geometries are concerned, but the consequences of solvation are significant and of interest in respect of the resultant crystal packing. As noted above, there is an interesting quasi-threefold arrangement among the three independent molecules of the asymmetric unit of **3** {[(Me_2Im)AuCl]$_3$ · CH_2Cl_2}, but no close Au···Au approaches are present. In the unsolvated form of **3** reported previously [18], however, close Au···Au approaches (3.5405(3) Å) within the layers normal to *c* are exhibited.

3. Experimental

3.1. General

Nuclear magnetic resonance spectra were recorded using Bruker ARX-300 (300.1 MHz for ^{1}H, 75.5 MHz for ^{13}C), Bruker AV-500 (500.1 MHz for ^{1}H, 125.8 MHz for ^{13}C) or Bruker AV-600 (600.1 MHz for ^{1}H, 150.9 MHz for ^{13}C, 242.9 for ^{31}P) spectrometers at ambient temperature unless otherwise specified. ^{1}H and ^{13}C chemical shifts were referenced to solvent resonances. Microanalyses were performed at the Microanalytical Laboratory at the Australian National University, Research School of Chemistry, Canberra, Australia. All solvents were redistilled prior to use. All compounds were prepared under an atmosphere of dry nitrogen unless otherwise specified. 1,3-Di-*n*-butylimidazolium hexafluorophosphate was prepared by metathesis of the bromide salt with potassium hexafluorophosphate. Other 1,3-dialkylimidazolium salts [25], tetra-*O*-acetyl-1-thio-β-D-glucopyranose [26], chloro(dimethylsulfide)gold [27] and chloro(1,3-di-*t*-butylimidazol-2-ylidine)gold (**6**) [19] were prepared using literature procedures.

3.2. Synthesis of complexes

3.2.1. [(^{i}Pr$_2$Im)AuCl] (4)

Method A: 1,3-Diisopropylimidazolium chloride (101 mg, 0.53 mmol) was treated with lithium bis(trimethylsilyl)amide (93.1 mg, 0.56 mmol) in DMF (5 mL). After 10 min the solution was added dropwise to a stirred solution of [(Me_2S)AuCl] (125 mg, 424 μmol) in DMF (2 mL). After 1 h the solvent was removed in vacuo and water (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with aqueous $NaHCO_3$ and brine, and dried with $MgSO_4$. The solution was concentrated to 5 mL and the crude product was precipitated by addition of hexane (10 mL). After recrystallisation from CH_2Cl_2/hexane, **4** was obtained as a white crystalline solid (50 mg, 31%).

Method B: A mixture of Ag_2O (15.2 mg, 65.6 μmol) and 1,3-diisopropylimidazolium chloride (22.5 mg, 119 μmol) in CH_2Cl_2/MeOH (1:1, 1 mL) was stirred for 6 h, during which time almost all the Ag_2O dissolved. [(Me_2S)AuCl] (21.4 mg, 72.6 μmol) was added and the mixture was stirred for 4 h. The mixture was filtered through Celite, the solvent was removed in vacuo and the residue was re-dissolved in CH_2Cl_2 and passed through a plug of silica. The eluate was concentrated to 1 mL and hexanes (2 mL) was added. The resulting white crystalline solid was collected, washed with hexane and recrystallised from CH_2Cl_2/hexanes to yield **4** as a white powder (19.7 mg, 70%). Crystals suitable for X-ray diffraction studies were grown by diffusion of vapours between hexanes and a concentrated solution of the compound in CH_2Cl_2. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 6.98 (2H, s, H4/H5), 5.04 (2H, septet, $J = 6.8$ Hz, C*H*CH$_3$), 1.47 (12H, d, $J = 6.8$ Hz, CH$_3$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 168.72 (C2), 116.87 (C4/C5), 53.81 (*C*H(CH$_3$)$_2$), 23.52 (CH$_3$). Anal. Calc. for $C_9H_{16}N_2AuCl$: C, 28.10; H, 4.19; N 7.28. Found: C, 28.26; H, 4.34; N, 7.17%.

3.2.2. [(Me_2Im)AuCl] (3)

Method B, using a mixture of 1,3-dimethylimidazolium hexafluorophosphate and tetraethylammonium chloride. The product **3** was purified by chromatography on silica (CH_2Cl_2) and recrystallisation from THF/hexanes and was obtained as a white solid (16.5 mg, 81%). Crystals suitable for X-ray diffraction studies were grown by diffusion of vapours between hexanes and a concentrated solution of the complex in CH_2Cl_2. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 6.92 (2H, s,

H4/H5), 3.81 (6H, s, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.85 (C2), 121.86 (C4/C5), 38.31 (CH_3). Anal. Calc. for $C_5H_8N_2AuCl$: C, 18.28; H, 2.45; N 8.53. Found: C, 18.32; H, 2.40; N, 8.34%.

3.2.3. [(^{n}Bu$_2$Im)AuCl] (5)

Method A, from 1,3-di-*n*-butylimidazolium chloride. The product was obtained as a colourless oil after chromatography on silica (CH_2Cl_2). Yield, 51%.

Method B, using a mixture of 1,3-di-*n*-butylimidazolium hexafluorophosphate and the procedure as described for the formation of **3**. After chromatography on silica (CH_2Cl_2), **5** was obtained as a colourless oil (120 mg, 73%). ^1H NMR (300.1 MHz, $CDCl_3$): δ 6.97 (2H, s, H4/H5), 4.11 (4H, t, $J = 7.3$ Hz, H6), 1.77 (4H, apparent quintet, splitting 7.5 Hz, $CH_2CH_2CH_2$), 1.36 (4H, apparent sextet, splitting 7.7 Hz, CH_2CH_3), 0.85 (6H, t, $J = 7.4$ Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.91 (C2), 120.50 (C4/C5), 51.27 (NCH_2), 33.12 ($CH_2CH_2CH_2$), 19.69 (CH_2CH_3), 13.67 (CH_3). Anal. Calc. for $C_{11}H_{20}N_2AuCl$: C, 32.01; H, 4.88; N, 6.79. Found: C, 31.96; H, 4.51; N, 6.93%.

3.2.4. [(Cy$_2$Im)AuCl] (7)

Method A, from 1,3-dicyclohexylimidazolium chloride. The product was obtained as a colourless crystalline solid after recrystallisation twice from CH_2Cl_2/hexane. Yield, 42%.

Method B, from 1,3-dicyclohexylimidazolium chloride. Yield, 60% after recrystallisation once from CH_2Cl_2/hexane. Crystals suitable for X-ray diffraction studies were grown by diffusion of vapours between hexanes and a concentrated solution of the complex in CH_2Cl_2. ^1H NMR (300.1 MHz, $CDCl_3$): δ 6.94 (2H, s, H4/H5), 4.46–4.70 (2H, m, $NCHCH_2$), 2.04–2.17 (4H, m, CH_2), 1.82–1.96 (4H, m, CH_2), 1.69–1.81 (2H, m, CH_2), 1.35–1.67 (8H, m, CH_2), 1.08–1.30 (2H, m, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.09 (C2), 118.84 (C4/C5), 60.54 ($NCHCH_2$), 33.12, 25.06, 24.56 (CH_2). Anal. Calc. for $C_{15}H_{24}N_2AuCl$: C, 38.76; H, 5.20; N, 6.03. Found: C, 38.93; H, 5.17; N, 5.74%.

3.2.5. [(Mes$_2$Im)AuCl] (8)

Method B, from 1,3-bis(2,4,6-trimethylphenyl)imidazolium hexafluorophosphate as for the synthesis of **3**. Obtained as a fluffy white solid (yield, 82%) after chromatography on silica (CH_2Cl_2) and precipitation from CH_2Cl_2 by addition of pentane. ^1H NMR (500.1 MHz, $CDCl_3$): δ 7.09 (2H, s, H4/H5), 7.01–6.97 (4H, m, Ar H), 2.34 (6H, s, CH_3), 2.10 (12H, s, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 173.58 (C2), 134.78, 134.84, 139.94 (Ar C), 129.64 (Ar CH), 122.29 (C4/C5), 21.29 (CH_3), 17.90 (CH_3). Anal. Calc. for $C_{21}H_{24}N_2AuCl$: C, 46.98; H, 4.51; N, 5.22. Found: C, 47.05; H, 4.45; N, 5.22%.

3.2.6. [(Me$_2$Im)AuSR′] (9)

Method D: [(Me_2Im)AuCl] **3** (15 mg, 46 μmol) and tetra-*O*-acetyl-1-thio-β-D-glucopyranose (17.5 mg, 48 μmol) were dissolved in CH_2Cl_2 (1 mL) and triethylamine (7 μL, 50 μmol) was added. The reaction was monitored by TLC (CH_2Cl_2) and was complete after 2 h. The solvent was removed under reduced pressure and after chromatography on silica (THF) and recrystallisation from EtOH/H_2O, **9** was obtained as a fluffy white solid (11 mg, 38%). ^1H NMR (300.1 MHz, $CDCl_3$): δ 6.88 (2H, s, H4/H5), 4.96–5.13 (4H, m, H1′-H4′), 4.22 (1H, dd, $J_{6b',6a'} = 12.2$ Hz, $J_{6a',5'} = 4.9$ Hz, H6a′), 4.07 (1H, dd, $J_{6b',6a'} = 12.2$ Hz, $J_{6b',5'} = 2.3$ Hz, H6b′), 3.80 (6H, s, NCH_3), 3.68–3.73 (1H, m, H5′), 2.05 (3H, s, OAc), 1.99 (3H, s, OAc), 1.96 (3H, s, OAc), 1.93 (3H, s, OAc). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 183.83 (C2), 170.88 (C=O), 170.40 (C=O), 169.99 (C=O), 169.81 (C=O), 121.63 (C4/C5), 83.30 (C1′), 77.83 (C2′), 75.76 (C5′), 74.50 (C3′), 69.12 (C4′), 63.09 (C6′), 37.94 (NCH_3), 20.95 (O=CCH_3), 20.93 (O=CCH_3), 20.83 (O=CCH_3), 20.78 (O=CCH_3). Anal. Calc. for $C_{19}H_{19}N_2O_9SAu \cdot 0.1\ C_2H_5OH$: C, 35.34; H, 4.45; N, 4.21. Found: C, 35.5; H, 4.45; N, 3.61%.

3.2.7. [(^{i}Pr$_2$Im)AuSR′] (10)

Method D, starting with **4**, gave **10** as a white crystalline solid from EtOH/H_2O (Yield, 58%). ^1H NMR (500.1 MHz, $CDCl_3$): δ 6.96 (2H, s, H4/H5), 5.05–5.17 (6H, m, H1′-H4′ and $2 \times CHCH_3$), 4.25 (1H, dd, $J_{6b',6a'} = 12.2$ Hz, $J_{6b',5'} = 4.9$ Hz, H6a′), 4.10 (1H, dd, $J_{6a',6b'} = 12.2$ Hz, $J_{6a',5'} = 2.4$ Hz, H6b′), 3.74 (1H, ddd, $J_{5',4'} = 9.7$ Hz, $J_{5',6b'} = 4.9$ Hz, $J_{5',6a'} = 2.4$ Hz, H5′), 2.09 (3H, s, OAc), 2.03 (3H, s, OAc), 1.97 (3H, s, OAc), 2.01 (3H, s, OAc), 1.50 (6H, d, $J = 6.8$ Hz, $CHCH_3$a), 1.49 (6H, d, $J = 6.8$ Hz, $CHCH_3$b). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 181.01 (C2), 170.98 (C=O), 170.50 (C=O), 169.90 (C=O), 169.84 (C=O), 116.54 (C4/C5), 83.34 (C1′), 78.03 (C2′), 75.71 (C5′), 74.58 (C3′), 69.22 (C4′), 63.19 (C6′), 53.27 ($CHCH_3$), 23.65, 23.52 ($CHCH_3$), 21.36 (O=CCH_3), 21.00 (O=CCH_3), 20.88 (O=CCH_3), 20.84 (O=CCH_3). Anal. Calc. for $C_{23}H_{35}N_2O_9SAu$: C, 38.77; H, 4.95; N, 3.93. Found: C, 38.99; H, 5.08; N, 3.60%.

3.2.8. [(^{n}Bu$_2$Im)AuSR′] (11)

Method D, starting with **5**, gave **11** as a colourless waxy solid after chromatography (silica/diethyl ether). Yield, 90%. ^1H NMR (300.1 MHz, $CDCl_3$): δ 6.89 (2H, s, H4/H5), 5.00–5.17 (4H, m, H1′–H4′), 4.05–4.27 (6H, m, $2 \times NCH_2$ and H6a′ and H6b′), 3.68–3.75 (1H, m, H5′), 2.08 (3H, s, OAc), 2.02 (3H, s, OAc), 1.99 (3H, s, OAc), 1.96 (3H, s, OAc), 1.83 (4H, apparent quintet, splitting = 7.5 Hz, $CH_2CH_2CH_2$), 1.37 (4H, app sext, splitting = 7.7 Hz, CH_3CH_2), 0.96 (6H, t, $J = 7.4$ Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ

182.66 (C2), 170.95 (C=O), 170.46 (C=O), 169.93 (C=O), 169.75 (C=O), 120.15 (C4/C5), 83.33 (C1′), 77.91 (C2′), 75.71 (C5′), 74.47 (C3′), 69.20 (C4′), 63.17 (C6′), 51.01 (NCH_2), 33.38 ($CH_2CH_2CH_2$), 20.96 ($2\times O{=}CCH_3$), 20.80 ($2\times O{=}CCH_3$), 19.82 (CH_3CH_2), 13.83 (CH_3). Anal. Calc. for $C_{25}H_{39}N_2O_9SAu$: C, 40.54; H, 5.31; N, 3.78. Found: C, 40.93; H, 5.39; N, 3.84%.

3.2.9. [(*t*Bu$_2$Im)AuSR′] (**12**)

Method D, starting with **6**, gave **12** as white solid. Yield, 67%.

Method C: [(*t*Bu$_2$Im)AuCl] (**6**) (50.0 mg, 121 μmol) in cold ethanol (3 mL) was added dropwise to a stirred suspension of tetra-*O*-acetyl-1-thio-β-D-glucopyranose (46.4 mg, 127 μmol) in degassed ethanol:water (6:4, 5 mL) at −10 °C. The mixture was treated with aqueous K_2CO_3 solution (0.7 mL, 0.2 M, 140 μmol) and stirred at −5 °C for 2 h. The solution was concentrated and **12** precipitated as white crystals (48 mg, 54%) that were collected by filtration. Crystals suitable for X-ray diffraction studies were grown by diffusion of vapours between pentane and a concentrated solution of the complex in THF. ^{1}H NMR (600.1 MHz, $CDCl_3$): δ 7.05 (2H, s, H4/H5), 5.15 (1H, t, $J_{3',2'/4'} = 9.3$ Hz, H3′), 5.09 (1H, t, $J_{4',3'/5'} = 9.7$ Hz, H4′), 5.03 (1H, t, $J_{2',1'/3'}$ 9.3 Hz, H2′), 4.95 (1H, d, $J_{1',2'} = 9.5$ Hz, H1′), 4.25 (1H, dd, $J_{6a',6b'} = 12.2$ Hz, $J_{6',5'} = 4.7$ Hz, H6a′ or H6b′), 4.06 (1H, dd, $J_{6a',6b'} = 12.2$ Hz, $J_{6',5'} =$ 2.6 Hz, H6a′ or H6b′), 3.72 (1H, ddd, $J_{5',4'} = 9.9$ Hz, $J_{5',6'b} = 4.7$ Hz, $J_{5',6'a} = 2.6$ Hz, H5′), 2.06 (3H, s, OAc), 2.02 (3H, s, OAc), 2.00 (3H, s, OAc), 1.97 (3H, s, OAc), 1.87 (18H, s, $C(CH_3)_3$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 181.61 (C2), 170.96 (C=O), 170.56 (C=O), 169.78 ($2\times C{=}O$), 116.18 (C4/C5), 83.19 (C1′), 78.13 (C2′), 75.66 (C5′), 74.57 (C3′), 69.30 (C4′), 63.14 (C6′), 58.91 ($C(CH_3)_3$), 31.92 ($C(CH_3)_3$), 21.26 ($O{=}CCH_3$), 21.00 ($O{=}CCH_3$), 20.86 ($O{=}CCH_3$), 20.82 ($O{=}CCH_3$). Anal. Calc. for $C_{25}H_{39}N_2O_9 \cdot 0.5C_2H_5OH$: C, 40.95; H, 5.42; N, 3.67. Found: C, 41.03; H, 5.41; N, 3.77%.

3.2.10. [(Cy$_2$Im)Au(SR)] (**13**)

Method C, starting with **7** gave **13** as a white crystalline solid (52 mg, 63%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 6.92 (2H, s, H4/H5), 5.02–5.18 (H1′-H4′), 4.58–4.70 (2H, m, $CHCH_2$), 4.25 (1H, dd, $J_{6a',6b'} = 12.2$ Hz, $J_{6',5'} = 4.6$ Hz, H6a′ or H6b′), 4.10 (1H, dd, $J_{6a',6b'} =$ 12.2 Hz, $J_{6',5'} = 2.3$ Hz, H6a′ or H6b′), 3.72–3.75 (1H, m, H5′), 2.13–2.20 (4H, m, CH_2), 2.10 (3H, s, OAc), 2.02 (3H, s, OAc), 2.00 (3H, s, OAc), 1.96 (3H, s, OAc), 1.83–1.90 (4H, m, CH_2), 1.74–1.78 (4H, m, CH_2), 1.50–1.63 (6H, m, CH_2), 1.20–1.25 (2H, m, CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 181.05 (C2), 170.96 (C=O), 170.37 (C=O), 169.86 (C=O), 169.73 (C=O), 116.81 (C4/C5), 83.47 (C1′), 78.15 (C2′), 75.68 (C5′), 74.51 (C3′), 69.19 (C4′), 63.05 (C6′), 60.59 ($CHCH_2$), 34.50, 34.10, 25.54, 25.45, 25.42 (CH_2), 21.39 ($O{=}CCH_3$), 20.90 ($O{=}CCH_3$), 20.81 ($O{=}CCH_3$), 20.76 ($O{=}CCH_3$). Anal. Calc. for $C_{29}H_{45}N_2O_9SAu \cdot H_2O$: C, 43.13; H, 5.24; N, 3.47. Found: C, 42.88; H, 5.64; N, 3.42%.

3.2.11. [(*t*Bu$_2$Im)Au(PPh$_3$)]PF$_6$ (**14**)

A solution of potassium hexafluorophosphate (10 mg, 54.3 μmol), (1,3-di-*tert*-butylimidazol-2-ylidine)gold chloride (**6**) (12 mg, 29.1 μmol) and triphenylphosphine (10 mg, 38 μmol) in acetone (3 mL) was stirred for 1 h. The mixture was filtered and the solid was extracted with additional acetone (2×1 mL). Water (1 mL) was added to the combined filtrates and the mixture was evaporated to dryness. The residue was washed with water (2×5 mL), dried in vacuo, and recrystallised from dichloromethane/benzene to give the product as a white solid (20 mg, 88%). Crystals suitable for X-ray diffraction studies were grown by diffusion of vapours between pentane and a concentrated solution of the complex in d_6-acetone. ^{1}H NMR (600.1 MHz, d_6-acetone): δ 7.57–7.70 (m, 15H, Ar H), 7.64 (s, 2H, H4/5), 1.93 (s, 18H, CH_3). ^{13}C NMR (150.9 MHz, d_6-acetone): δ 184.67 (C2), 134.84 (d, $J_{P-C} = 13.9$ Hz, C2′/6′ or C3′/5′), 133.09 (d, $J_{P-C} = 2.3$ Hz, C4′), 130.59 (d, $J_{P-C} = 11.2$ Hz, C3′/5′ or C2′/6′), 130.39 (d, $J_{P-C} = 53.9$ Hz, C1′), 119.42 (C4/5), 59.97 (CCH_3), 32.51 (CH_3). ^{31}P NMR (242.9 MHz, d_6-acetone): δ 39.67 (br, PPh_3), −143.75 (septet, $J = 707.4$ Hz, PF_6^-). Anal. Calc. for $C_{29}H_{35}AuF_6N_2P_2$: C, 44.40; H, 4.50; N, 3.57. Found: C, 44.44; H, 4.51; N, 3.50%.

3.3. Structure determinations

Full spheres of 'low'-temperature (T ca. 153 K) CCD area-detector diffractometer data were measured (Bruker AXS instrument, ω-scans; monochromatic Mo Kα radiation, $\lambda = 0.7107_3$ Å) yielding $N_{(total)}$ reflections, these merging to N unique after 'empirical'/multiscan absorption correction (proprietary software), N_0 with $F > 4\sigma(F)$ considered 'observed' and used in the full matrix least squares refinements, refining anisotropic displacement parameter forms for the non-hydrogen atoms, (x,y,z, $U_{iso})_H$ being constrained at estimates. Conventional residuals R, R_w (reflection weights: $(\sigma^2(F) + 0.000n_wF^2)^{-1}$) at convergence are cited on $|F|$. Neutral atom complex scattering factors were employed within the context of the Xtal 3.7 program system [28]. Pertinent results are given below and in the tables and figures, the latter showing 50% probability amplitude displacement ellipsoids (**12** excepted) for the non-hydrogen atoms; hydrogen atoms where shown have arbitrary radii of 0.1 Å. Crystal/refinement data are summarised in Table 2. Individual divergences in procedure are cited as 'variata'. Full .cif depositions (excluding structure factor amplitude

Table 2
Crystal/refinement data $[(R_2Im)AuX]^{(+)}(Anion^-)(.nS)$

R (compd.)	Me (**3**)	^{i}Pr (**4**)	Cy (**7**)	Mes (**8**)	^{t}Bu (**12**)	^{t}Bu (**14**)[a]
X (nS)	Cl (1/3 CH_2Cl_2)	Cl	Cl(1/2 CH_2Cl_2)	Cl	$C_{14}H_{19}O_9S$	PPh_3
Formula	$C_5H_8AuClN_2 \cdot$ 1/3 CH_2Cl_2	$C_9H_{16}AuClN_2$	$C_{15}H_{24}AuClN_2 \cdot$ 1/2 CH_2Cl_2	$C_{21}H_{24}AuClN_2$	$C_{25}H_{39}AuN_2O_9S$	$C_{29}H_{35}AuF_6N_2P_2$
M_r (Dalton)	356.9	384.7	507.3	536.9	740.6	784.6
Crystal system	Triclinic	Monoclinic	Tetragonal	Orthorhombic	Triclinic	Monoclinic
Space group	$P\bar{1}$ (#2)	$P2_1/c$ (#14)	$I4_1/acd$ (#142)	$Fdd2$ (#43)	$P1$ (#1)	$P2_1/c$ (#14)
a (Å)	10.753(2)	10.275(1)	17.727(3)	14.7115(8)	9.708(3)	18.833(2)
b (Å)	10.943(3)	9.797(1)		28.779(2)	11.556(3)	11.1584(9)
c (Å)	11.413(4)	12.188(1)	49.380(8)	9.6879(5)	15.455(4)	28.784(2)
α (°)	93.099(5)				105.607(4)	
β (°)	99.003(5)	108.456(2)			97.373(4)	93.410(2)
γ (°)	90.627(5)				106.298(4)	
V (Å^3)	1324	1164	15520	4102	1563	6038
D_c (g cm^{-3})	2.68_5	2.19_5	1.73_6	1.73_8	1.57_3	1.72_6
Z (f.u.)	6	4	32	8	2	8
μ_{Mo} (mm^{-1})	17.1	12.8	7.9	7.3	4.8	5.0
Spec. (mm)	$0.14 \times 0.12 \times 0.10$	$0.06 \times 0.05 \times 0.04$	$0.16 \times 0.09 \times 0.06$	$0.14 \times 0.07 \times 0.06$	$0.25 \times 0.18 \times 0.14$	$0.16 \times 0.12 \times 0.07$
'T'$_{min/max}$	0.23	0.65	0.44	0.54	0.58	0.63
$2\theta_{max}$ (°)	55	70	55	75	53	67.5
N_t	11,434	22,840	67,998	21,010	13,776	85,173
N (R_{int})	5762 (0.087)	4980 (0.073)	4459 (0.083)	2802 (0.042)	5793 (0.034)	23016 (0.044)
N_0 ($F>4\sigma(F)$)	3659	3466	3480	2384	4669	16099
R	0.067	0.044	0.043	0.029	0.066	0.036
R_w (n_w)	0.083 (21)	0.052 (6)	0.071 (25)	0.048 (2.5)	0.090 (20)	0.056 (18)

[a] Cation; anion is $(PF_6)^-$.

Tables) have been made with the Cambridge Crystallographic Data Centre (CCDC #250394-6, 250398-9).

4. Conclusions

A series of (NHC)–Au(I)–X complexes having X = Cl and 2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl-1-thiolato have been prepared as analogues of Auranofin (**1**) and [(Et_3P)AuCl] (**2**). The ease of synthesis of these complexes shows that NHC systems are promising as vehicles for preparing a range of similar compounds with controlled lipophilicity for biological evaluation. Preliminary biological studies show that the antimitochondrial activity of these complexes correlates with their lipophilicity, and results of those studies will be reported in due course.

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