Synthesis and characterization of gold(III) complexes possessing 2,9-dialkylphenanthroline ligands: to bind or not to bind?†

Zachary D. Hudson,[a] Chinar D. Sanghvi,[a] Melody A. Rhine,[a] Julia J. Ng,[b] Scott D. Bunge,[b] Kenneth I. Hardcastle,[c] Mohammad R. Saadein,[a] Cora E. MacBeth[c] and Jack F. Eichler*[a]

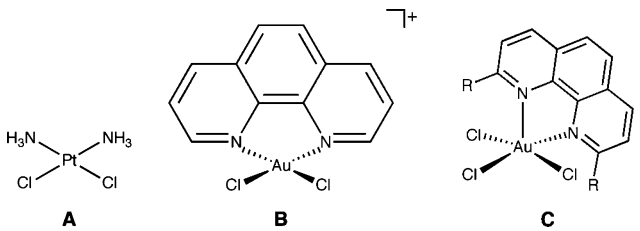
Received 24th December 2008, Accepted 10th June 2009
First published as an Advance Article on the web 21st July 2009
DOI: 10.1039/b823215f

In an effort to discover potential alternatives to the anti-cancer drug cisplatin, the synthesis of gold(III) polypyridyl coordination complexes was pursued. Specifically, this report describes the synthesis and characterization of a series of 2,9-dialkyl-1,10-phenanthroline (^{R}phen) gold(III) coordination complexes (R = *n*-butyl, *sec*-butyl, and *tert*-butyl). Due to the steric hindrance imparted by the alkyl substituents, these ligands do not react with $HAuCl_4$ to form square-planar gold(III) dichloride complex ions, as is the case with 1,10-phenanthroline, but instead form salts comprised of $[AuCl_4]^-$ anions and protonated 2,9-dialkylphenanthroline cations (compounds **1** and **2**). In an effort to facilitate direct binding between the substituted phenanthroline and the gold(III) metal center, reactions were carried out between the ligand and $NaAuCl_4$ in the presence of a Ag(I) salt. The precipitation of one equivalent of AgCl afforded the formation of neutral, distorted square-pyramidal gold(III) trichloride complexes (compounds **3** and **4**). Primary or secondary substitutions at the alpha carbon of the alkyl substituent allow direct metal–ligand coordination, whereas a tertiary substituent inhibits chelation and results only in the formation of a salt comprised of a protonated phenanthroline cation and a $[AuCl_2]^-$ anion (compound **5**). Compounds **1–4** have been characterized by ^{1}H NMR, UV/vis, IR spectroscopy, and X-ray crystallography.

Introduction

Cisplatin (Fig. 1(A)) is often cited as the standard for anti-cancer metallotherapeutics, and has been successfully implemented in the treatment of a variety of cancers (*e.g.*, ovarian, testicular, and head and neck cancers).[1] Though it possesses potent anti-cancer activity, cisplatin has therapeutic drawbacks. Among these is the development of resistant tumor lines, which presumably arise due to the increased efficacy of biological reductants and/or cellular DNA repair mechanisms.[2] In addition, because cisplatin's anti-cancer activity is afforded by its ability to disrupt DNA replication, normal tissues that undergo rapid proliferation are often adversely affected during treatment.[3–5]

There is an ongoing effort to discover new metal-based drugs that might alleviate the negative side effects of cisplatin. Gold therapies, which have been previously used as rheumatoid arthritis therapies, have recently been recognized as potential anti-cancer drugs upon the discovery that their administration during arthritis treatment lowered the risk of several classes of malignancy.[6] Gold has also been found to enter cells *via* a unique thiol-shuttle, potentially providing a more selective mechanism of uptake.[7,8]



A B C

Fig. 1 Structures of (A) cisplatin; (B) the square-planar 1,10-phenanthroline gold(III) dichloride cation;[16] (C) 2,9-di-alkyl-1,10-phenanthroline gold(III) species (R = methyl,[13] *n*-butyl, *sec*-butyl).

Gold(III) compounds were originally proposed as possible anti-cancer agents because they are isoelectronic to platinum(II), and thus might exhibit similar modes of DNA binding.[9] However, even though gold(III) coordination compounds have been found to interact with DNA, the strength of this interaction is often variable and has lower affinity than cisplatin.[10] In fact, it has now been shown that the therapeutic effect of gold therapies may originate within the mitochondria, with cell death possibly being initiated *via* the inhibition of the enzyme thioredoxin reductase.[11] Preliminary research has indeed shown that gold(III) complexes maintain cytotoxicity in cisplatin resistant tumor cell lines, suggesting a different mechanism of action.[12]

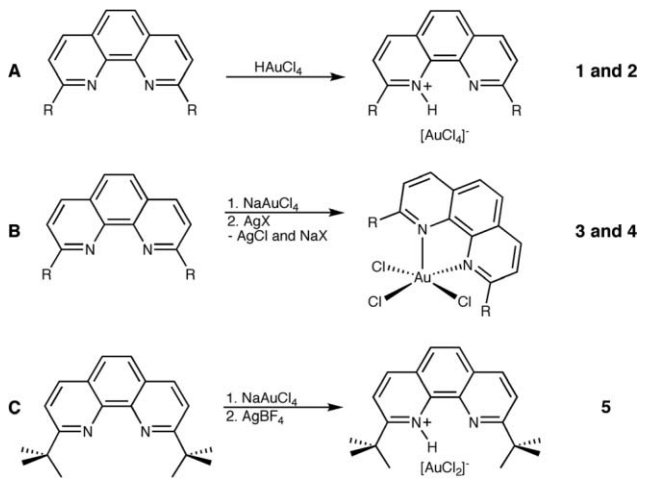
After searching the literature, we found there was a dearth of structurally characterized gold(III) phenanthroline compounds (Fig. 1(B)),[16] and to our knowledge, there is only one example of a gold(III) complex with a substituted phenanthroline (phen) ligand that has been structurally characterized (Fig. 1(C)).[13] In

[a]*Department of Chemistry, Division of Natural Science and Mathematics, Oxford College of Emory University, 100 Hamill Street, Oxford, GA 30054, USA. E-mail: jack.eichler@emory.edu; Fax: 770-784-8423; Tel: 770-784-8340*
[b]*Department of Chemistry, Kent State University, Kent, OH 44242, USA*
[c]*Department of Chemistry, Emory University, Atlanta, GA 30322, USA*

† Electronic supplementary information (ESI) available: Fig. S1: molecular structures and numbering schemes for compounds **2** and **4**; Table S1: crystal and refinement data for complex **4**; Fig. S2: ellipsoid plot of compounds **1** and **2**; Fig. S3: UV/vis spectra of compound **2**. CCDC reference numbers 713225–713229. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b823215f

addition, given that phen complexes of other metals have been found to exhibit anti-cancer activity,[14] it was prudent to pursue the synthesis of new gold(III) complexes possessing substituted phen ligands. It was decided that the initial ligand targets would be 2,9-dialkylphen (^{R}phen) derivatives because these ligands are readily prepared *via* the synthesis reported by Pallenberg *et al.*,[15] and they have the potential to sterically protect the gold(III) metal center from biological reductants. Additionally these complexes should provide an opportunity to probe the nature of DNA binding (if gold drugs coordinate to DNA in an analogous fashion to cisplatin, bulky substituents on the 2,9 positions of the phen ligand should limit DNA binding).

More specifically, given that 2,9-dimethylphen gold(III) trichloride (Fig. 1(C)) is the only previously reported gold(III) complex possessing a substituted phen ligand, we sought to prepare analogous gold(III) phen complexes bearing bulkier alkyl substituents. In the course of synthesizing these ^{R}phen gold(III) complexes (R = *sec*-butyl, *n*-butyl), it was found that the use of auric acid ($HAuCl_4$) yielded salts comprised of protonated phen cations ($[phenH]^+$) and $[AuCl_4]^-$ anions, and not coordination complexes (Scheme 1(A)). This result prompted the development of an alternative synthetic route, and $NaAuCl_4$ was subsequently reacted with the substituted phen ligands in the presence of silver(I) salts to promote direct coordination of the substituted phenanthroline. It was found that this reaction resulted in the formation of one equivalent of AgCl and a neutral, distorted square pyramidal ^{R}phen gold(III) trichloride coordination complex (Scheme 1(B)). Attempts to prepare the $^{t\text{-Bu}}$phen congener failed to yield direct coordination to gold(III) (Scheme 1(C)). Herein, we report the X-ray crystal structures, full spectroscopic characterization, and preliminary stability data for both the $[AuCl_4]^-$ salts (**1**, **2**) and the neutral distorted square pyramidal complexes (**3**, **4**).



Scheme 1 Reaction schema for the syntheses of (A) $[^{R}phenH][AuCl_4]$ salts (**1**, **2**); (B) the neutral, distorted square pyramidal $[Au(^{R}phen)Cl_3]$ complexes (**3**, **4**); and (C) the $[^{t\text{-Bu}}phenH][AuCl_2]$ salt (**5**). (**1** and **3**, R = *n*-butyl; **2** and **4**, R = *sec*-butyl.)

Results and discussion

Synthesis and spectroscopic characterization

A 1 : 1 molar ratio of ^{R}phen [R = *n*-butyl ($^{n\text{-Bu}}$phen), *sec*-butyl ($^{sec\text{-Bu}}$phen)] and $HAuCl_4$ was refluxed in methanol, yielding $[^{R}phenH][AuCl_4]$ salts; this is in contrast to the successful metal–ligand chelation reported for unsubstituted phenanthroline.[16] The difference in reactivity may be explained both by issues of steric hindrance introduced by the substitution and by the increase in nitrogen basicity by the addition of alkyl groups to the aromatic ligand backbone. Refluxing molar equivalents of $^{n\text{-Bu}}$phen and $^{sec\text{-Bu}}$phen with $NaAuCl_4$, along with silver(I) salts in acetonitrile, yielded neutral ^{R}phen gold(III) trichloride coordination complexes, $[Au(^{R}phen)Cl_3]$ while the use of the analogous synthetic procedure with 2,9-di-*tert*-butyl substituted ligand yielded the $[^{t\text{-Bu}}phenH][AuCl_2]$ salt (**5**).

The synthesis of gold(III) salts possessing protonated nitrogen donor ligands, such as compounds **1** and **2**, is not unprecedented. Cao *et al.* recently reported the reaction of $HAuCl_4$ with bis(2-pyridylmethyl)-N-benzylamine (BBPMA), which resulted in a salt complex of $[AuCl_4]^-$ and the protonated BBPMA ligand. These authors were also able to obtain direct coordination between the ligand and gold(III) metal center by using $NaAuCl_4$ instead of $HAuCl_4$.[17] The synthesis of 2,9-di-methylphen gold(III)trichloride (Fig. 1(C)),[13] a structural analogue of compounds **3** and **4**, was originally carried out using $KAuCl_4$, however these authors did not require the use of a silver(I) salt to facilitate direct coordination of the substituted phen ligand. In our laboratory, we were not able to obtain isolable gold(III) complexes without the use of silver(I) salts.

In comparison to the free phen ligands, a general downfield shift occurs for the aromatic and alkyl hydrogens in both the $[^{R}phenH][AuCl_4]$ salts and the neutral $[Au(^{R}phen)Cl_3]$ complexes (see Fig. 2(C) and the ^{1}H NMR data in the experimental section). Given the expected downfield shift of the ligand protons upon coordination to a cationic metal center {$[CuCl(^{sec\text{-Bu}}phen)_2]$: δ 8.73, 8.15, 7.77 (aromatic), 3.01(–CH)]},[15] we initially interpreted the ^{1}H NMR data for **1** and **2** as evidence that the ^{R}phen ligands were directly coordinated to the gold(III) centers. However, after characterizing compounds **1** and **2** using FT-IR spectroscopy [**1**: ν = 3178 cm^{-1} (N–H); **2**: ν = 3183 cm^{-1} (N–H)], as well as elemental analysis (see experimental) and X-ray crystallography (see Fig. 3(A) and ESI Fig. S1(A)†), we found that the use of $HAuCl_4$ led only to the formation of the $[^{R}phenH][AuCl_4]$ salts. Given these results, we caution against the use of ^{1}H NMR as a singular diagnostic of phen coordination to gold(III), especially if $HAuCl_4$ is used as the gold source. Previous reports have described the reaction of substituted phen ligands with $HAuCl_4$ and claim that the substituted phen was directly bound to the Au(III) center.[18,19] However, this was deduced only by ^{1}H NMR studies; without additional structural characterization, it may not be prudent to make such a conclusion.

The characterization of compounds **1**–**4** by UV/vis further demonstrated the difficulty in using spectroscopic data to determine if coordination of the phen ligand occurred. Comparison of the UV/vis absorption spectra of compounds **1** and **3** (Fig. 2(A)) and compounds **2** and **4** (Fig. 2(B)) reveal the close similarity of the absorption properties of the $[^{R}phenH][AuCl_4]$ salts and the neutral $[Au(^{R}phen)Cl_3]$ complexes. The $[^{R}phenH][AuCl_4]$ salts (**1** and **2**) possess a series of strong absorption maxima at approximately 225–230, 270–275, and 280–285 nm, assigned as intraligand phen $\pi \rightarrow \pi^*$ transitions; and 320 nm, assigned as a Cl–Au ligand-to-metal charge transfer (LMCT) band (it is noted that the $NaAuCl_4$ starting material exhibits a similar Cl–Au LMCT at approximately

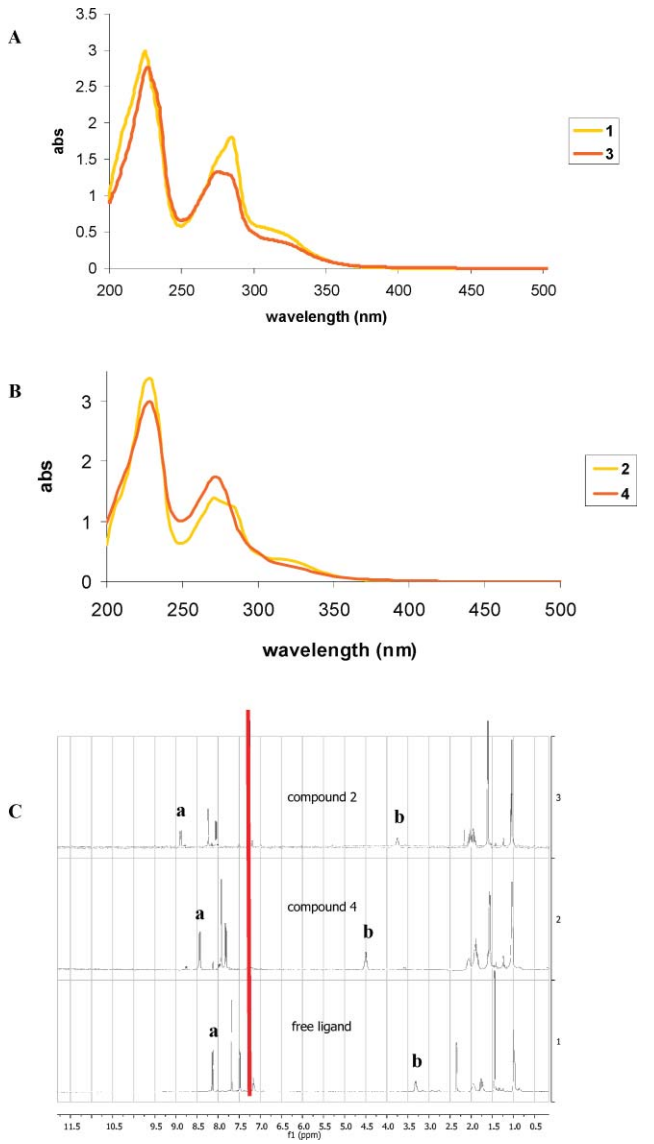


Fig. 2 Spectroscopic data: UV/vis spectra of compounds **1** and **3** (A) and compounds **2** and **4** (B); all compounds were dissolved in a 3 : 1 2-propanol–acetonitrile solvent mixture at a concentration of 5.0×10^{-5} M; spectra were collected at 20 °C; (C) ^{1}H NMR spectra of compounds **2**, **4**, and the free $^{sec\text{-}Bu}$phen ligand. All spectra were run in $CDCl_3$ solvent at 20 °C; residual chloroform resonances are overlaid in red; "a" denotes the most downfield aromatic $^{sec\text{-}Bu}$phen hydrogen (H6 and 13 in Scheme 4) and "b" denotes the –CH hydrogen from the *sec*-butyl pendant (H3 and 15 in Scheme 4).

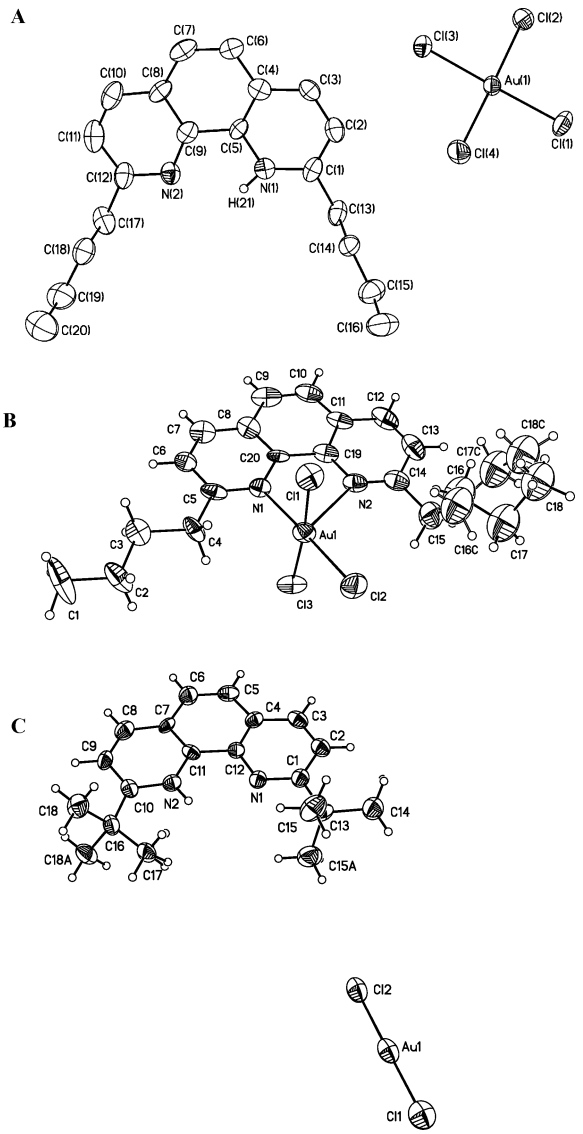


Fig. 3 Molecular structures and numbering schemes for (A) $[^{n\text{-}Bu}phenH]^+[AuCl_4]^-$ (**1**), (B) $[Au(^{n\text{-}Bu}phen)Cl_3]$ (**3**), and (C) $[^{t\text{-}Bu}phenH]^+[AuCl_2]^-$ (**5**). Thermal ellipsoids drawn at 50% probability. Selected bond lengths (Å) and angles (°) for **1**: Au–Cl···H–N 2.906, Au(1)–Cl(2) 2.271(3), Au(1)–Cl(3) 2.273(3), Au(1)–Cl(1) 2.275(3), Au(1)–Cl(4) 2.278(3), Cl(2)–Au(1)–Cl(3) 88.85(10), Cl(2)–Au(1)–Cl(1) 90.30(11), Cl(3)–Au(1)–Cl(1) 178.79(13), Cl(2)–Au(1)–Cl(4) 178.43(12); **3**: Au(1)–N(1) 2.066(9), Au(1)–N(2) 2.597(9), Au(1)–Cl(2) 2.273(3), Au(1)–Cl(1) 2.291(3), Au(1)–Cl(3) 2.296(3), Au(1)–N(2) 2.597(9), N(1)–Au(1)–Cl(2)177.7(3), N(1)–Au(1)–Cl(1)89.6(3), Cl(2)–Au(1)–Cl(3)91.87(13), Cl(1)–Au(1)–Cl(3)174.31(12); and **5**: Au–Cl···H–N 3.549, Au(1)–Cl(1) 2.258(4), Au(1)–Cl(2) 2.262(4), Cl(1)–Au(1)–Cl(2) 179.50(12) N(1)–Au(1)–Cl(3) 88.6(3), Cl(2)–Au(1)–Cl(1) 89.81(13).

320 nm).[16,20] The $[Au(^{R}phen)Cl_3]$ complexes (**3** and **4**) displayed absorption maxima that were not clearly distinguishable from those observed in **1** and **2** (the intraligand transitions were observed at 225, 270–275, and 280–285 nm; and the LMCT bands were observed at approximately 320 nm). The difference in the electronic properties of these two types of compounds is evidenced by the distinct difference in color between the two classes of compounds (**1–2** are bright yellow; **3–4** are orange), presumed to be differences in the d–d transitions, though this is not clearly discernable in the UV/vis absorption spectra.

X-Ray crystal structures†

Though $[phenH]^+$ salts have been structurally characterized, compounds **1** and **2** appear to be the first examples reported with the $[AuCl_4]^-$ anion. Salts with $[AuCl_4]^-$ have been reported for other protonated nitrogen donor ligands however, including protonated bipyridine,[21] protonated bis(2-pyridylmethyl)amine,[17] and protonated N-benzyl-C(2-pyridyl)nitrone.[22] Analogous to these structures, compounds **1** and **2** feature square-planar $[AuCl_4]^-$

anions [see Fig. 3(A) (**1**) and ESI Fig. S1(A) (**2**)†], and possess an equal number of [^{R}phenH]$^{+}$ units within the unit cell ($Z = 8$ for **1**, $Z = 2$ for **2**). However, **1** and **2** are, to our knowledge, the only examples of $[AuCl_4]^-$ salts possessing a hydrogen bond between one of the chloride ligands and the protonated nitrogen donor ligand; compounds **1** and **2** possess Au–Cl$\cdots$H–N interatomic distances of 2.906 Å and 3.000 Å, respectively (see ESI Fig. S2(A) and S2(B) for depictions of the Au–Cl$\cdots$H–N interactions in compounds **1** and **2**, respectively†). According to a review of M–Cl$\cdots$H–N interactions from the crystallographic database, completed by Aullón *et al.*, the hydrogen bonds in **1** and **2** are characterized as intermediate to long (M–Cl$\cdots$H–N distances from 2.52–2.95 Å are classified as intermediate, and 2.95–3.15 Å are classified as long).[23]

As described above, the use of $NaAuCl_4$ and silver(I) salts in the synthetic protocol afforded direct coordination of the $^{n\text{-Bu}}$phen and $^{sec\text{-Bu}}$phen ligands to gold(III). The coordination environment of [Au($^{n\text{-Bu}}$phen)Cl_3] (**3**) and [Au($^{sec\text{-Bu}}$phen)Cl_3] (**4**) was determined by X-ray crystallography to be distorted square pyramidal [range of bond angles for adjacent atoms in the base of the square pyramid; 88.6–91.87° (**3**); 89.6–90.9° (**4**)], where three chloride ligands and one of the ^{R}phen nitrogen donors occupy the coordination sites on the base of the square pyramid, and the remaining ^{R}phen nitrogen donor lies in the axial position [see Fig. 3(B) (**3**) and ESI Fig. S1(B) (**4**)†]. These compounds are structural analogues of the ^{methyl}phen gold(III) trichloride (DMP–gold) previously reported by Robinson and Sinn (Fig. 1(C)).[13] The formation of the distorted square pyramidal geometry is likely to be caused by the steric hindrance introduced by the alkyl substituents on the phen ligand.

Structurally characterized gold(III) complexes possessing this distorted square-pyramidal geometry are rare (only six gold(III) structures possessing two nitrogen donor ligands and three halide ligands can be found in the CCDC),[24–27] and compounds **3** and **4**, along with DMP–gold, represent the only examples bearing substituted phen ligands. It is noted that a complete crystal structure was obtained for compound **4**, however the structure could not be refined to the point where more detailed structural comparisons with **3** and DMP–gold could be made (this was due to the disorder present in the *sec*-butyl pendant groups, which is observed to a lesser extent in the *n*-butyl substituents on compound **3**). The data that were collected for compound **4** do indicate that it is structurally analogous to **3** and DMP–gold. The noteworthy feature of these complexes, as previously reported by Robinson and Sinn, is the elongation of the Au–N_{axial} bond [Au–N_{axial}: 2.594 Å; Au–$N_{equatorial}$, 2.066 Å (**3**) and Au–N_{axial}, 2.584 Å; Au–$N_{equatorial}$, 2.09 Å (DMP–gold)[13]], and the "lean" of the square pyramid [angle of Au–N_{axial} axis to the plane of square pyramid base: 73.2°, 109.1° (**3**); 73.4°, 111.1° (DMP–gold)[13]]. This geometric "lean" is thought to be caused by the electron repulsion between the filled d_z^2 orbital and the loan pair of electrons on the axial nitrogen donor, as well as the steric influence of the phen alkyl groups. The Au–Cl interatomic distances are in the range expected for square-pyramidal geometry [range of Au–Cl distances: 2.262–2.300 Å (**3**); 2.267–2.2.285 Å (DMP–gold)[13]].

Attempts to synthesize the neutral square-pyramidal gold(III) complex with the $^{t\text{-Bu}}$phen ligand were not successful. In fact, even when silver(I) salts were used to encourage coordination of the phen ligand, the only product that could be isolated was a reduced gold species comprised of a linear $[AuCl_2]^-$ anion and the protonated [$^{t\text{-Bu}}$phenH]$^{+}$ ligand (Fig. 3(C)); given the bulk of the *tert*-butyl groups, this result was not completely unexpected. The effect of the steric bulk of this phen ligand can be seen by comparing the Au–Cl$\cdots$H–N hydrogen bonding distance of **5** (3.459 Å) to that observed in **1** and **2** (2.906 Å and 3.000 Å). A similar complex was reported by Cao *et al.*, in which the [BBPMA–H_2Cl][$AuCl_4$] salt underwent reduction to form the [BBPMA–H_2Cl][$AuCl_2$] salt.[17]

Stability studies

Given that these gold(III) complexes will be tested for their anti-cancer properties, preliminary experiments to determine their stability in physiological buffer were carried out. In parallel experiments, compounds **2** and **4** were dissolved in a 3 : 1 2-propanol–acetonitrile solvent mixture, and then an aliquot of this solution for each compound was dissolved in phosphate buffer (0.1 M, pH 7.4) to make a final gold concentration of 1.0×10^{-5} M. These solutions were immediately analyzed by UV/vis spectroscopy, and spectra were then collected hourly over a 24 h period. As seen in Fig. 4 (compound **4**) and ESI Fig. S3(A) (compound **2**),† there was a gradual decrease in the absorption maxima of the gold complexes. After 24 h, an observable, but immeasurable pale yellow precipitate was present in the cuvette. Given that the hydrolysis of other gold(III) chloride species in aqueous buffer has been previously reported,[28] this precipitate was assumed to be a gold(III) hydroxide species ([Au(^{R}phen)$(OH)_x(Cl)_y$]) (see Scheme 2). The formation of these hydrolysis products appear to be evidenced in the UV/vis spectra, as the spectra taken after the initial scan indicate the presence of some intermediate complex, which after complete precipitation over a 24 h period results in spectra which resemble those of the initial gold complexes, but at lower concentrations (see Fig. 4 and ESI Fig. S3(A)†).

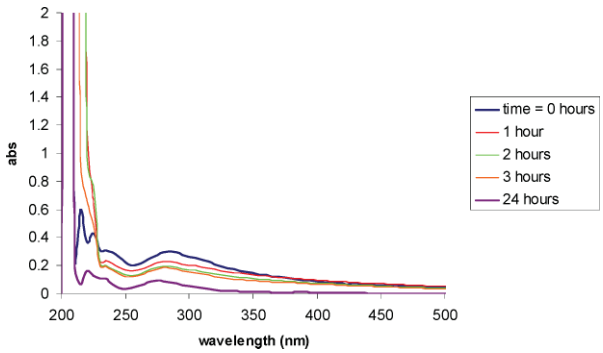


Fig. 4 Stability data: UV/vis spectra of compound **4** in phosphate buffer pH 7.4 over a 24 h period (1.0×10^{-5} M solution, 20 °C).

In an effort to corroborate this hypothesis, more concentrated samples of compound **4** (a dark orange solid) were prepared in both phosphate buffer and distilled water (5.0×10^{-4} M gold complex). A pale yellow precipitate formed in both water and phosphate buffer, though considerably less precipitate formed in the buffer solution.

The pH of both solutions was measured immediately after the addition of the gold complex; the pH of the water solution dropped considerably (the pH after the addition of the gold complex was 3.8), while the pH of the buffer solution, as expected, did not

significantly change. The decrease in pH in the gold complex–water solution seems to support the hypothesis that hydrolysis of the gold complex is likely to occur in aqueous solution, as the formation of the hydroxo complex would generate H^+ ions (see Scheme 2). The solid precipitate from both solutions was then isolated and characterized by IR spectroscopy. The formation of the hydroxo complex was further confirmed by the presence of an intense OH stretch in the IR (3442 cm^{-1}). Also of note was the observation of =C–H stretches at 3069 cm^{-1}, and C=C stretches at 1594 cm^{-1} and 1624 cm^{-1}, indicative of the presence of the phen ligand on the gold hydroxo complex.

$$[Au(phen)Cl_3]_{(aq)} + xH_2O_{(l)} \rightleftharpoons Au(phen)(H_2O)_x(Cl)_y]_{(aq)} + (3\text{-}y)Cl_{(aq)}$$

$$[Au(phen)(H_2O)_x(Cl)_y]_{(aq)} \rightleftharpoons [Au(phen)(OH)_x(Cl)_y]_{(s)} + xH^+_{(aq)}$$

Scheme 2 Proposed mechanism of gold(III) hydroxo precipitate formation.

Even though gold(III)–chloride bonds are not completely inert in aqueous solution, the fact that the gold–phen binding appears to be stable may provide an opportunity to extend the *in vitro* molecular design of this class of complexes to biological systems. Additionally, the fact that the gold(III) hydroxo complexes demonstrated higher solubility in phosphate buffer fosters optimism that these gold compounds may show promise in future anti-cancer studies.

Experimental

General

The 2,9-dialkylphen ligands (^{R}phen; where R = *n*-butyl, *sec*-butyl, *tert*-butyl) were synthesized as described in the literature.[15] $HAuCl_4{\cdot}3H_2O$, $NaAuCl_4{\cdot}2H_2O$, silver tetrafluoroborate, silver trifluoroacetate (Alfa Aesar), and all solvents were used without further purification. The gold starting materials were weighed and solvated under a nitrogen atmosphere (either in an inert atmosphere glovebox or in a nitrogen-purged glovebox) and subsequently refluxed under normal atmospheric conditions with the appropriate phen ligand. Aside from eliminating exposure to direct sunlight, no special handling measures were taken with the final gold(III) complexes. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz spectrophotometer at 20 °C; chemical shifts were referenced to residual solvent peaks. Infrared spectra were recorded as KBr pellets on a Varian Scimitar 800 Series FT-IR spectrophotometer, UV/vis spectra were recorded on a Cary 50 UV/vis spectrophotometer using 1.0 cm quartz cuvettes, and elemental analyses were completed by Atlantic Microlab Inc., Norcross, GA.

Stability studies

The UV/vis spectra of compound **4** were collected in phosphate buffer pH 7.2 over a 24 h period. A 0.010 g sample of the solid gold complex was dissolved in 4.00 mL of a 3 : 1 2-propanal–acetonitrile solvent mixture, yielding a 5.0×10^{-5} M solution; a 7.0 uL aliquot of this solution was diluted in phosphate buffer to a final volume of 3.50 mL, which yielded a final gold concentration of 1.0×10^{-5} M. The spectra were collected at 20 °C.

FT-IR data were collected for the precipitate that formed upon dissolving compound **4** in water. The precipitate was isolated after letting a 5×10^{-4} M solution of **4** in water stir at room temperature overnight. The solid was washed three times with cold diethyl ether, the diethyl ether washes discarded, and the solid dissolved in chloroform. The chloroform solution was dried with $MgSO_4$ and filtered. The solid was isolated *via* removal of the chloroform *in vacuo* and then mixed with dry KBr to create a solid pellet.

X-Ray crystallography†

Compounds 1 and 2

X-Ray crystallography was performed by mounting each crystal onto a thin glass fiber from a pool of Fluorolube(tm) and immediately placing it under a liquid nitrogen cooled N_2 stream, on a Bruker AXS diffractometer. The radiation used was graphite monochromatized Mo Kα radiation ($\lambda = 0.7107$ Å). The lattice parameters were optimized from a least-squares calculation on carefully centered reflections. Lattice determination, data collection, structure refinement, scaling, and data reduction were carried out using APEX2 version 1.0-27 software package.

Each structure was solved using direct methods. This procedure yielded the Au atoms, along with a number of the Cl, N, and C atoms. Subsequent Fourier synthesis yielded the remaining atom positions. The hydrogen atoms were fixed in positions of ideal geometry and refined within the XSHELL software. These idealized hydrogen atoms had their isotropic temperature factors fixed at 1.2 or 1.5 times the equivalent isotropic *U* of the C atoms to which they were bonded. The final refinement of each compound included anisotropic thermal parameters on all non-hydrogen atoms.

Compounds 3–5

For X-ray crystallography, suitable crystals of **3–5** were coated with Paratone-N oil, suspended in a small fiber loop and placed in a cooled nitrogen gas stream at 173 K on a Bruker D8 APEX II CCD sealed tube diffractometer with graphite monochromated Cu Kα (1.54178 Å) radiation. Data were measured using a series of combinations of φ and ω scans with 10 s frame exposures and 0.5° frame widths. Data collection, indexing and initial cell refinements were all carried out using APEX II software.[29] Frame integration and final cell refinements were done using SAINT software.[30] The structure was solved using Direct methods and difference Fourier techniques (SHELXTL, V6.12).[31] Hydrogen atoms were placed in their expected chemical positions using the HFIX command and were included in the final cycles of least squares with isotropic U_{ij}'s related to the atom's ridden upon. All non-hydrogen atoms were refined anisotropically. Scattering factors and anomalous dispersion corrections are taken from the International Tables for X-ray Crystallography. Structure solution, refinement, graphics and generation of publication materials were performed by using SHELXTL, V6.12 software.

Syntheses and characterization

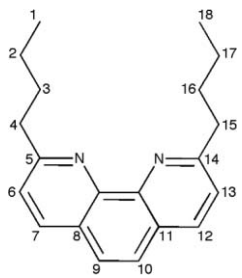
[$^{n\text{-Bu}}$phenH][$AuCl_4$], 1

2,9-Di-*n*-butyl-1,10-phenanthroline (0.340 g, 1.2 mmol) was dissolved in 15 mL of MeOH and added dropwise to $HAuCl_4{\cdot}3H_2O$

Table 1 Crystal and refinement data for compounds **1–3, 5**

Complex	**1**	**2**	**3**	**5**
Empirical formula	$C_{20}H_{25}AuCl_4N_2$	$C_{20}H_{25}AuCl_4N_2$	$C_{20}H_{24}AuCl_3N_2$	$C_{20}H_{25}AuCl_2N_2$
Formula weight	632.19	632.19	595.73	561.29
Temperature/K	160(2)	160(2)	173(2)	173(2)
Wavelength/Å	0.71073	0.71073	0.71073	0.71073
Crystal system	Tetragonal	Triclinic	Triclinic	Orthorhombic
Space group	*P*4/*n*	$P\bar{1}$	$P\bar{1}$	*Pnma*
V/Å^3	4683.6(10)	1111.5(5)	3255.0(3)	2033.0(3)
Z	8	2	6	4
a/Å	24.553(3)	9.013(2)	14.3221(6)	27.523(2)
b/Å	24.553(3)	10.472(3)	15.3810(7)	6.7821(5)
c/Å	7.7689(12)	11.909(3)	15.9327(8)	10.8909(9)
α/°	90	92.196(4)	107.374(4)	90
β/°	90	93.497(4)	102.677(3)	90
γ/°	90	97.375(4)	90.992(3)	90
D_{calc}/Mg m^{-3}	1.793	1.889	1.823	1.834
Reflections collected	23 975	8947	22 063	22 152
Independent reflections	4157	3945	12 705	2276
Max., min. transmission	0.5519 and 0.1733	0.4153 and 0.2243	0.7628 and 0.2151	0.8644 and 0.3153
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0443$, w$R_2 = 0.1337$	$R_1 = 0.0321$, w$R_2 = 0.0772$	$R_1 = 0.0605$, w$R_2 = 0.1257$	$R_1 = 0.0464$, w$R_2 = 0.0883$
R indices (all data)	$R_1 = 0.0771$, w$R_2 = 0.1636$	$R_1 = 0.0547$, w$R_2 = 0.0871$	$R_1 = 0.1094$, w$R_2 = 0.1488$	$R_1 = 0.1014$, w$R_2 = 0.1071$
Goodness of fit	1.091	1.036	1.013	1.008

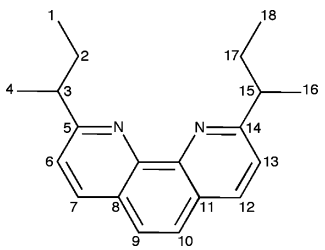
(0.447 g, 1.2 mmol) in 20 mL of MeOH, upon which a deep purple solution was produced. After refluxing for 1 h at 80 °C, the solution turned dark yellow; the reaction was then refluxed overnight. Evaporation *in vacuo* produced a red-orange pasty solid, which was washed with 20 mL of ether (the ether wash was discarded). A yellow solid (**1**) was isolated and then dried under vacuum at 35 °C (0.361 g, 49%). Yellow needles suitable for X-ray diffraction studies (for crystal and refinement data for compound **1**, see Table 1) were obtained by slow-evaporation from ethanol. Elemental analysis found: C, 38.27%; H, 3.98%; calculated: C, 37.98%; H 3.99%. λ_{max}(^{i}PrOH–CH_3CN, 20 °C)/nm (ε, M^{-1} cm^{-1}) 224 (59 200), 275 (30 400), 282 (35 200) and 320 (9600). IR: ν_{max}/cm^{-1} 3178 (NH), 3073 (CH), 2958, 2930, 2872 (CH), 1624, 1605 (conj. CC). ^{1}H NMR (300 MHz, DMSO-d_6, 20 °C) δ 8.85 (d, 2H, H7,12), 8.17 (s, 2H, H9,10), 8.06 (d, 2H, H6,13), 3.26 (m, 4H, H4,15), 1.81 (m, 4H, H3,16), 1.42 (m, 4H, H2,17), 0.94 (t, 6H, H1,18) (see Scheme 3 for NMR numbering scheme).



Scheme 3 Numbering scheme for compounds **1** and **3**.

[$^{sec\text{-}Bu}$phenH][$AuCl_4$], 2

2,9-Di-sec-butyl-1,10-phenanthroline (0.523 g, 1.8 mmol) and HAuCl4·3H_2O (0.705 g, 1.8 mmol) were reacted in a procedure analogous to the synthesis of **1**, yielding 0.900 g of a reddish-orange solid, **2** (79.6%). Yellow needles suitable for X-ray diffraction studies (for crystal and refinement data for compound **2**, see Table 1) were obtained by slow-evaporation from ethanol. Elemental analysis found: C, 37.99%; H, 3.99%; calculated: C, 37.98%; H, 3.99%. λ_{max}(^{i}PrOH–CH_3CN, 20 °C)/nm (ε, M^{-1} cm^{-1}) 230 (67 200), 270 (27 500), 280 (25 600) and 320 (7200). IR: ν_{max}/cm^{-1} 3183 (NH), 3079 (CH), 2963, 2928, 2871 (CH), 1619, 1602 (conj. CC). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ 8.88 (d, 2H, H7,12), 8.24 (s, 2H, H9,10), 8.06 (d, 2H, H6,13), 3.75 (m, 14.2, 2H, H3,15), 2.02 (m, 2H, H2, 17), 1.96 (m, 2H, H2, 17), 1.60 (d, 6H, H4,16), 1.04 (t, 6H, H1,18) (see Scheme 4 for NMR numbering scheme).



Scheme 4 Numbering scheme for compounds **2** and **4**.

[Au($^{n\text{-}Bu}$phen)Cl_3], 3

2,9-Di-*n*-butyl-1,10-phenanthroline (0.265 g, 0.900 mmol) and $NaAuCl_4$·2H_2O (0.365 g, 0.900 mmol) were added to 50 ml of acetonitrile, upon which a brown solution was produced. This reaction mixture was refluxed for 1 h, and $AgBF_4$ (0.176 g, 0.9 mmol) was dissolved in acetonitrile and delivered to the reaction solution. The final reaction mixture was refluxed overnight, and the precipitate (AgCl) was filtered through a glass frit covered with a Celite pad. The filtrate was placed on a rotary evaporator, and the resulting red-orange residue was dissolved in approximately 20 mL of dichloromethane. This solution was extracted with 20 mL of water; the aqueous layer was discarded, and the organic layer was dried with $MgSO_4$. The dichloromethane was removed *in vacuo* and a red-orange paste was isolated. This crude product

was washed with a small amount of methanol, leaving behind a red-orange solid. The methanol wash was discarded and the solid was dried under vacuum to give **3** (0.313 g, 58%). Orange needles suitable for X-ray diffraction studies were obtained by slow-evaporation from dichloromethane (for crystal and refinement data for compound **3**, see Table 1). Mp: 134 °C (EtOH). Elemental analysis found: C, 40.33%; H, 3.99%; calculated: C, 40.30%; H, 4.06%. λ_{max}(^{i}PrOH–CH_3CN, 20 °C)/nm (ε, M^{-1} cm^{-1}) 225 (57 800), 273 (27 600), 282 (27 200), and 320 (7490) IR: ν_{max}/cm^{-1} 3052 (CH), 2957, 2929, and 2860 (CH), 1619 and 1594 (conj. CC). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ 8.53 (d, 2H, H7,12), 7.98 (s, 2H, H9,10), 7.80 (d, 2H, H6,13), 3.79 (m, 4H, H4,15), 2.01 (m, 4H, H3,16), 1.57 (m, 4H, H2,17), 1.03 (t, 6H, H1,18) (see Scheme 3 for NMR numbering scheme).

[Au($^{sec\text{-}Bu}$phen)Cl_3], 4

2,9-*sec*-Butyl-1,10-phenanthroline (0.199 g, 0.681 mmol) and $NaAuCl_4{\cdot}2H_2O$ (0.271 g, 0.681 mmol) were added to 50 mL of acetonitrile, upon which a deep purple solution was produced. The addition of silver trifluoroacetate (0.150 g, 0.681 mmol) produced a cloudy green solution, which developed into a pale yellow solution after refluxing at 65 °C for 6 h. At this point, the reaction mixture was filtered through a glass frit covered with a Celite pad and worked up as described for compound **3**; a red-orange solid was isolated (0.371 g, 86%). Orange needles suitable for X-ray diffraction studies were obtained by slow-evaporation from dichloromethane. Mp: 137 °C (EtOH). Elemental analysis found: C, 40.42%; H, 4.12%; calculated: C, 40.30%; H, 4.06%. λ_{max}(^{i}PrOH–CH_3CN, 20 °C)/nm (ε, M^{-1} cm^{-1}) 225 (59 000), 275 (34 200), 280 (31 700), and 320 (7520). IR: ν_{max}/cm^{-1} 3067 (CH), 2964, 2930, 2871 (CH), 1623, 1595 (conj. CC). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ 8.43 (d, 2H, H7,13), 7.93 (s, 2H, H6,13), 7.83 (d, 2H, H9,10), 4.50 (m, 2H, H3,15), 2.06 (m, 2H, H2), 1.88 (m, 2H, H17), 1.57 (d, 6H, H4,16), 1.03 (t, 6H, H1,18) (see Scheme 4 for NMR numbering scheme).

[$^{t\text{-}Bu}$phenH][$AuCl_2$], 5

2,9-Di-*tert*-butyl-1,10-phenanthroline (0.125 g, 0.43 mmol) was combined with $NaAuCl_4{\cdot}2H_2O$ (0.170 g (0.43 mmol) in acetonitrile with a procedure analogous to the synthesis of **4**, upon which a brown solution was produced. After refluxing for one hour, $AgBF_4$ (0.083 g (0.43 mmol) was added, yielding a grey precipitate. The reaction mixture was refluxed overnight, and a yellow solution formed. The solvent was removed *in vacuo*, yielding a brown-yellow solid. Yellow needles suitable for X-ray diffraction (for crystal and refinement data for compound **5**, see Table 1) were obtained by slow evaporation out of ethanol (0.100 g, 42%).

Conclusions

In summary, neutral distorted square pyramidal gold(III) coordination compounds possessing substituted phen ligands have been synthesized and fully characterized. These compounds (**3** and **4**) represent rare examples of gold(III) complexes that bear bulky substituents on the 2,9-positions of phenanthroline, and have been obtained through a modified synthetic route that uses silver(I) salts to help facilitate direct coordination of the ^{R}phen ligands. We have demonstrated that the choice of the synthetic conditions can have a dramatic impact on the type of gold(III) complex that can be obtained, and in particular have shown that the use of $HAuCl_4$ can lead to the formation of salts comprised of $[AuCl_4]^-$ anions and protonated $[^{R}phenH]^+$ ligands (compounds **1** and **2**). Finally, the results of this research seem to indicate that the synthesis of gold(III) complexes that undergo direct coordination with 2,9-dialkylphen is limited to ligands that have methyl, 1°, or 2° carbons on the α-carbon of the alkyl substituent. The successful synthesis of **3** and **4** may provide access to a class of gold compounds that can potentially be used to probe the resistance to biological reductants, as well as the nature of DNA binding; information that is necessary to determine the efficacy of gold(III) complexes as anti-cancer therapies. These efforts, in addition to testing compounds **1–4** on existing cancer cell lines, are currently ongoing in our laboratory.

Acknowledgements

J. F. Eichler gratefully acknowledges the Emory University Research Council and the Oxford College Research Scholars Program for funding this research. Z. D. Hudson, C. D. Sanghvi and M. A. Rhine gratefully acknowledge the Howard Hughes Medical Institute for supporting their summer research efforts under grant 52005873. J. J. Ng and S. D. Binge acknowledge the Ohio Consortium for Undergraduate Research: Research Experiences to Enhance Learning (REEL) Award for partial funding of this work. We also thank Dr Shaoxiong Wu and Dr Bing Wang at the Emory NMR center for their support and assistance.

Notes and references

1 (*a*) W. I. Sunquist and S. J. Lippard, *Coord. Chem. Rev.*, 1990, **100**, 293–322; (*b*) S. van Zutphen and J. Reedijk, *Coord. Chem. Rev.*, 2005, **249**, 2845–2853.
2 L. R. Kelland, in *Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug*, ed. B. Lippert, Verlag Helvetica Chimica Acta, Zurich, Wiley-VCH, Weinheim, Germany, 1999, 497–521.
3 A. Agarwal, J. Balla1, J. Alam, A. J. Croatt and K. A. Nath, *Kidney Int.*, 1995, **48**, 1298.
4 F. Hamers, J. Brakkee, M. Cavalletti, L. Marmonti, J. Pezzoni and W. Gispen, *Cancer Res.*, 1993, **53**, 544–549.
5 C. Deegan, B. Coyle, M. McCann, M. Devereux and D. A. Egan, *Chem.-Biol. Interact.*, 2006, **164**, 115.
6 J. F. Fries, D. Bloch, P. Spitz and D. M. Mitchell, *Am. J. Med.*, 1985, **78**, 56.
7 R. M. Snyder, C. K. Mirabelli and S. T. Crooke, *Biochem. Pharmacol.*, 1986, **35**, 923.
8 S. Y. HoE. R. T. Tiekink*Metallotherapeutic Drugs and Metal-Based Diagnostic Agents: The Use of Metals in Medicine*, ed. M. Gielen and E. R. T. Tiekink, Wiley and Sons, West Sussex, England, 2005.
9 L. Messori, P. Orioli, C. Tempi and G. Marcon, *Biochem. Biophys. Res. Commun.*, 2001, **281**, 352.
10 E. R. Tiekink, *Crit. Rev. Oncol. Hematol.*, 2002, **42**, 225.
11 M. P. Rigobello, L. Messori, G. Marcon, M. A. Cinellu, M. Bragadin, A. Folda, G. Scutari and A. Bindoli, *J. Inorg. Biochem.*, 2004, **98**, 1634.
12 K. Fritz-Wolf1, S. Urig and K. Becker, *J. Mol. Biol.*, 2007, **370**, 116.
13 W. T. Robinson and E. Sinn, *J. Chem. Soc., Dalton Trans.*, 1975, 726.
14 L. Messori, F. Abbate, G. Marcon, P. Orioli, M. Fontani, E. Mini, T. Mazzei, S. Carotti, T. O'Connell and P. Zanello, *J. Med. Chem.*, 2000, **43**, 3541.
15 A. J. Pallenberg, K. S. Koenig and D. M. Barnhart, *Inorg. Chem.*, 1995, **34**, 2833.
16 F. Abbate, P. Orioli, B. Bruni, G. Marcon and L. Messori, *Inorg. Chim. Acta*, 2000, **311**, 1.
17 L. Cao, M. C. Jennings and R. J. Puddephatt, *Inorg. Chem.*, 2007, **46**, 1361.

18 M. A. Ivanov, M. V. Puzyk, T. A. Tkacheva and K. P. Balashev, *Russ. J. Gen. Chem.*, 2006, **76**, 165.
19 M. A. Ivanov, M. V. Puzyk and K. P. Balashev, *Russ. J. Gen. Chem.*, 2003, **73**, 1821.
20 A. Casini, M. A. Cinellu, G. Minghetti, C. Gabbbiani, M. Coronnello, E. Mini and L. Messori, *J. Med. Chem.*, 2006, **49**, 5524–5531.
21 X. P Zhang, G. Yang and S. W. Ng, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2006, **62**, m2618.
22 A. Ade, E. Cerrada, M. Contel, M. Laguna, P. Merino and T. Tejero, *J. Organmet. Chem.*, 2004, **689**, 1788.
23 G. Aullón, D. Bellamy, L. Brammer, E. A. Bruton and A. G. Orpen, *Chem. Commun.*, 1998, 653.
24 R. J. Charlton, C. M. Harris, H. Patil and N. C. Stephenson, *Inorg. Nucl. Chem. Lett.*, 1966, **2**, 409.
25 M. A. Cinellu, A. Zucca, S. Stoccoro, G. Minghetti, M. Manassero and M. Sansuri, *J. Chem. Soc., Dalton Trans.*, 1966, 4217.
26 C. J. O'Connor and E. Sinn, *Inorg. Chem. Inorg. Chem.*, 1978, **17**, 2067.
27 W. Micklitz, B. Lippert, G. Muller, P. Mikulcik and J. Riede, *Inorg. Chim. Acta*, 1989, **165**, 57.
28 (*a*) B. Pitteri, G. Marangoni, F. Visentin, T. Bobbo, V. Bertolasi and P. Gilli, *J. Chem. Soc., Dalton Trans.*, 1999, 677; (*b*) P. Calamai, S. Carotti, A. Guerri, L. Messori, E. Mini, P. Orioli and G. P. Speroni, *J. Inorg. Biochem.*, 1997, **66**, 103.
29 L. M. C. Beltran and J. R. Long, *Acc. Chem. Res.*, 2005, **38**, 325–334.
30 *SAINT Version 6.45A*, Bruker AXS, Inc., Analytical X-Ray Systems, 5465 East Cheryl Parkway, Madison, WI, USA, 53711-5373, 2003.
31 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2008, **64**, 112–122.