Coordination Chemistry Reviews 253 (2009) 1661–1669

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Structures and properties of gold(I) complexes of interest in biochemical applications

Hanan E. Abdou[a], Ahmed A. Mohamed[a], John P. Fackler Jr.[a,*], Alfredo Burini[b], Rossana Galassi[b], José M. López-de-Luzuriaga[c], M. Elena Olmos[c]

[a] Department of Chemistry and Laboratory for Molecular Structure and Bonding, Texas A&M University, P.O. Box 30012, College Station, TX 77842-3012, USA
[b] Dipartimento di Scienze Chimiche dell' Università via S. Agostino 1, I-62032 Camerino, Italy
[c] Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, UA-CSIC, Madre de Dios 51, E-26004 Logroño, Spain

Contents

ARTICLE INFO

Article history:
Received 16 December 2008
Accepted 9 February 2009
Available online 21 February 2009

Keywords:
Gold(I)
Thiolates
Amidinates
Ylides
Carbeniates
Pyrazolates
Luminescence
Sensors

ABSTRACT

Gold(I) compounds have several potential roles in biologically related chemistry. The relatively low toxicity of gold and its lability allows human consumption of drugs formed with this element. Trinuclear and tetranuclear clusters look particularly interesting because of the strong basicity of the gold(I) centers in these molecules. Future studies are expected to lead to interesting new bio-related observations. The ability of gold(I) compounds to interact with themselves aurophilically and with other heavy element ions has produced spectroscopic properties which are sensitive to volatile organic compounds (VOCs) and other molecular interactions. Thus bio-applicability for sensing toxic components appears reasonable.

1. Introduction

Long ago, gold was found to be a metal that was valuable for biological applications. The fact that pre-Roman *Eutruscians* formed gold bridges for teeth is an example [1]. However, the modern use of gold(I) compounds in medicine appears to have originated with the bacteriologist Robert Koch using $K[Au(CN)_2]$. The excellent article in *Gold, Progress in Chemistry, Biochemistry and Technology* by C. Frank Shaw updates biochemically related activity through 1999 [2]. A recent review by Milacic et al. [3] covers some of the studies with gold(I) and gold(III) complexes used in cancer treatment. Targeted results are described by Rackham et al. [4] on breast cancer cells using a gold(I) phosphine complex.

Although several plausible explanations have been suggested for the biological activity of gold(I) compounds in treatment of various diseases, there is little definitive understanding of the specific role of gold(I) compounds important to the control of the diseases. The gold(I) triethylphosphine acetylated thiosugar "Auranofin" appears

* Corresponding author. Tel.: +1 979 845 0648; fax: +1 979 845 2373.
E-mail address: fackler@mail.chem.tamu.edu (J.P. Fackler Jr.).

0010-8545/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ccr.2009.02.010

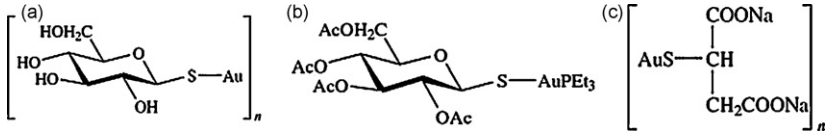

Fig. 1. Chemical representations of some of the anti-rheumatoid arthritis gold drugs. (a) Solganol, (b) Auranofin, and (c) Myochrysine.

to be the last gold drug clinically approved for treatment of any human disease. It has been an excellent oral drug for some patients having rheumatoid arthritis.

Auranofin (or Ridaura) was approved by the FDA in 1976 as an orally active drug for the treatment of rheumatoid arthritis (RA). Gold sodium thiomalate, Myochrysine, is typically used to treat active RA in juvenile and adult patients, while Auranofin (Fig. 1) is targeted for adult patients who have not responded well to one or more courses of non-steroidal anti-inflammatory drugs (NSAIDS) [5]. Gold drugs are prodrugs, i.e., they are converted into other, as yet unknown, active forms *in vivo* during chrysotherapy. Gold(I) complexes typically undergo rapid ligand displacement reactions and it is likely that *in vivo*, Au(I) coordinates to cysteine sites in glutathione, proteins, and enzymes. Hemple and co-workers [6] concluded that a significant percentage of Auranofin is converted into the cationic digold complex $[(Et_3PAu)_2(\mu\text{-TATG})]^+$, TATG = 2,3,4,6-tetra-acetyl-1-thio-D-glucopyranosato, in stomach acid.

In spite of continued use, the avenue by which gold drugs modify the inflammatory response is still unknown. Although the inorganic chemistry of gold has been an active area for some time, there also appears to be some fairly large gaps in our understanding of basic reaction mechanisms involving gold–sulfur compounds, especially with regard to redox transformations of gold(I) compounds.

The thioglucose of gold(I), "Solganol" appears to be the drug of choice used by veterinarians [7] to treat the small animal skin disease *pamphigus* which has some autoimmune characteristics similar to rheumatoid arthritis. This animal skin disease [7] suggests that the toxicity of oxygen metabolites such as singlet oxygen, superoxide or peroxynitrite might be controlled by these gold drugs. The known cellular toxicity of gold(I) compounds, however, has limited use in the treatment of human disease. It has been stated that 25% of the arthritic persons for whom gold drugs have been tried have developed a contact allergy to gold sodium thiomalate use [5b]. Beyond the general belief based upon good experimental data that gold(I) is transported in the body by attachment to sulfur residues in proteins, little specific detail exists. Metabolic elimination of gold(I) as $[Au(CN)_2]^-$ does occur from humans and there is some evidence of gold(III) formation in oxidative bursts [2].

While our interest in gold chemistry began in the early 1970s with some gold(III) organometallic complexes, it was soon apparent to us that very little was known then regarding the basic chemistry of this element. We were surprised to learn how stable trimethylgold(III) ylides are since they can remain open to air after formation. The structurally related $[Au(CH_3)_4]^+$ cation inflames in air. The stable dimethylgold(III) dithiolates were first studied in the 1930s. The structural features of these compounds, planar four coordination, are consistent with the $5d^8$ electron configuration also found with platinum(II) species. Currently there is a renewal of interest in gold(III) complexes because of electronic and structural relationships to the well known *cis*-Platin, *cis*-$(NH_3)PtCl_2$, cancer drug.

Our studies have focused largely on the basic chemistry of gold(I). Along with the pioneering work of Schmidbaur and his students, our laboratory developed considerably the chemistry of gold(I), gold(II) and some gold(III) ylide organometallics [8,9]. Gold(I) complexes tend to be linearly two coordinate species, although examples of planar three coordination and tetrahedral four coordination of gold(I) are well known. Gold(I) complexes generally are easily oxidized to gold(III) but in the presence of weak gold(I)···gold(I) interactions, oxidative addition of oxidants such as the halogens can produce metal–metal bonded gold(II) species wherein the gold(II) has a planar four coordinate arrangement. This type of oxidative addition also has been observed with platinum(II) as a neighboring metal atom. In the course of our work, we have examined many gold(I) complexes with Au–C, Au–N, Au–S and Au–P bonding. A major review of the amidinate chemistry of dinuclear and tetranuclear gold(I) chemistry has been published recently [10].

The gold(I) chemistry using pyrazolate nitrogen ligands led to the use of other nitrogen ligands to form dinuclear, cyclic trinuclear complexes, CTCs, and tetranuclear amidinate gold(I) complexes [10] with properties significantly different from the organometallic and sulfur coordinated species [11]. The electronic properties of these gold(I) complexes have been studied in detail and it is recognized that π accepting ligands can strongly influence the properties associated with the metal ion [12]. Although nitrogen ligands are very important biochemically, only in recent years has the nature of gold(I) bonding to nitrogen ligands been studied. The π-basicity associated with gold(I) centers in trinuclear species with nitrogen–gold(I) and carbon–gold coordination has led to the observation of Lewis and π-acid/π-base interactions of these trinuclear complexes with organic π acids and cations [12a].

With the anion $[Au(C_6F_5)_2]^-$, and related species, porous solids have formed into which small molecules may enter which change the optical properties of the gold complexes. Their potential use as biosensors for hazardous organic and/or metabolites is a result.

2. Dinuclear gold(I) compounds

Schmidbaur's synthesis of dinuclear gold(I) ylide complexes $\{Au_2[(CH_2)_2PR_2]_2\}$, R = aliphatic or aromatic groups, and their oxidation to stable metal–metal bonded gold(II) species opened up new thinking in gold chemistry. Our studies showed that the distance between the metal atoms in these complexes drops from about 3.0 Å in the dinuclear gold(I) complexes to as short as 2.5 Å when oxidative addition occurs. The gold(I) species contain linear C–Au–C bonds, as in $[Au(CN)_2]^-$ while the metal–metal bonded dinuclear Au(II) species have a planar, four coordinate geometry with a Au(II) atom in one of the four bonding positions. A major review of this work can be found in *Comprehensive Organometallic Chemistry* [8]. Efforts to isolate and characterize a one-electron oxidation intermediate have not succeeded and the electrochemical oxidation in solution is not reversible. The electrochemical oxidation of dinuclear gold(I) complexes [12b] generally varies considerably with the type of ligands coordinated to the gold(I) with the carbon bonded ylides showing the lowest potential to oxidation compared with neutral dinuclear complexes involving N, S, and P (Fig. 2).

Dinuclear phosphine, sulfur and nitrogen ligand complexes of gold(I) were an outgrowth of the ylide work with very interesting differences in the results. Unlike the dinuclear ylide complexes which readily undergo oxidative addition to form metal–metal bonded gold(II) species, the phosphine bridged species for no stable metal–metal bonded products. With sulfur ligand complexes such as the dithiocarbamates, dithiophosphinates, dithiophosphates and dithiolates, oxidative addition can be observed but not universally. It occurs readily with the anionic dinuclear 1,1-dithiolates but not at all with the neutral dinuclear gold(I) xanthates. While halo-

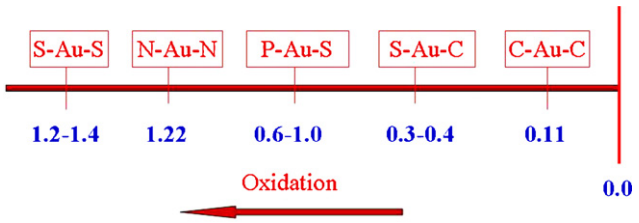

Fig. 2. Oxidation potentials reported of neutral dinuclear gold(I) complexes with various ligand $[Au(LXL)]_2$ coordination *vs.* Ag/AgCl with 0.1 M $[Bu_4N]PF_6$ in CH_2Cl_2, 12b].

gen oxidative addition forms a metal–metal bonded gold(II) trans addition product with the dinuclear diethyldithiocarbamate, the product is unstable in solution. Mixed ligand ylide, thiophosphinate complexes show reversible oxidative addition of halogens with the dinuclear gold(II) product releasing the halogen upon heating [13].

Dinuclear amidinate nitrogen based ligand complexes also can be formed which undergo oxidative addition like the ylides [10]. In the dinuclear ylide system, the HOMO has been shown to be a metal–metal sigma anti-bonding orbital with the LUMO being sigma bonding [9]. With guanidinate like nitrogen based ligands, a dinuclear gold(I) complex has not been isolated although a tetranuclear gold(I) complex has been formed. A dinuclear gold(II) oxidative addition product forms readily in the presence of halide or halogenated solvents from gold(I) starting materials. With these delocalized nitrogen amidinate and guanidinate ligands, DFT calculations [14] suggest interactions between the filled d–π orbitals on the metal and the ligand π orbitals are important. Unlike the dinuclear ylide complexes, the HOMO is d–π/ligand p–π anti-bonding with the HOMO-1 being gold–gold sigma anti-bonding. Oxidative addition involves this metal–ligand π anti-bonding orbital although the two-electron oxidative addition product contains a sigma gold(II)–gold(II) bond. A metal–ligand π-anti-bonding interaction is also like to be important in the chemistry of the carbeniates, benzylimidazolates and pyrazolates. The excited states of emissive complexes show considerable ligand involvement. With the sulfur ligand complexes, filled metal d–π, ligand π orbital interactions also may be dictating the chemical differences observed although to date this has not been clearly defined experimentally.

3. Cyclic trinuclear gold(I) compounds

Intermolecular interactions involving aromatic rings and cations or anions are key processes in both chemical and biological recognition [15]. Understanding these interactions is essential for rational drug design and lead optimization in medicinal chemistry. Various non-covalent interactions involving aromatic rings, such as electrostatic cation/aromatic ring, and other π-acid/π-base bonds are pivotal to protein–ligand recognition and concomitantly to drug design [16]. However, if the drug molecule contains metal ions in its framework, Lewis acid–base interactions occupy a special role in the overall description of the forces occurring in the action of the metal based drugs. Several examples of organometallic compounds employed in medicine as drugs or diagnostic media are known [17]. The presence of one or more metal atoms may play different roles: they can act as Lewis-acidic binding sites, sensing units, carry positive charge and increase the strength of electrostatic interactions by restricting the conformations available or structuring the core onto which binding groups are assembled [18].

The chemistry of gold(I) cyclic trinuclear gold(I) complexes, CTCs (Fig. 3) includes supramolecular derivatives where electrostatic interactions play a cooperative role. They do this by recognition of Lewis acid metal ions, acidic organometallic complexes and small organic π-acid molecules. CTCs are a class of gold(I) compounds wherein three linearly coordinated gold(I) ions are bridged by three exo-bidentate ligands, forming nine-membered cycles. The ligand can be a N,N or C,N donor molecules. CTCs are generally air and light exposure stable and soluble in organic solvents depending on the nature of the bridging ligand. The CTCs are white solids which, when exposed to UV light, often exhibit emissive properties, commonly as a result of aurophilic gold–gold interactions. These latter are non-covalent attractive interactions occurring between gold(I) centers caused by correlation and relativistic effects; they are often responsible of emissive, structural, and biological features of the CTC compounds.

From the point of view of gold–gold interactions producing unusual emissive behavior the $[\mu\text{-C(OMe)=N(Me)Au}]_3$, complex is the most interesting CTC observed to date. It displays the phenomenon Balch and co-workers described as "solvoluminescence" when UV irradiated crystals, which have a columnar structural assembly [19], give off a burst of visible light when a drop of solvent interacts with them. The syntheses, reactivity and structural properties of these neutral gold(I) complexes have been reviewed [12a].

Depending upon the steric hindrance of the substituents on the bridging ligands, the solid state crystal structures of CTCs show dimeric or oligomeric arrangements, through intermolecular aurophilic contacts.

The neutral C,N-CTCs (i.e. $[\mu\text{-(1-benzyl-2-yl-imidazolate)Au}]_3$ and $[\mu\text{-C(OEt)=N(tolyl)Au}]_3$) react with silver(I) or thallium cations to give intensely colored yellow or green microcrystalline powders where the CTCs and the metal ions are in the 2:1 ratio. The ions are bound exclusively to the gold by metallophilic interactions. The CTC's interact with each other by aurophilic interactions in a ABA···ABA fashion (Fig. 4) [20,21]. The supramolecular stacks, i.e. $\{Ag[(Au(\mu\text{-C,N-1-benzylimidazolate})]_3)_2\}BF_4$ or $\{Tl[(Au(\mu\text{-C,N-1-benzylimidazolate})]_3)_2\}PF_6$ possess a luminescence thermochromism, observed as red shifts in the emission maxima upon cooling the crystals from room temperature to 77 K. Low energy phosphorescence generally is observed when extended chain structures are present [22]. These cooperative metallophilic interactions stabilize the structures conferring thermal stability in the solid state and a reversible dissociation in solution as observed in NMR studies [23]. Solubility of the complexes is connected to the polarity of the solvent used and to the nature of the bridging ligand of the CTC, with the carbeniate derivative generally more soluble than the imidazolate homologue.

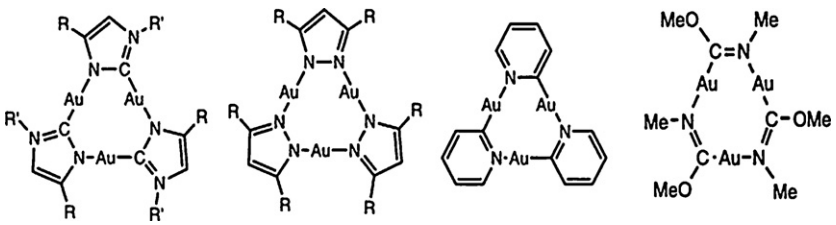

Fig. 3. Schematic representation of some trinuclear CTCs.

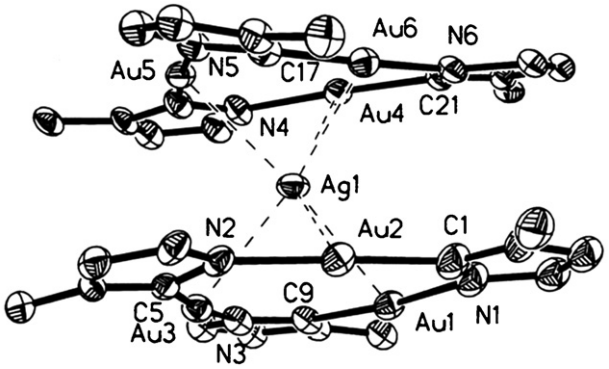

Fig. 4. Side view of the cationic complex $\{Ag[(Au(\mu\text{-}C,N\text{-}1\text{-benzylimidazolate})]_3)_2\}^+$. The anion is not shown.

The reaction between metal ion salts and the CTC's is restricted to those with C,N donor ligands. When the bridging ligand presents a N,N coordination to gold such as in $[\mu\text{-}(3,5\text{-}(R)\text{-pyrazolateAu}]_3$, R = H, Me, Ph, adduct products with silver and thallium salts are not obtained and the starting materials were recovered from the reaction mixture. Thus the electronic properties of the bridging ligands play an important role in the nucleophilicity of the CTCs. To date only Ag(I), Tl(I) and Cu(I) and Au(I) have been successfully intercalated into the C,N CTC's although Li^+, Na^+, K^+. Cs^+, Cu^{2+}, Hg^{2+}, $Hg_2{}^{2+}$, Hg^0, have been tested for such an interaction.

The reactivity described above may be explained by considering the pi–basicity of the gold metallacyclic rings [24]. Direct evidence of the acid–base interactions in solution was observed by ^{19}F,^1H-HOESY and PGSE NMR measurements, revealing the persistence of the $[Au_3Hg_3Au_3]_n$ and $[Au_3Hg_3]$ adducts [25]. The reaction of C,N CTCs with electrophilic π-acid organic molecules such as hexafluorobenzene, C_6F_6, and 7,7,8,8-tetracyanoquinodimethane, TCNQ, produces stacked derivatives in the ratio 1:1 and 2:1 ratio, respectively. No aurophilic Au···Au bonds are observed in the hexafluorobenzene intercalate (Fig. 5). Thus intermolecular aurophilic interactions are not fundamental to the formation of extended acid–base chains [26]. Moreover, when $[\mu\text{-}C(OEt)=N(tolyl)Au]_3$ is suspended in C_6F_6, the blue luminescence, associated with the Au···Au bonded chain quenches as the aromatic hexafluorobenzene disrupts the chains. Electron acceptors and fluorine containing compounds play a role in many biological systems. The fluorine atom is isosteric and isoelectronic with the hydroxyl group [27], and its presence can enhance the metabolic stability of drugs modifying their electronic and physical properties [28].

By reacting the nucleophilic trinuclear Au(I) ring complex $[\mu\text{-}C(OEt)=N(tolyl)Au]_3$, with the organic Lewis acid octafluoronaphthalene, $C_{10}F_8$ a supramolecular structure consisting of stacks in which the $[\mu\text{-}C(OEt)=N(tolyl)Au]_3$ π-base molecules alternate with the octafluoronaphthalene π-acid molecules was obtained. The stacking completely quenches the blue photoluminescence of $[\mu\text{-}C(OEt)=N(tolyl)Au]_3$, and leads to the appearance of a bright yellow emission band from the $C_{10}F_8$, at room temperature, shifted a bit by the interaction with the gold complex [12]. Other electron acceptors also produce π-acid/π-base stacking [29].

Along with the experimental studies, theoretical calculations on the electronic density distribution on the metallacycles CTCs have been obtained. DFT calculations on $[\mu\text{-}C,N\text{-}(1\text{-benzyl-2-yl-imidazolate})Au]_3$ and $[\mu\text{-}C(OEt)=N(tolyl)Au]_3$ show a negative electrostatic potential at the center of the CTC rings (Fig. 6), leading to the π-base character [24]. Omary et al. [30] also report the calculated molecular electrostatic potentials (MEPs) for some N,N CTCs namely $\{3,5\text{-}(R)_2Pz]M\}_3$ (pz = pyrazolate) (Fig. 7). The results suggest that N,N CTCs complexes with R = H or Me are bases with the relative basicity order Ag ≪ Cu < Au. However fluorination ($R = CF_3$)

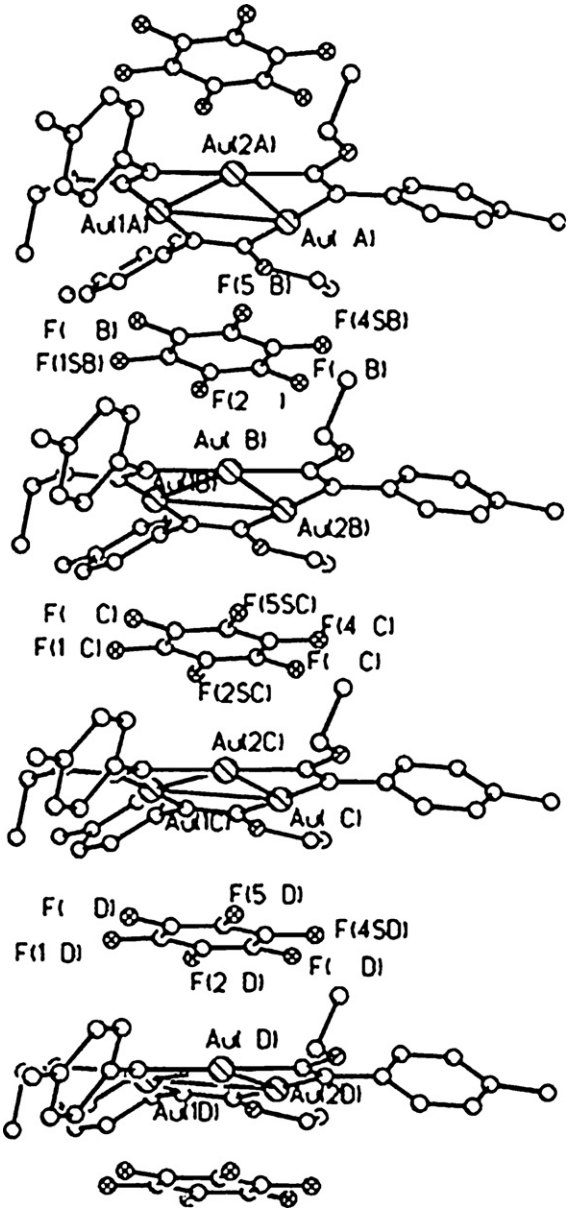

Fig. 5. Crystal structure of the stacking of $[\mu\text{-}C(OEt)=N(tolyl)Au]_3$ and C_6F_6.

of the pyrazolates makes even the Au trimeric acidic, showing that the ligand can countermand the metal-based acidity/basicity in these CTCs. This theoretical result has been confirmed by the intercalation of toluene in a 1:2 stacks with $\{3,5\text{-}(CF_3)_2Pz]Au\}_3$.

The MEP calculations [30] clearly indicate that the π-acidity/π-basicity results are ligand mediated (Fig. 8). Upon comparing CTCs with organic analogues, it is calculated that the former have a much wider π-acidity and π-basicity range than the organics at typical bonding distances. By comparing CTCs with different bridging ligands a scale of π-basicity was obtained: $[M(\mu\text{-}Im)]_3 > [M(\mu\text{-}py)]_3 > [M(\mu\text{-}Cb)]_3$ $[M(\mu\text{-}Pz)]_3 > [M(\mu\text{-}Tz)]_3$ where Im = imidazolate, py = pyridinate, Cb = carbeniate, Pz = pyrazolate, Tz = triazolate. These theoretical results provide a reasonable explanation for the lack of reactivity of N,N CTCs with regard to the electrophiles (π-acids and Lewis acid metal ions) discussed above.

The acid–base chemistry of the gold(I) CTCs promises to be a very interesting field of gold CTCs chemistry. The parallel experimental and theoretical studies have allowed rationalization of their behavior with the potential for designing new CTCs useful

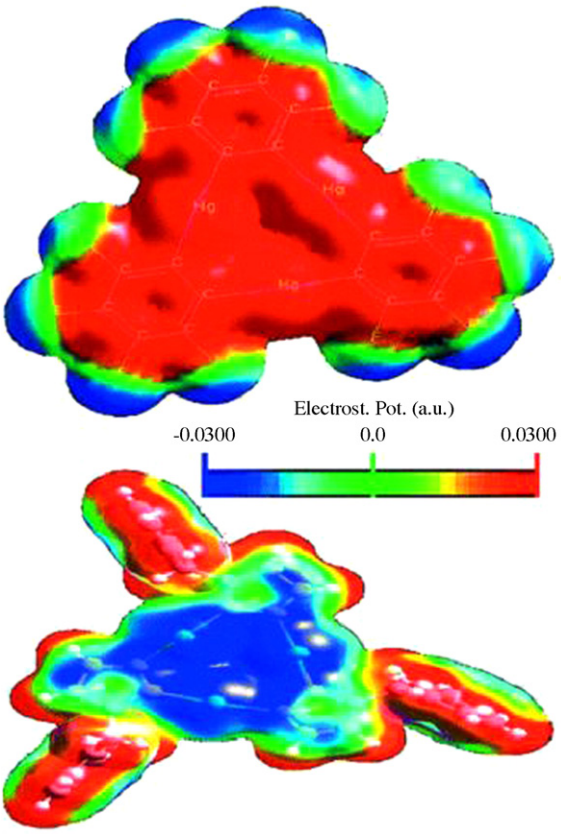

Fig. 6. DFT-derived molecular electrostatic potentials (MEP) mapped onto the electron density surfaces of [μ-C,N-(1-benzyl-2-yl-imidazolate)Au]$_3$ compared to those of the electrophilic [μ-C,C-(tetrafluorophenylene)Hg]$_3$.

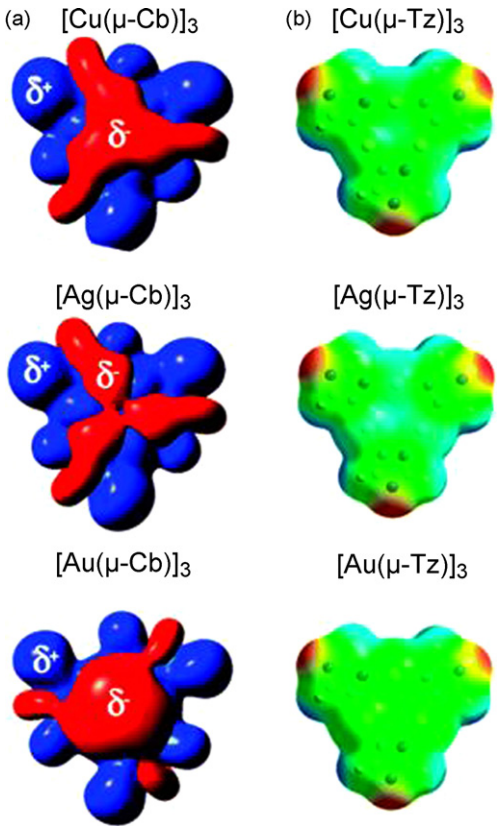

Fig. 8. MEP surfaces showing the relative π-basicity of some CTCs as a function of the metal (Cu(I), Ag(I) and Au(I) and different ligands as (a) carbeniate and (b) triazolate. Basicity increases in the direction blue → green → yellow → orange → red.

for host–guest chemistry. These special properties such as luminescence and acid–base recognition are likely to produce fruitful applications in medicinal chemistry and biological sensing.

4. Gold(I) sulfur chemistry

4.1. Structure and bonding aspects of gold(I) sulfur chemistry

Sulfur containing ligands bond readily to gold(I) through formation of Au–S sigma bonds. The Au–S distances are around 2.3 Å. This subject has been reviewed [1]. The two coordinate gold(I) centers have a linear or near linear LAuS arrangement, where L = phosphines, thiolates, halides, etc. Bonding of AuCl to the symmetrical trithiapentalene (Fig. 9), causes the formation of a zwitterion in which the solid state structural dimensions suggest formation of a cationic charge on the pentalene and negative charge at the S–Au–Cl center [31]. Furthermore, this study demonstrated the lability of Cl–Au–S bonding and the rapid migration of the Au across the molecule in solution. Proton NMR results estimated that the activation energy for Au–S exchange in this system is of the order of 7–8 kcal/mol.

Chemical lability and relatively strong affinity for sulfur have led to the formation of a large number of different structures with thiols, thiolates and sulfides. The phosphine coordinated gold(I) unit [LAu]$^+$, often has been used to coordinate to various of these sulfur containing species, presumably mimicking possible attachment of the [Et$_3$PAu]$^+$ moiety in Auranofin. These studies have shown that one can expect terminal, bridging, and partial interaction with both sulfur and other gold(I) centers [32]. A particularly interesting example was found in the product of [Cp$_2$Fe]PF$_6$ oxidation of the bis(diphenylphosphine)methane complex, dppm coordinated to *p*-thiocresolate, dppm(Au-*p*-tc)$_2$. This product, a nine gold(I) atom visibly luminescent cluster [Au$_9$(μ-dppm)$_4$(μ-*p*-tc)$_6$](PF$_6$)$_3$, con-

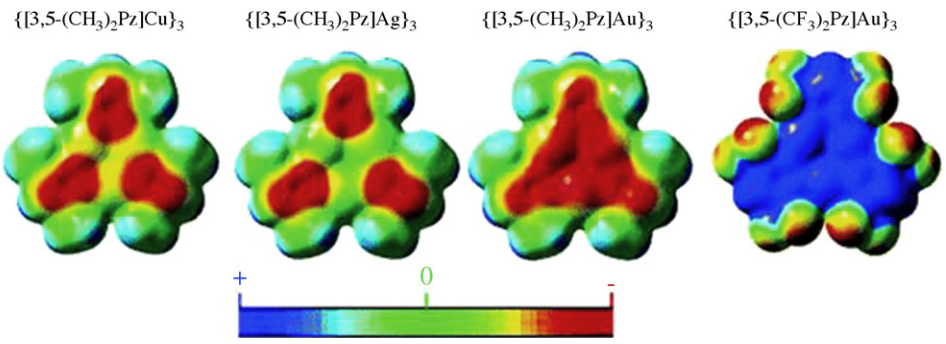

Fig. 7. DFT-derived molecular electrostatic potentials (MEP) mapped onto the electron density surfaces of selected {[3,5-(R)$_2$Pz]M}$_3$ models.

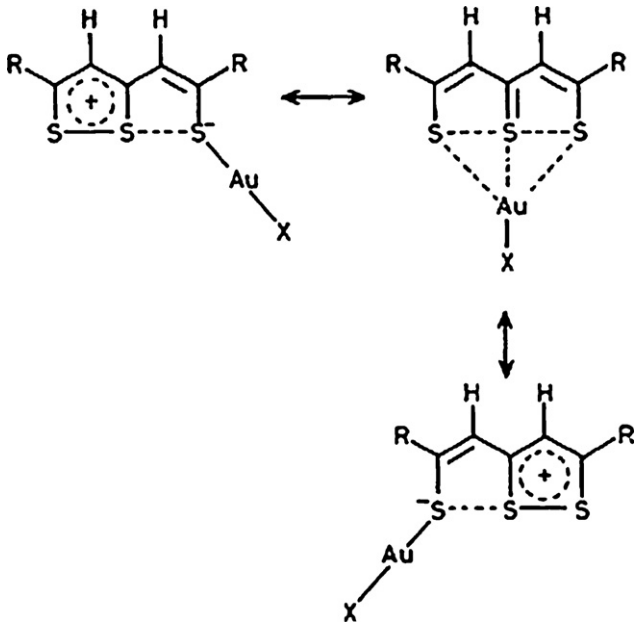

Fig. 9. The rearrangement of AuX bonded to trithiapentalene occurs on a NMR time scale.

tains a range of Au···Au interactions with bridging Au–SR–Au bonds [33]. The basic Au, P, and S geometry is seen in Fig. 10 with nearest neighbor Au···Au distances ranging from 2.99 to 3.96 Å.

Gold(I) sulfur complexes show a remarkable affinity for oligomer formation with aurophilic Au···Au interactions. The $[AuS_2CMe]_4$ structure is an early example of a near square of Au(I) atoms separated to a distance of only 3.0 Å by the bridging thiolate ligands, each Au(I) atom being coordinated linearly by two sulfur atoms [34]. This structural motif is very common also in gold(I) amidinate chemistry with linear N–Au–N coordination [10] (Fig. 11).

4.2. Redox studies of gold(I) thiolate drugs and related compounds

The reduction of Auranofin at a dropping mercury electrode shows that Auranofin undergoes a diffusion controlled and reversible reduction process at −0.5 V *vs.* SCE at pH greater than 9.5 [35]. Bulk electrolysis at −0.8 V yields an *n* value of 1, indicative of an $Au^{1/0}$ redox couple. Electrochemical studies of a variety of Au(I) complexes with phosphine and/or sulfur ligands show that metal, phosphine or sulfur ligands can be redox sites [12b]. For compounds that model Auranofin, i.e. Au(I) phosphine thiolates experimental studies in nonaqueous solvents demonstrate that sulfur is initially oxidized leading to gold sulfur clusters (*vide infra*) [36].

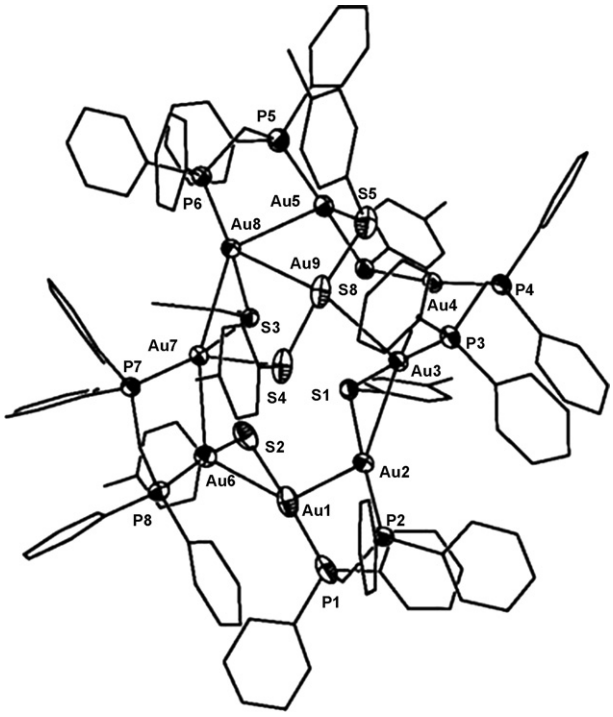

Fig. 10. The cationic cluster $[Au_9(\mu\text{-dppm})_4(\mu\text{-}p\text{-tc})_6]^{3+}$.

Gold(I) phosphine thiolate complexes each undergo a broad irreversible oxidation at about +0.6 to +1.1 V and a second, sharper, irreversible oxidation at more positive potentials, +1.2 to +1.6 V (*vs.* SCE) [36]. The cyclic complexes with the aliphatic thiolates are in general easier to oxidize. Auranofin $(Et_3P)Au(TATG)$ (TATG = 2,3,4,6-tetra-acetyl-1-thio-D-glucopyranosato), is found to be more difficult to oxidize. The irreversible nature and the number of electrons involved in the oxidation of Auranofin are consistent with oxidation of Au(I) to Au(III), followed by a rapid chemical step. The electrochemical results are consistent with the observations made by Shaw et al. during the chemical oxidation of Auranofin and Myochrysine with hypochlorite [37].

4.3. Mechanism of oxidation

Electrochemical and chemical oxidation studies of the trimethylphosphine derivative of Auranofin demonstrate that oxidation of phosphine Au(I) thiolate complexes is largely sulfur based rather than oxidation of the gold(I) metal ion. This is consistent with electronic structure studies in which the HOMO was

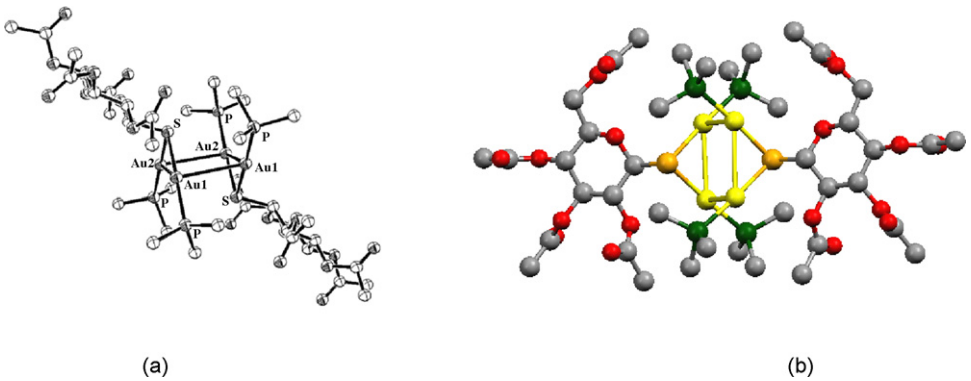

Fig. 11. Dicationic structure of $[(Me_3P)_2Au_2(TATG)]_2^{2+}$ with hydrogen atoms and NO_3^- anions omitted for clarity. (a) Thermal ellipsoid representation (50%) looking down on the gold square and (b) a ball-and-stick representation shown as a side view.

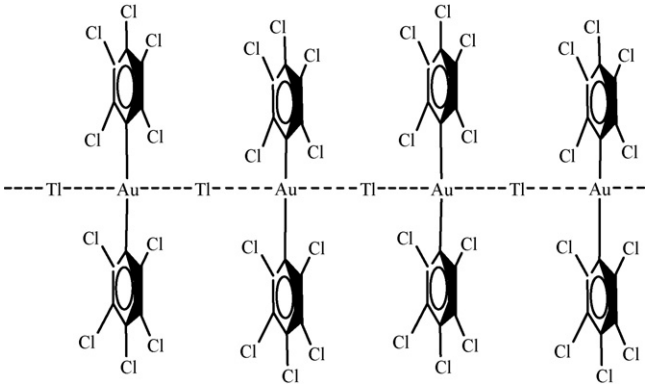

Fig. 12. Structure of $[AuTl(C_6Cl_5)_2]_n$.

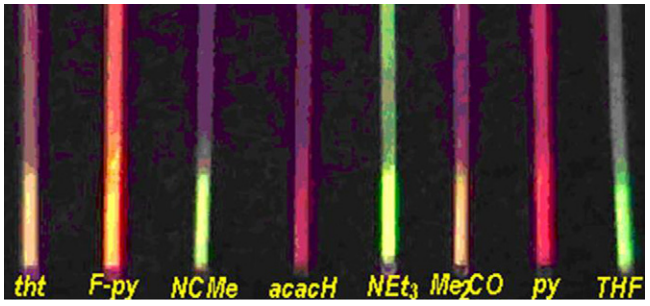

Fig. 13. Color changes, under UV-light, of $[AuTl(C_6Cl_5)_2]_n$ after exposure to vapors of VOCs.

assigned as primarily sulfur in character [38,39]. Upon oxidation, an electron is removed from the largely sulfur ligand based HOMO of the mononuclear gold(I) complexes. This loss of an electron from the complex leads to cleavage of the Au–S bond and formation of $LAu(I)^+$ and a thiyl radical. The thiyl radical rapidly dimerizes to form disulfide. The coordinately unsaturated LAu^+ reacts with another molecule of starting material to form a digold cationic complex which then dimerizes via Au···Au bonding to form the observed tetranuclear gold(I) cluster (Fig. 11). The net result is a one-electron oxidation per two molecules of gold complex. Thus only one-half equivalent of oxidant is required per mole of mononuclear gold complex to complete the oxidation. Support of this mechanism is provided by the independent syntheses of the various clusters via reaction of LAuCl with a silver salt (e.g. $AgNO_3$) followed by addition of LAuSR.

5. Photochemical small molecule detection using gold

The reliable monitoring of volatile organic compounds (VOCs) has become more important in environmental and public safety control due to the potential health hazards that exposure to these substances possess. Apart from the interest in improving the screening of carcinogenic agents, an increasing effort is also being made in the search of efficient detectors of small biomolecules that may be present in biological fluids. In fact, the development of stable and reversible chemical sensors based on vapochromism or vapoluminescence, the dramatic color or luminescence change of a material upon exposure to vapors of VOCs, has become the subject of intensive study in the last few years. Complexes containing a variety of metal centers, such as Re/Co [40], Ru [41–48], Sn [49], Pt [50–52], Pt/M (M = Pd, Pt) [53–57] or Cu [58,59] have been reported.

Apart from the gold materials commented upon above, some vapochromic gold/thallium polymeric compounds have been synthesized making use of an acid–base synthetic strategy. Obviously, the toxicity of thallium makes these compounds less useful for medical or biological use, but such Au/Tl systems may have potential for screening carcinogenic agents in the air and in detecting excreted biomolecules, especially ketones. Drug metabolites also might be screened easily with these compounds. The simplest one $[AuTl(C_6Cl_5)_2]_n$ [60], was prepared by reaction of equimolecular amounts of $NBu_4[Au(C_6Cl_5)_2]$ and $TlPF_6$ in THF. Its crystal structure consists of a perfectly linear chain running parallel to the crystallographic *z* axis built via unsupported Au···Tl interactions of 3.0045(5) and 2.9726(5) Å (Fig. 12).

Although $[AuTl(C_6Cl_5)_2]_n$ crystallizes as a free solvent complex with almost "naked" thallium atoms, which only exhibit Au···Tl and Tl···Cl interactions, the holes present in the net (as large as 10 Å) allow certain small molecules to enter the network and replace the weak Tl···Cl contacts even in gas phase [61]. Consequently, it behaves like a VOCs sensor. In fact, it reacts with vapors of donor molecules, such as tetrahydrofuran, tetrahydrothiophene, acetylacetone, 2-fluorpyridine, triethylamine, pyridine, acetonitrile or acetone, producing marked changes in the color of the sample, which are even greater under UV radiation (Fig. 13). This is a fully reversible process thanks to the interaction of the molecules only

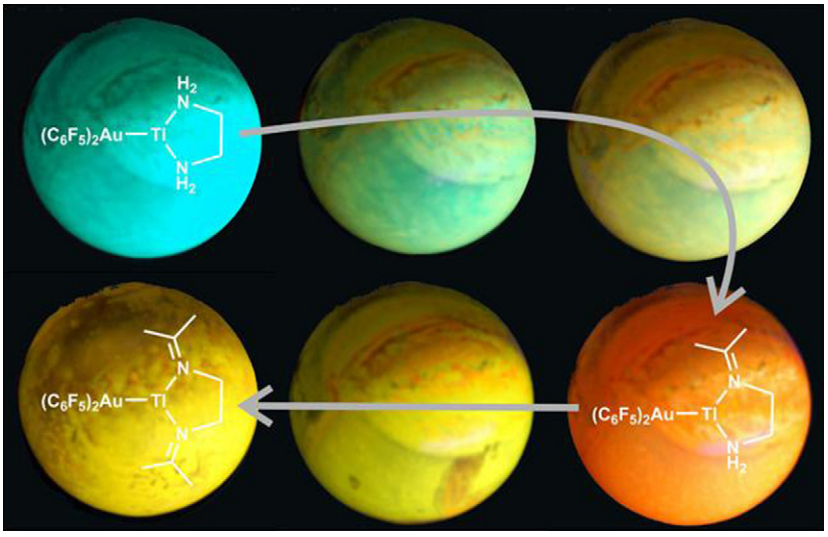

Fig. 14. Color changes, under UV-light, of $[AuTl(C_6F_5)_2(en)]$ by exposure to acetone vapor.

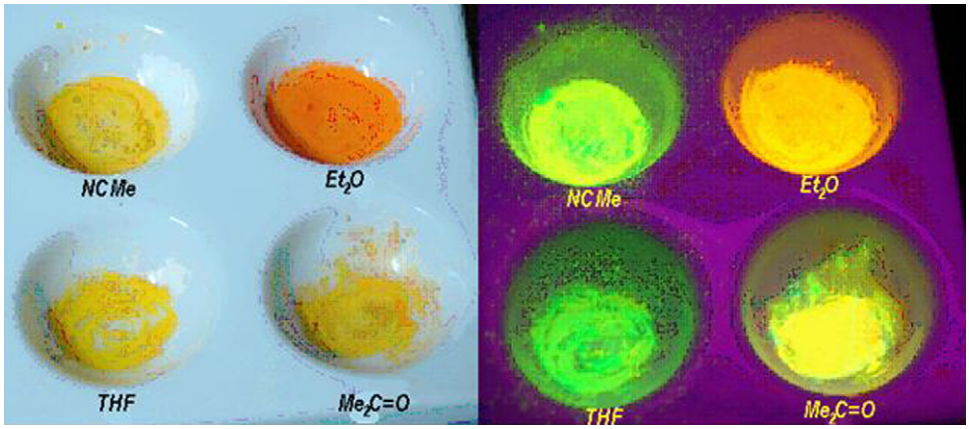

Fig. 15. Left: Color changes of $\{[AuAg(C_6F_5)_2(Et_2O)]_2\}_n$ exposed to selected organic vapors. Right: the same samples under UV-light.

with some of the thallium centers, which prevents the supramolecular structure from collapsing and avoids the total rupture of the contacts between different chains, which would have lead to irreversibility.

The related gold/thallium systems $[AuTlR_2(en)]$ ($R = C_6Cl_5, C_6F_5$) can also be employed as a very sensitive detector of excreted biomolecules, particularly ketones, since it reacts with acetone or phenylmethylketone (even in gas phase) leading to the conversion of ethylenediamine into imine or diimine with loss of water at room temperature in a few seconds [62]. This reaction takes place with the striking change of color of the green starting complex, which turns orange (imine) or yellow (diimine) (Fig. 14). It is worth mentioning that the Au···Tl contact is of capital importance in this process, since the exposition of the diamine to the same ketones in the absence of one of the metals do not produce any change and the starting products are recovered unaltered.

Finally, all the Au/Tl compounds are strongly luminescent under UV light in the solid state, but none of them exhibit luminescence in solution. Consequently, the luminescence originates in the Au···Tl interactions present in the polymetallic chains and is influenced by the coordination environment of thallium. As confirmed by X-ray diffraction studies carried out for many of these compounds, interactions are broken in solution.

While the toxicity of thallium makes thallium based materials less attractive for direct biological uses, combinations of other less toxic metals can be considered. One candidate is the gold/copper coordination polymer $\{Cu[Au(CN)_2]_2(DMSO)_2\}_n$ [63], an heterometallic system that displays two polymorphs, one green and one blue. While the former exhibits five-coordinate Cu(II) centers and generates polymeric chains, the latter generates corrugated sheets with six-coordinate Cu(II) atoms. Both polymorphs form 3D networks through aurophilic interactions of 3.220(1) and 3.419(3) Å, respectively, and, despite their different structures, both of them display essentially an identical vapochromic behavior. The DMSO molecules of the green and blue polymorphs can be replaced easily by a variety of vapors of donor solvents at room temperature, and both polymorphs convert to the same $\{Cu[Au(CN)_2]_2(solvent)_x\}_n$ complex (solvent = water, acetonitrile, dioxane, *N*,*N*-dimethylformamide, pyridine, ammonia). The vapochromism can be readily observed both by perceptible color variations and by large IR changes in the ν_{CN} region. Each $\{Cu[Au(CN)_2]_2(solvent)_x\}_n$ complex can be distinguished easily by its color, which changes from its initial green or blue to colors that vary from yellow-greenish (with H_2O) to dark blue (with NH_3). Importantly, this gas-phase solvent exchange is completely reversible, thus permitting dynamic solvent sensing.

A similar applicability can be found for the one-dimensional gold/silver polymer $\{[AuAg(C_6F_5)_2(Et_2O)]_2\}_n$, obtained by reaction of $NBu_4[Au(C_6F_5)_2]$ and silver perchlorate in presence of diethyl ether. Although complexes of the type $[Au_2Ag_2(C_6F_5)_4L_2]_n$ (L = neutral ligand) have been known since the eighties [64,65], their capability to act as detectors of vapors of VOCs has been studied much more recently, and the diethyl ether derivative has been the subject of a Spanish patent as an "electronic nose" [66]. This promising future as sensors of small organic molecules has to do with the lability of some ligands, such as Et_2O, in the coordination sphere of silver.

Very recently the vapochromic behavior of $\{[AuAg(C_6F_5)_2(Et_2O)]_2\}_n$ has been reported [67]. It reacts with VOCs both in solution and in solid/gas phase leading to the synthesis of complexes with the stoichiometry $\{[AuAg(C_6F_5)_2(L)]_2\}_n$ (L = Me_2CO, THF, CH_3CN), which maintain the polymeric nature of the precursor. Thus exposure of solid $\{[AuAg(C_6F_5)_2(Et_2O)]_2\}_n$ to vapors of the VOCs at room temperature leads to a quick change in the color of the samples which is perceptible to the human eye (Fig. 15, left). The emission under UV light (Fig. 15, right) produces even greater color changes, where the color is specific for each molecule. This is an additional advantage for the applicability of this material.

These four complexes are luminescent in solid state at room temperature and at 77 K. A plausible origin of the emission spectra in these complexes is that the excited states responsible for the emissions are localized in the tetranuclear $[Au_2Ag_2(C_6F_5)_2L_2]$ core, with an energy which is influenced by the gold–gold or gold–silver interactions and by molecular aggregation.

6. Summary

The studies described here demonstrate that gold(I) compounds have several potential roles in biologically related chemistry. The relatively low toxicity of gold and its lability allows human consumption of drugs formed with this element, although allergenic reactions have limited the use in treatment of rheumatoid arthritis, it is a disease for which gold drugs have proved effective. The cause of the allergenic reactions is not known. Treatment of diseased animals with Solganol undoubtedly will continue until new, less expensive drugs are obtained. The ability of gold(I) compounds to interact with themselves aurophilically and with other heavy element ions has produced spectroscopic properties which are sensitive to VOCs and other molecular interactions. Thus bioapplicability for sensing toxic components appears reasonable. Trinuclear and tetranuclear clusters look particularly interesting because of the strong basicity of the gold(I) centers in these

molecules. Future studies are expected to lead to interesting new bio-related observations.

Acknowledgements

The Robert A. Welch Foundation of Houston, Texas, the University of Camerino, Italy, and the Camille and Henry Dreyfus Foundation, Inc. are acknowledged for financial support of this work.

References

[1] H. Schmidbaur (Ed.), Gold: Progress in Chemistry Biochemistry and Technology, John Wiley & Sons, Chichester, UK, 1999.
[2] C.F. Shaw, Gold: Progress in Chemistry, Biochemistry and Technology, John Wiley & Sons, Chichester, UK, 1999.
[3] V. Milacic, D. Fregona, Q.P. Dou, Histol. Histopathol. 23 (2008) 101.
[4] O. Rackham, S.J. Nichols, P.J. Leedman, S.J. Berners-Price, A. Filipovska, Biochem. Pharmacol. 74 (2007) 992.
[5] (a) American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines, Arthritis Rheum. 46 (2002) 328;
(b) A. Svensson, H. Möller, B. Björkner, M. Bruze, I. Leden, J. Theander, K. Ohlsson, C. Linder, BMC Dermatol. 2 (2002) 2.
[6] (a) J. Hempel, Y. Mikuriya, Proceeding of a Symposium on the Bioinorganic Chemistry of Gold Compounds, Philadelphia Pennsylvania, 1981, p. 37;
(b) D.L.B. Bryan, Y. Mikuriya, J.C. Hempel, D. Mellinger, M. Hashim, R.F. Pasternack, Inorg. Chem. 26 (1987) 4180.
[7] (a) D.H. Brown, W.E. Smith, Chem. Soc. Rev. 9 (1980) 217;
(b) T. Tonn, C. Goebel, M. Wilhelm, E. Gleichmann, British J. Rheum. 33 (1994) 724.
[8] A. Grohmann, H. Schmidbaur, Comprehensive Organometallic Chemistry II, Elsevier, UK, 1995.
[9] J.P. Fackler Jr., Inorg. Chem. 41 (2002) 6959.
[10] H.E. Abdou, A.A. Mohamed, J.P. Fackler Jr., J. Chin. Chem. Soc. 54 (2007) 1107.
[11] J.M. Forward, J.P. Fackler, Jr., Z. Assefa, in: D.M. Roundhill, J.P. Fackler, Jr. (Eds.), Optoelectronic Properties of Inorganic Compounds, Plenum, N.Y., (1999).
[12] (a) A. Burini, A.A. Mohamed, J.P. Fackler Jr., Comments Inorg. Chem. 24 (2003) 253;
(b) A.A. Mohamed, A.E. Bruce, M.R.M. Bruce, The Chemistry of Organic Derivatives of Gold and Silver, John Wiley & Sons Ltd., 1999 (Chapter 9).
[13] W.E. Van Zyl, J.M. Lopez-De-Luzuriaga, J.P. Fackler Jr., R.J. Staples, Can. J. Chem. 79 (2001) 896.
[14] A.A. Mohamed, A.P. Mayer, H.E. Abdou, M.D. Irwin, L.M. Pérez, J.P. Fackler Jr., Inorg. Chem. 46 (2007) 11165.
[15] R.K. Castellano, F. Diederich, E.A. Meyer, Angew. Chem. Int. Ed. 42 (2003) 1210.
[16] U. Obst, D.W. Banner, L. Weber, F. Diederich, Chem. Biol. 4 (1997) 287.
[17] P.V. Bernhardt, P.C. Sharpe, Inorg. Chem. 39 (2000) 4123.
[18] C.F. Shaw III, Chem. Rev. 99 (1999) 2589.
[19] M.B. Taylor, G.D. Barrera, N.L. Allan, T.H.K. Barron, W.C. Mackrodt, E.Y. Fung, M.M. Olmstead, J.C. Vickery, A.L. Balch, Coord. Chem. Rev. 171 (1998) 151.
[20] A. Burini, J.P. Fackler Jr., R. Galassi, B.R. Pietroni, R.J. Staples, Chem Commun. (1998) 95.
[21] A. Burini, R. Bravi, J.P. Fackler Jr., R. Galassi, T.A. Grant, M.A. Omary, B.R. Pietroni, R.J. Staples, Inorg. Chem. 39 (2000) 3158.
[22] W.E. van Zyl, J.M. Lopez de Luzuriaga, J.P. Fackler Jr., J. Mol. Struct. 516 (2000) 99.
[23] J.P. Fackler, Jr., unpublished results.
[24] A. Burini, J.P. Fackler Jr., R. Galassi, T.A. Grant, M.A. Rawashdeh-Omary, B.R. Pietroni, R.J. Staples, J. Am. Chem. Soc. 122 (2000) 11264.
[25] A. Burini, J.P. Fackler Jr., R. Galassi, A. Macchioni, M.A. Omary, M.A. Rawashdeh-Omary, B.R. Pietroni, S. Sabatini, C. Zuccaccia, J. Am. Chem. Soc. 124 (2002) 4570.
[26] M.A. Rawashdeh-Omary, M.A. Omary, J.P. Fackler Jr., A. Burini, R. Galassi, B. Bianca, R. Pietroni, J. Am. Chem. Soc. 123 (2001) 9689.
[27] D. O'Hagan, H.S. Rzepa, Chem. Commun. (1997) 645.
[28] J.T. Welch, Tetrahedron 43 (1987) 3123.
[29] M.M. Olmstead, F. Jiang, S. Attar, A.L. Balch, J. Am. Chem. Soc. 123 (2001) 3260.
[30] M.A. Omary, M. Rawashdeh-Omary, M.W.A. Gonser, O. Elbjeirami, H.V.K. Diyabalanage, C.S.P. Gamage, H.V.R. Dias, Inorg. Chem. 44 (2005) 8200.
[31] R.M. Dávila, A. Elduque, T. Grant, R.J. Staples, J.P. Fackler Jr., Inorg. Chem. 32 (1993) 1749.
[32] S. Wang, J.P. Fackler Jr., Inorg. Chem. 29 (1990) 4404.
[33] J. Chen, A.A. Mohamed, H.E. Abdou, J.A. Krause Bauer, J.P. Fackler Jr., A.E. Bruce, M.R.M. Bruce, Chem. Commun. (2005) 1575.
[34] B. Chiari, O. Piovesana, T. Tarantelli, P.F. Zanazzi, Inorg. Chem. 24 (1985) 366.
[35] J.H. Mendez, A.S. Perez, M.D. Zamarreno, J. Pharm. Sci. 78 (1989) 589.
[36] (a) T. Jiang, G. Wei, C. Turmel, A.E. Bruce, M.R.M. Bruce, Metal Based Drugs 1 (1994) 419;
(b) J. Chen, T. Jiang, G. Wei, A.A. Mohamed, C. Homrighausen, J.A. Krause Bauer, A.E. Bruce, M.R.M. Bruce, J. Am. Chem. Soc. 121 (1999) 9225;
(c) A.A. Mohamed, M.R.M. Bruce, A.E. Bruce, Metal Based Drugs 6 (1999) 233;
(d) A.A. Mohamed, J. Chen, J.A. Krause Bauer, D.T. Hill, A.E. Bruce, M.R.M. Bruce, Inorg. Chem. 42 (2003) 2203.
[37] C.F. Shaw III, S. Schraa, E. Gleichmann, Y.P. Grover, L. Dunemann, A. Jagarlamudi, Metal Based Drugs 1 (1994) 351.
[38] R. Narayanaswamy, M.A. Young, E. Parkhurst, M. Ouellette, M.E. Kerr, D.M. Ho, R.C. Elder, A.E. Bruce, M.R.M. Bruce, Inorg. Chem. 32 (1993) 2506.
[39] W.B. Jones, J. Yuan, R. Narayanaswamy, M.A. Young, R.C. Elder, A.E. Bruce, M.R.M. Bruce, Inorg. Chem. 34 (1995) 1996.
[40] L.G. Beauvais, M.P. Shores, J.R. Long, J. Am. Chem. Soc. 122 (2000) 2763.
[41] Q. Chang, Z. Murtaza, J.R. Lakowicz, G. Rao, Anal. Chim. Acta 350 (1997) 97.
[42] C.J. Murphy, W.D. Drane, Proc. SPIE Int. Soc. Opt. Eng. 2388 (1995) 266.
[43] M.E.G. Poss, N.E. Katz, L.M. Baraldo, D.D. Polonuer, C.G. Colombano, J.A. Olabe, Inorg. Chem. 34 (1995) 1830.
[44] E. Waldhör, J. Poppe, W. Kaim, Inorg. Chem. 34 (1995) 3093.
[45] A.C. Samuels, M.K. DeArmond, Inorg. Chem. 34 (1995) 5548.
[46] C.J. Timpson, C.A. Bignozzi, B.P. Sullivan, E.M. Kober, T.J. Meyer, J. Phys. Chem. 100 (1996) 2915.
[47] M.A. Rampi, M.T. Indelli, F. Scandola, F. Pina, A.J. Parola, Inorg. Chem. 35 (1996) 3355.
[48] J.K. Evju, K.R. Mann, Chem. Mater 11 (1999) 1425.
[49] E.A. Baldauff, J.M. Buriak, Chem. Commun. (2004) 2028.
[50] W. Lu, M.C.W. Chan, N. Zhu, C.M. Che, Z. He, K.Y. Wong, Chem. Eur. J. 9 (2003) 6155.
[51] S.M. Drew, D.E. Janzen, C.E. Buss, D.I. MacEwan, K.M. Dublin, K.R. Mann, J. Am. Chem. Soc. 123 (2001) 8414.
[52] C.E. Buss, K.R. Mann, J. Am. Chem. Soc. 124 (2002) 1031.
[53] J.W. Grate, L.K. Moore, D.E. Janzen, D.J. Veltkamp, S. Kaganove, S.M. Drew, K.R. Mann, Chem. Mater. 14 (2002) 1058.
[54] C.L. Exstrom, J.R. Sowa Jr., C.A. Daws, D. Janzen, K.R. Mann, Chem. Mater. 7 (1995) 15.
[55] C.A. Daws, C.L. Exstrom, J.R. Sowa Jr., K.R. Mann, Chem. Mater. 9 (1997) 363.
[56] C.E. Buss, C.E. Anderson, M.K. Pomije, C.M. Lutz, D. Britton, K.R. Mann, J. Am. Chem. Soc. 120 (1998) 7783.
[57] C.L. Exstrom, M.K. Pomije, K.R. Mann, Chem. Mater. 10 (1998) 942.
[58] H.V.R. Dias, H.V.K. Diyabalanage, M.A. Rawashdeh-Omary, M.A. Franzman, M.A. Omary, J. Am. Chem. Soc. 125 (2003) 12072.
[59] E. Cariati, X. Bu, P.C. Ford, Chem. Mater. 12 (2000) 3385.
[60] E.J. Fernández, J.M. López-de-Luzuriaga, M. Monge, M.E. Olmos, J. Pérez, A. Laguna, A.A. Mohamed, J.P. Fackler Jr., J. Am. Chem. Soc. 125 (2003) 2022.
[61] E.J. Fernández, J.M. López-de-Luzuriaga, M. Monge, M. Montiel, M.E. Olmos, J. Pérez, A. Laguna, F. Mendizabal, A.A. Mohamed, J.P. Fackler Jr., Inorg. Chem. 43 (2004) 3573.
[62] E.J. Fernández, A. Laguna, J.M. López-de-Luzuriaga, M. Montiel, M.E. Olmos, J. Pérez, Organometallics 25 (2006) 1689.
[63] J. Lefebvre, R.J. Batchelor, D.B. Leznoff, J. Am. Chem. Soc. 126 (2006) 16117.
[64] R. Usón, A. Laguna, M. Laguna, P.G. Jones, G.M. Sheldrick, Chem. Commun. (1981) 1097.
[65] R. Usón, A. Laguna, M. Laguna, B.R. Manzano, P.G. Jones, G.M. Sheldrick, J. Chem. Soc. Dalton Trans. (1984) 285.
[66] E.J. Fernández, A. Laguna, J.M. López-de-Luzuriaga, M. Monge, Spanish Patent P200001391, 2003.
[67] E.J. Fernández, J.M. López-de-Luzuriaga, M. Monge, M.E. Olmos, R.C. Puelles, A. Laguna, A.A. Mohamed, J.P. Fackler Jr., Inorg. Chem. 47 (2008) 8069.