

# Supra-molecular synthons based on gold... $\pi$ (arene) interactions

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## Introduction

Colloquially described as modern day “Gold Rush”, use of gold in catalysis is a research area attracting intensive and increasing attention. This is evidenced, for example, by nearly exponential increase in publications appearing in the past decade in the field of homogeneous catalysis with gold [1]. Molecular gold or in the form of nanoparticles/thin films prove to be efficient catalysts offering benefits over other transition metals, properties that relate, in no small part, to electrophilic nature of gold which, in turn, is correlated with reduction in energy of the  $6s^2$  atomic orbital, owing to relativistic effects [2]. Such is the propensity for molecular gold to associate with alkynes, in particular, the term alkynophilicity is often used to describe this property. Other advantages of gold often relate to gold not being likely to be involved in oxidative addition or reductive elimination reactions unlike square planar palladium(II), for example. Not surprisingly, there are many recent and thorough reviews of gold in the catalysis literature e.g., [3–7].

Given that gold is a carbophilic Lewis acid, the question then arises: does this property influence the type of supra-molecular association formed by gold in its crystal structures?

Gold holds a special fascination for crystal engineers owing to its propensity to form Au...Au or aurophilic interactions [8, 9]. Not only do Au...Au interactions lead to fascinating supra-molecular architectures, the fact that the energy of stabilisation afforded to their crystal structures can match that provided by conventional hydrogen bonding [10] led to competition studies between these synthons [11–14]. By contrast, considerably less attention has been directed to ascertaining formation of Au... $\pi$ (arene) interactions [15]; analogous interactions are well established in the supra-molecular chemistry of the main group elements [16–18]. Herein, an overview of Au... $\pi$ (arene) interactions, formed both intra- and inter-molecularly, operating in the crystal structures of molecular gold compounds is given, and their presence in macro-molecular structures is also discussed, along with future prospects for this type of interaction.

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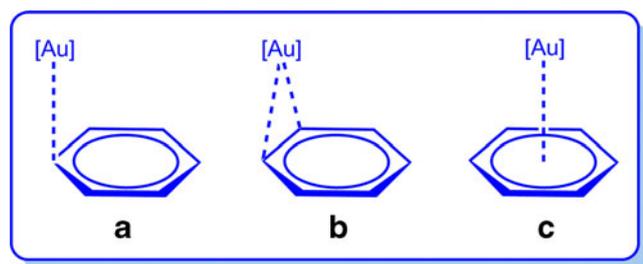
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## Background

Before embarking on a survey of Au... $\pi$ (arene) interactions, some general remarks are in order. These will address search protocols, nature and energy of this type of interaction as well as their prevalence. Au... $\pi$ (arene) interactions may be classified in an analogous fashion as for cation (or anion)... $\pi$ (arene) interactions [19, 20] as illustrated in Fig. 1.

When a gold atom approaches an arene ring, it can do so from various directions. In cases where the gold atom is directed exclusively towards a single carbon atom, the interaction is described as *localised*. When directed to one



**Fig. 1** **a** Localised, **b** semi-localised and **c** de-localised Au... $\pi$ (arene) interactions

bond within a ring, the term *semi-localised* is applied. Finally, if the gold atom is (approximately) equally disposed from all six carbon atoms of the arene ring, the term employed is *de-localised*. Herein, the discussion is largely focussed upon de-localised Au... $\pi$ (arene) interactions.

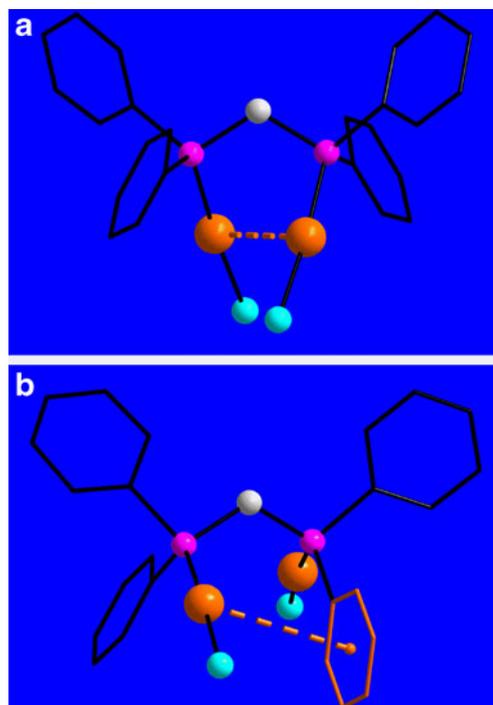
Au... $\pi$ (arene) interactions were identified from a survey of the Cambridge Structural Database [21], whereby a de-localised Au... $\pi$  interaction was considered significant if the distance between the gold atom and the ring centroid was less than 4.0 Å, based on van der Waals radii considerations [15], and the angle of inclination between the vector between the gold atom and the ring centroid of the arene ring, and the vector normal to the ring was less than 20° [15]. Progressive relaxation of the angle restraint will indicate formation of semi-localised and localised Au... $\pi$  interactions. Relative prevalence of these interactions can be estimated by a search of all crystal structures having gold and at least one phenyl ring, i.e., 3,636 structures. There are approximately 60, 360 and 100 examples of de-localised, semi-localised and localised Au... $\pi$  interactions, respectively. As yet, no detailed analysis of semi-localised and localised Au... $\pi$  interactions is available but in this context, it is salutary to consider emerging discoveries on rare Au... $\pi$ (alkene) interactions [22, 23], an example of which is described below. There has been little detailed theoretical analysis of the energy associated with intermolecular Au... $\pi$  interactions but the aforementioned Au... $\pi$ (alkene) interactions provide a benchmark. Thus, based on variable temperature Nuclear Magnetic Resonance (NMR) spectroscopy, the energy of interaction between gold and an alkene is approximately 10 kcal mol<sup>-1</sup> [22], a value that must be considered an upper estimate for Au... $\pi$ (alkene) interactions described herein.

### Intra-molecular Au... $\pi$ (arene) interactions

Intra-molecular Au... $\pi$ (arene) interactions in molecular gold structures are comparatively rare and have not attracted significant systematic study with relatively few notable exceptions.

However, they can and do exist with polymorphic structures of bis(diphenylphosphino)methane-di[chloridogold(I)], (Ph<sub>2</sub>PCH<sub>2</sub>PPh<sub>2</sub>)(AuCl)<sub>2</sub>, a good entrée to this topic. In initial X-ray crystal structure determination of (Ph<sub>2</sub>PCH<sub>2</sub>PPh<sub>2</sub>)(AuCl)<sub>2</sub> reported by Schmidbaur et al. [24], a distorted A-frame was found that was stabilised by an intra-molecular Au...Au interaction (Fig. 2a). A subsequent study by Healy [25] revealed a second polymorph, where a rearrangement of the original structure had occurred that allowed for the formation of an intra-molecular Au... $\pi$ (arene) interaction at the expense of the Au...Au contact; no intermolecular Au...Au interaction was formed in the crystal structure. Such structural diversity suggests that the energy of stabilisation imparted by Au...Au and Au... $\pi$ (arene) interactions can be of the same order of magnitude.

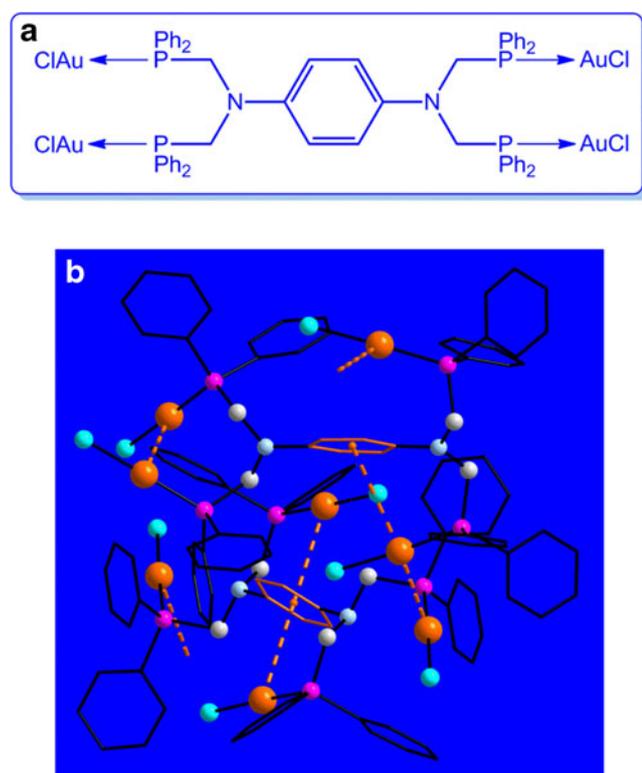
This latter comment is neatly borne out in a series of catalytically active phosphane-gold(I) chlorido structures designed to feature intra-molecular Au... $\pi$ (arene) interactions to enhance stabilisation of intermediate species formed during the catalytic cycle to obviate the need for silver-based co-catalysts [26]. In one of these tetra-nuclear structures



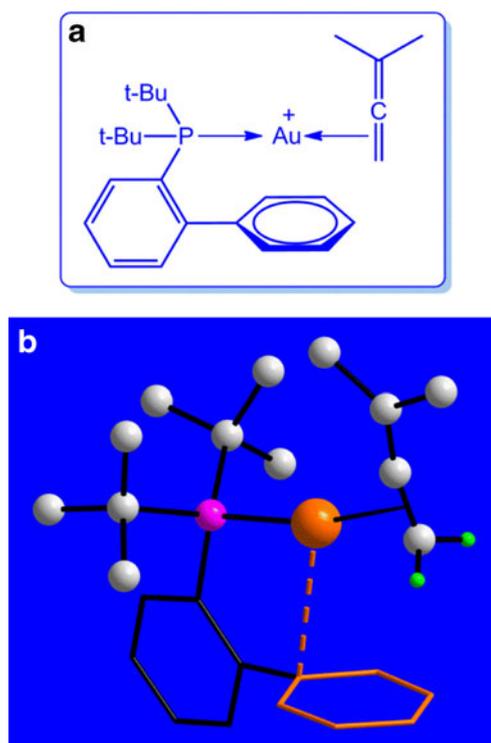
**Fig. 2** Molecular structures of bis(diphenylphosphino)methane-di[chloridogold(I)], (Ph<sub>2</sub>PCH<sub>2</sub>PPh<sub>2</sub>)(AuCl)<sub>2</sub>: **a** monoclinic polymorph featuring an intra-molecular Au...Au interaction (3.34 Å) and **b** monoclinic polymorph with an intra-molecular Au... $\pi$ (arene) interaction (3.58 Å). Colour codes for this and subsequent figures: orange, gold any halide, cyan phosphorous, pink carbon, grey, gold and black hexagons aryl rings. Hydrogen atoms have been omitted for clarity. Rings participating in Au... $\pi$ (arene) interactions are highlighted in gold. Both Au... $\pi$ (arene) and Au...Au interactions are shown as gold dashed lines

(see chemical structure in Fig. 3a), with one and a half molecules in the crystallographic asymmetric unit, i.e., six independent gold atoms, there are both Au... $\pi$ (arene) and Au...Au interactions. As seen from Fig. 3b, one arene ring, located about the centre of inversion, bridges two gold atoms ( $d=3.53$  Å) and a second independent gold atom interacts with a ring ( $d=3.73$  Å) as well as with another gold atom via a Au...Au contact ( $d=3.36$  Å). The remaining gold atoms form Au...Au interactions exclusively ( $d=3.10$  and  $3.51$  Å). In this way, molecules self-assemble into a supra-molecular chain.

Following a similar theme, cationic phosphanegold  $\pi$ -allene compounds, e.g., Fig. 4a, have been developed [27], as such species are crucial in many catalytic applications of gold [28]. X-ray crystal structure determination shows the  $\pi$ -allene ligand to be coordinated at the least congested side (Fig. 4b). An intra-molecular Au... $\pi$ (arene) interaction is also found, showing that such interactions are capable of stabilising cationic gold  $\pi$ -allene species. In the present case, the Au... $\pi$ (arene) interaction is best described as being localised (Fig. 1a) as the gold atom is  $3.00$  Å from the ipso-carbon atom,



**Fig. 3** **a** Chemical structure of  $\{(\text{Ph}_2\text{PCH}_2)_2\text{NC}_6\text{H}_4\text{N}(\text{CH}_2\text{PPh}_2)_2\}(\text{AuCl})_4$ ; only interacting species are represented in this and subsequent chemical structures with innocent counter ions and solvent molecules omitted for clarity. **b** Portion of the supra-molecular chain showing the co-existence of Au...Au and Au... $\pi$ (arene) interactions. Additional colour code: light blue nitrogen

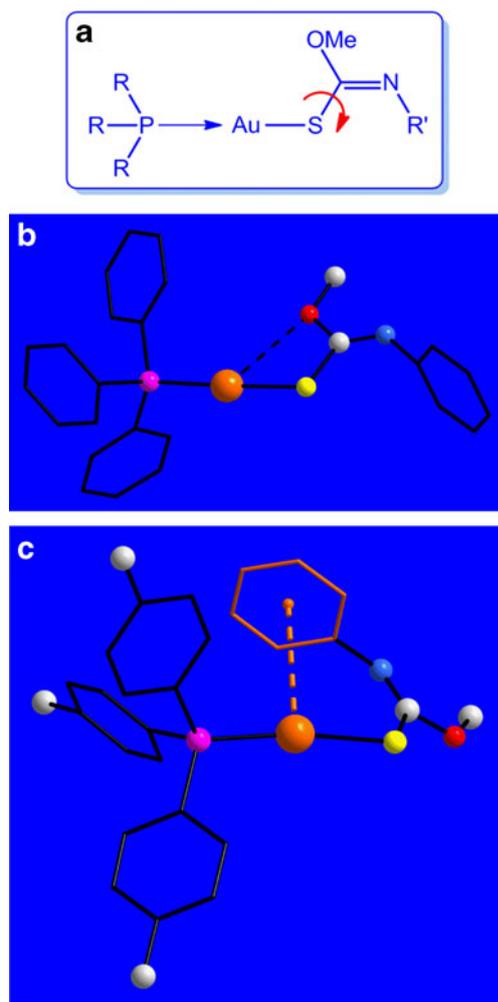


**Fig. 4** **a** Chemical structure of the cation in  $[(t\text{-Bu}_2\text{PC}_6\text{H}_4\text{Ph})\text{Au}(\text{H}_2\text{C}=\text{C}=\text{CMe}_2)][\text{SbF}_6]\cdot 0.5\text{CH}_2\text{Cl}_2$ . **b** Molecular structure showing the localised Au... $\pi$ (arene) interaction. Additional colour code: green hydrogen

the next closest distances ( $3.21$  and  $3.23$  Å) are formed with the carbon atoms on either side of the ipso-carbon atom, and the Au...C distances increase to a maximum of  $3.99$  Å.

Similar intra-molecular Au... $\pi$ (arene) interactions have been noted previously in other systematic investigations, for example, in cationic phosphanegold compounds of simple  $\eta^2$ -bound arenes [29] as well as in neutral acyclic diaminocarbene goldchlorido structures [30]. Attention is now directed to deliberately tailoring of ring-bound substituents to promote the formation of intra-molecular Au... $\pi$ (arene) interactions.

Phosphanegold thiolate molecules of the general formula:  $\text{R}_3\text{PAu}[\text{SC}(\text{OMe})=\text{NR}']$ , where R, R'=aryl and alkyl (Fig. 5a), exhibit linear P–Au–S coordination geometries and in the overwhelming majority of cases, feature intra-molecular Au...O interactions [31]. However, it proved possible to fine tune the electronic structures of the substituents in the arene rings to promote the formation of Au... $\pi$ (arene) interactions. Figure 5b displays the molecular structure of  $\text{Ph}_3\text{PAu}[\text{SC}(\text{OMe})=\text{NPh}]$  [32], where the conventional Au...O interaction is found ( $3.05$  Å). When the phosphorous-bound phenyl rings were substituted with comparatively electron-rich p-tolyl rings to give  $(p\text{-tol})_3\text{PAu}[\text{SC}(\text{OMe})=\text{NPh}]$ , the gold



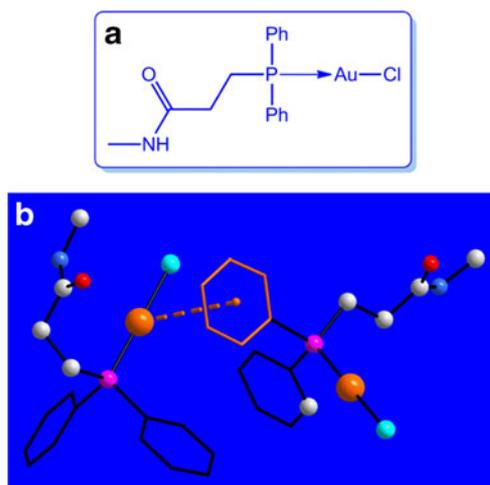
**Fig. 5** **a** Generic chemical structure of  $R_3PAu[SC(OMe)=NR']$ , where R, R'=aryl and alkyl. The red arrow indicates flexibility in the orientation of the thiolate ligand that is usually orientated so that the oxygen atom is in close proximity of the gold atom. With careful tailoring of R and R', an orientation can be promoted whereby the aryl ring is orientated over the gold atom, held in place by a  $Au...π(arene)$  interaction. **b** Molecular structure of  $Ph_3PAu[SC(OMe)=NPh]$  featuring an  $Au...O$  interaction (3.05 Å). **c** Molecular structure of  $(p\text{-tol})_3PAu[SC(OMe)=NPh]$  featuring a  $Au...π(arene)$  interaction (3.36 Å). Additional colour codes: yellow sulphur, red oxygen

atom was activated and a  $Au...π(arene)$  interaction (3.36 Å) was formed instead (Fig. 5c). This was the general observation for tolyl-phosphane derivatives except when steric hindrance proved decisive. Altering the electronic structure of the thiolate arene ring also proved determinant. Thus, the addition of highly electronegative nitro groups to the thiolate-arene ring in the tolyl-phosphane derivative,  $(p\text{-tol})_3PAu[SC(OMe)=NC_6H_4NO_2\text{-}p]$ , was sufficient to restore the status quo, i.e.,  $Au...O$  interactions were formed. Interestingly, in this instance,  $Au...Au$  interactions (3.09 Å) were formed but not in any other members of the series [32].

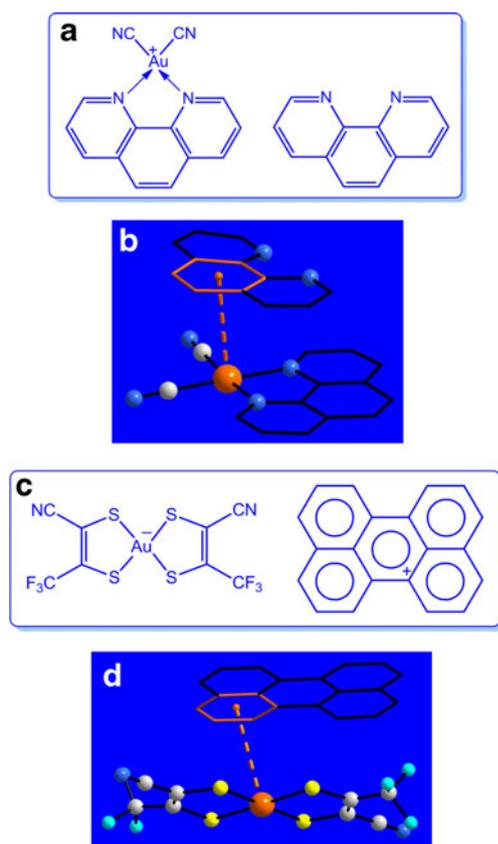
## Intermolecular $Au...π(arene)$ interactions

As mentioned in the “Introduction”, intermolecular  $Au...π(arene)$  interactions are known to provide stability to the crystal structures of molecular gold-containing compounds [15]. Herein, a brief survey of common supra-molecular motifs sustained by these interactions will be presented. The simplest motif is zero-dimensional and manifests in three different forms. The first of these is a two-molecule aggregate sustained by a single  $Au...π(arene)$  interaction (3.92 Å) between the two crystallographically independent molecules comprising the asymmetric unit, such as in the crystal structure of  $[MeNC(=O)CH_2CH_2]Ph_2PAuCl$  [33] (Fig. 6a and b). From the chemical composition, one notes the presence of an amide functionality that might be expected to form directional hydrogen bonding interactions. Indeed, these form to stabilise a supra-molecular chain. The  $Au...π(arene)$  interactions operate in a different dimension and, in fact, serve to link these chains into a supra-molecular array. This example emphasises that the  $Au...π(arene)$  interactions presented herein operate in isolation of other supra-molecular contacts and stabilise aggregation patterns in a given dimension independently. Whilst this example again features gold(I), gold(III) centres may also participate in such interactions as the following two examples demonstrate.

Two components of a gold(III) salt [34] interact via a single point of contact (3.48 Å) (Fig. 7a), i.e., cationic  $[(phen)Au(CN)_2]^+$ , with the central ring of a neutral phen molecule, as shown in Fig. 7b; phen is 1,10-phenanthroline. Anionic gold(III) species are also known to form  $Au...π(arene)$  interactions as evidenced in the structure comprising tris(peryleneum) *trans*-bis[(2-(trifluoromethyl)acrylonitrile-1,2-dithiolato)gold(III)] [35] (Fig. 7c), where a single point of



**Fig. 6** **a** Chemical structure of  $[MeNC(=O)CH_2CH_2]Ph_2PAuCl$ . **b** The single  $Au...π(arene)$  interaction between the two independent molecules comprising the asymmetric unit

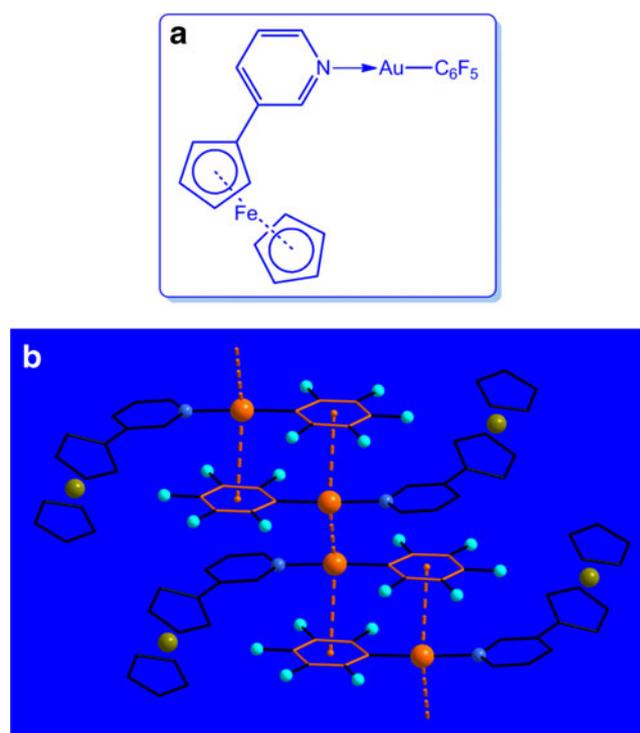


**Fig. 7** **a** Chemical structures of cationic dicyano(1,10-phenanthroline)gold(III) and 1,10-phenanthroline. **b** Molecular structure showing a Au... $\pi$ (arene) interaction occurring between a cationic gold(III) centre and a neutral molecule. **c** Chemical structures of tris(perylene) *trans*-bis[(2-(trifluoromethyl)acrylonitrile-1,2-dithiolato)gold(III)]. **d** Molecular structure showing a Au... $\pi$ (arene) interaction occurring between an anionic gold(III) centre and a cationic molecule

contact (3.78 Å) with a peripheral ring connects the ions into a zero-dimensional aggregate (Fig. 7d).

Zero-dimensional aggregation is also found in the structure of (3-ferrocenylpyridine)pentafluorophenylgold(I) [36] (Fig. 8a). Here, centrosymmetric molecules associate into dimers via two Au... $\pi$ (arene) interactions (3.51 Å) (Fig. 8b). Further aggregation between these molecules via Au...Au interactions (3.30 Å) occurs so that a supra-molecular chain ensues. Thus, this is another example exhibiting the cooperative nature of Au... $\pi$ (arene) and Au...Au interactions.

One-dimensional supra-molecular chains sustained solely by Au... $\pi$ (arene) interactions are also known. An example of a chain sustained by an average of one Au... $\pi$ (arene) interaction (3.96 Å) per molecule is found in the crystal structure of Ph<sub>3</sub>AsAuCl [37]. Whilst this chain has a helical topology (Fig. 9a), chains with linear and zigzag topology are also known [15]. Chains may also be consolidated by an average of two Au... $\pi$ (arene) interactions per molecule as found in the structure of bis[(2,6-xylylisocyno)thiocyanatogold(I)] [38]

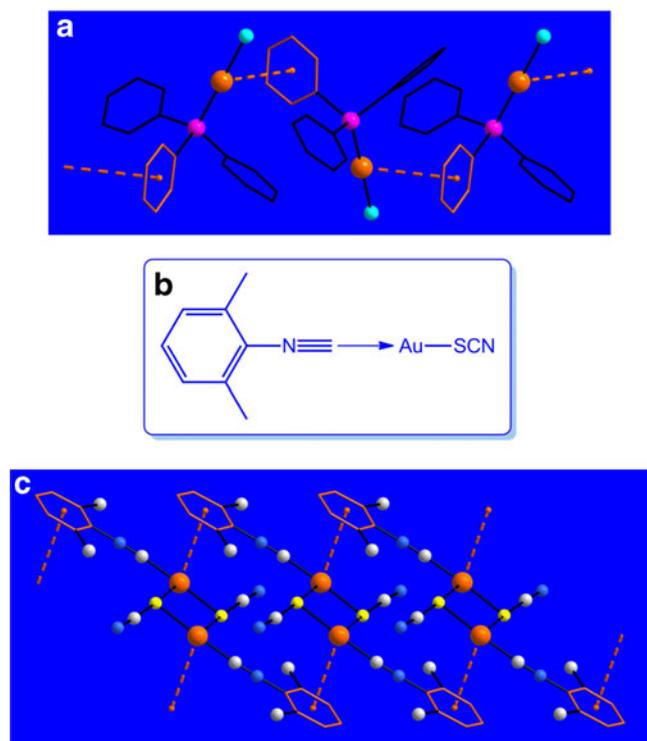


**Fig. 8** **a** Chemical structure of (3-ferrocenylpyridine)pentafluorophenylgold(I). **b** Dimeric aggregate sustained by two Au... $\pi$ (arene) interactions that, in turn, are linked into a supra-molecular chain via Au...Au interactions. Additional colour code: *olive green* iron

(Fig. 9b). Molecules are centrosymmetric featuring Au<sub>2</sub>S<sub>2</sub> cores arising from secondary Au...S interactions and assemble into a supra-molecular chain with a linear topology via an average of two Au... $\pi$ (arene) interactions (3.56 Å) per molecule.

Whilst, thus far, the focus has been upon Au... $\pi$ (arene) interactions, the discussion would be incomplete without a brief discussion of complementary Au... $\pi$ (aromatic) interactions [39] where the ring carries at least one non-carbon atom, i.e., the  $\pi$ -system is hetero-aromatic. Cationic bis(4-phenylpyridine)gold(I) [40] molecules (Fig. 10a), assemble into a linear supra-molecular chain sustained by an average of two Au... $\pi$ (pyridyl) interactions (3.49 Å) per molecule (Fig. 10b). In a sulphur-containing analogue, bromido[1-(4,6-dimethylthiine-2-yl)propene-2-thiolato]gold(I) [41] (Fig. 10c), centro-symmetric aggregates that are sustained by two Au... $\pi$ (thiine-2-yl) interactions (3.65 Å) (Fig. 10d) are found.

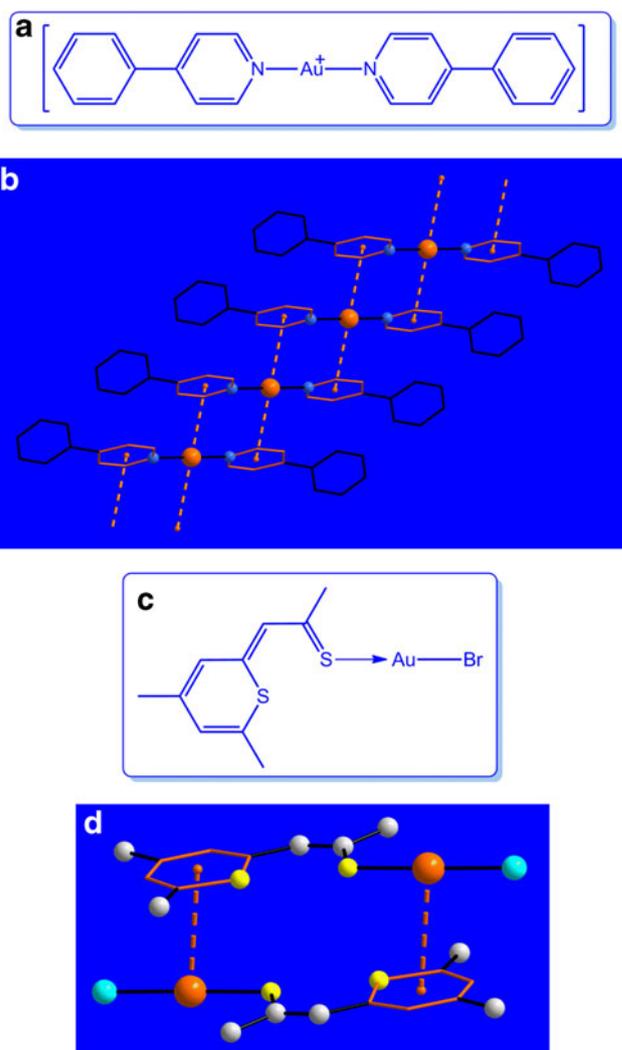
Finally, it is noteworthy that the chelate ring does not necessarily have to be “organic” in nature but can be a chelate ring. Metallo-aromatic character has been ascribed to chelate rings owing to their significant  $\pi$ -character [42] and these  $\pi$ -systems are increasingly becoming recognised as participating in C–H... $\pi$  and, indeed,  $\pi$ ... $\pi$  interactions [43–46]. In this context, the crystal structure containing the chlorido(2-pyridineformamide thiosemicarbazonato)gold(III)



**Fig. 9** **a** Helical supra-molecular chain sustained by an average of one Au... $\pi$ (arene) interaction per molecule in the structure of  $\text{Ph}_3\text{AsAuCl}$ . **b** Chemical structure of bis[(2,6-xylylisocyno)thiocyanatogold(I)]. **c** Supra-molecular chain with a linear topology sustained by an average of two Au... $\pi$ (arene) interactions per molecule. Additional colour code: pink arsenic

cation [47] (Fig. 11a) is of particular interest. The crystallographic asymmetric unit comprise two independent molecules. The first of these self-assembles over a centre of inversion via Au... $\pi$ (pyridyl) interactions (3.48 Å) to form a dimeric aggregate (Fig. 11b). The second independent molecule also self-assembles but about a twofold axis of symmetry and by Au...Au (3.56 Å) as well as Au... $\pi$ (chelate) (3.64 Å) interactions (Fig. 11c). Whilst the Au... $\pi$ (chelate) interactions are not operating in isolation, this aggregate demonstrates the potential of such interactions in the supra-molecular chemistry of gold compounds.

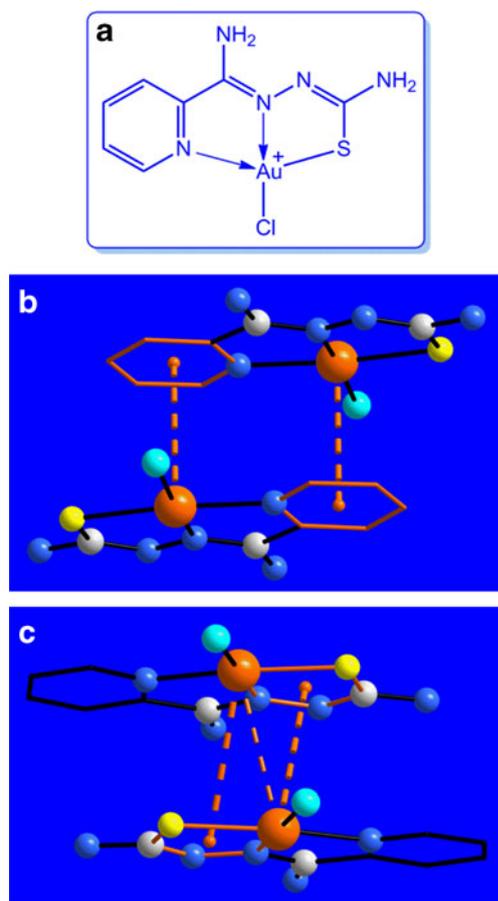
From the above, it is evident that de-localised Au... $\pi$ (arene) and analogous interactions can play a significant role in stabilising the crystal packing of gold-containing molecules. The shortest Au... $\pi$ (arene) contact distance is 3.43 Å and the contacts extend out to 4.0 Å, i.e., the search limit (see “Background”). The supra-molecular aggregates that are stabilised by these interactions are either zero-dimensional, comprising similar or dissimilar pairs of molecules, or one-dimensional, supra-molecular chains of varying topology. It has been demonstrated that Au... $\pi$ (arene) interactions occur in both neutral and charged gold(I)- and gold(III)-containing molecules and it has been estimated that when they potentially can form are found in approximately 2 % of their structures. To a



**Fig. 10** **a** Chemical structure of the cation in [bis(4-phenylpyridine)gold(I)][PF<sub>6</sub>]. **b** Supra-molecular chain sustained by an average of two Au... $\pi$ (pyridyl) interactions per molecule. **c** Chemical structure of bromido[1-(4,6-dimethylthiine-2-yl)propene-2-thiolato]gold(I). **d** Centro-symmetric dimeric aggregate sustained by two Au... $\pi$ (thiine-2-yl) interactions

first approximation, the nature of the interaction can be described as electron donation from the aromatic ring to the gold atom, akin to the C–H... $\pi$ (arene) interactions and in accord with the isolobal analogy between gold and hydrogen [48]. This being the case, it might be anticipated that increasing the electron density of the aromatic ring, say, by the incorporation of a nitrogen atom, should enhance the propensity of forming such interactions and their strength. Whilst correlating weak intermolecular interactions with distances is unwise [39, 49], it is interesting to note that the likelihood of forming Au... $\pi$ (pyridyl) over Au... $\pi$ (arene) interactions is at least double [39].

Having established the importance of Au... $\pi$ (arene) interactions, occurring either intra- or inter-molecularly for molecular gold-containing compounds, for completeness it was

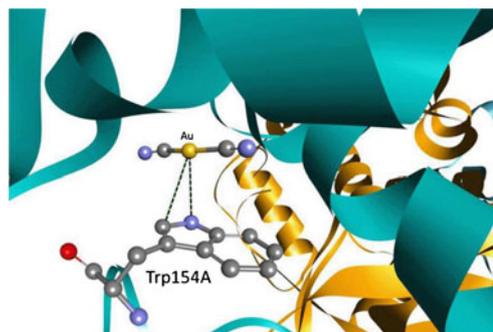


**Fig. 11** **a** Chemical structure of the cation in [chlorido(2-pyridineformamide thiosemicarbazonato)gold(III)]Cl·MeOH. **b** Supra-molecular dimer sustained by two Au...π(pyridyl) interactions. **c** Dimeric aggregate (twofold symmetry) sustained by Au...Au and two Au...π(chelate) interactions

thought of interest to examine the Protein Data Bank [50] for the presence of Au...π(aromatic) interactions in macro-molecular structures.

### Au...π(aromatic) interactions in macro-molecular structures

Gold(I) compounds are well established to present efficacious activity for treatment of rheumatoid arthritis [51]. Besides this pharmacological role, gold(I), and indeed gold(III), compounds continue to be developed as potential therapeutic agents for a range of ailments such as tropical diseases, viruses and, especially, cancer [52–54]. This being the case, it is not surprising that the interaction of gold compounds with biological macro-molecules attracts attention. Moreover, gold(I), e.g., AuCl, AuCN and  $[\text{Au}(\text{CN})_2]^-$ , and gold(III), e.g.,  $\text{AuCl}_3$ , compounds, are sometimes employed in macro-molecular crystallography in order to provide suitable species for the solution of the structure

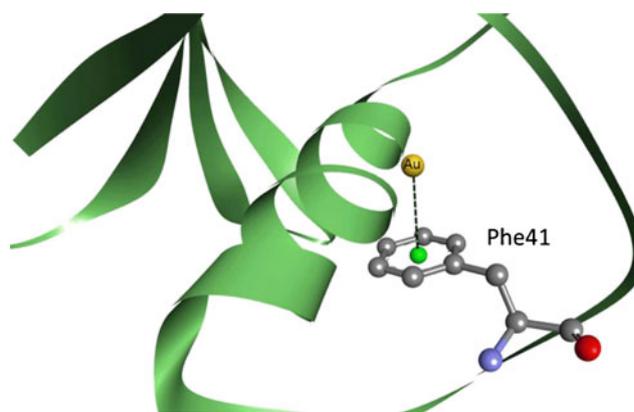


**Fig. 12** An example of a semi-localised Au...π interaction occurring between the gold atom of a  $[\text{Au}(\text{CN})_2]^-$  anion with the C–N bond of a pyrrole ring in the crystal structure of beta-lactamase

by exploiting the anomalous dispersion characteristics of gold.

A search of the Protein Data Bank [50] revealed 55 macro-molecular structures containing gold and in these, a total of 285 independent gold species were found. Gold was found in a sole example of a RNA molecule and in three examples of a protein/DNA complex with the remaining structures being of proteins. Gold was usually present as a cation, i.e.,  $\text{Au}^+$  or  $\text{Au}^{3+}$ , but there were six examples of gold being present as a dicyanoanion, i.e.,  $[\text{Au}(\text{CN})_2]^-$ . Manual sorting revealed that gold forms Au...π(arene) and related interactions in 26 of these structures. Semi-localised Au...π interactions were found in 16 examples with a representative example illustrated in Fig. 12, where the gold atom of a  $[\text{Au}(\text{CN})_2]^-$  anion interacts with the C–N bond of the pyrrole ring of a tryptophan residue ( $\text{Au}\dots\text{C}$ ,  $N=3.30$  and  $3.14$  Å) in the crystal structure of beta-lactamase [55].

The remaining ten Au...π interactions identified in macro-molecular crystal structures are de-localised Au...π interactions with an example shown in Fig. 13 of a  $\text{Au}^+$  cation interacting with a phenyl ring of a phenylalanine residue ( $3.37$  Å) in the crystal structure of *Arabidopsis*



**Fig. 13** An example of a de-localised Au...π interaction occurring between the  $\text{Au}^+$  cation and the phenyl ring of a phenylalanine residue in the crystal structure of a protein known to be involved in transcription regulation

abscisic acid-responsive NAC (NAC is an acronym derived from the names of the three genes first described as containing the domain, namely NAM (no apical meristem), ATAF1,2 and CUC2 (cup-shaped cotyledon)) protein, known to be involved in transcription regulation [56].

## Conclusion

From the foregoing, it is evident that gold is capable of forming intra- and inter-molecular Au... $\pi$  interactions with a variety of  $\pi$ -systems, both in molecular and macro-molecular species. Supra-molecular synthons based on Au... $\pi$  interactions may be zero- or one-dimensional. In summary, a complete analysis of a molecular and crystal structure of a gold-containing species needs to take into account an analysis for putative Au... $\pi$  interactions.

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