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Research paper

Synthetic strategies of gold(I)-selenolates from *ortho*-substituted diaryl diselenides *via* selenol and selenenyl sulfide intermediates

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ABSTRACT

In the present study we describe the synthetic strategies to gold(I)-selenolate complexes by the reaction of *ortho*-substituted diaryl diselenides and electrophilic anti-arthritic gold(I)-compounds in the presence of thiol such as PhSH. Diselenides react with thiol to generate a mixture of selenol and selenenyl sulfide. While selenols react with electrophilic Au(I) compounds to form gold(I)-selenolate complexes, the selenenyl sulfides do not react and therefore, a prior conversion of selenenyl sulfide to selenol is necessary for an effective formation of gold(I)-selenolate from diselenide. However, this process is associated with the ligand exchange reaction in selenenyl sulfide in the presence of PhSH that hampers the regeneration of selenol. The structural aspects as well as the mode of reactivities of selenenyl sulfides and the products (gold(I)-selenolates) were analyzed using experimental as well as computational methods. These studies indicated that the presence of *ortho*-coordinating donor groups and oxidation state of Se-center play crucial roles towards their reactivities. Density functional theory calculations were undertaken to determine the natural charges on heteroatoms and to find the site for nucleophilic attack related to ligand exchange reactions.

1. Introduction

Gold(I)-based compounds have been used for the treatment of many diseases such as tuberculosis, endocarditis, syphilis and rheumatoid arthritis (RA) for quite long time [1]. Particularly, gold(I) complexes such as gold thiomalate (myochrisine, GTM), gold thioglucose (solganol, GTG) and auranofin (AUR) are employed for the treatment of RA (chrysotherapy) for many years and this has attracted considerable research attention as these compounds have been shown to effectively slow down or even stop the progress of RA (Fig. 1) [2]. While GTM and GTG are polymeric in nature, AUR, which is considered as 2nd generation gold(I) drug, is monomeric containing linear -S-Au-PEt_3 moiety [3]. A considerable number of experimental evidences suggest that these compounds exert their therapeutic effects by inhibiting certain enzyme activities or affecting the functions of inflammatory cells. This is mostly due to the presence of electrophilic Au(I)-center that allows the nucleophilic reactivity in the presence of reactive groups in proteins/small molecules. The interaction of gold(I) complexes with cysteine (Cys)-containing proteins has been extensively studied. For example, serum albumin (Alb-SH) [4], human glutathione reductase (hGR) [5] and protein tyrosine phosphatases (PTPs) [6] are shown to bind rapidly with gold(I) drugs to produce the corresponding protein-gold-thiolate complexes. Furthermore, recent studies speculate that gold drugs effectively inhibit several selenoenzymes such as glutathione peroxidase (GPx) [7], type-I iodothyronine deiodinase (ID-1) [8] and thioredoxin reductase (TrxR) [9], probably by reacting with the protein active site selenocysteine (Sec) residues leading to the formation of protein-gold(I)-selenolate complexes.

While X-ray crystal structure of several protein-gold-thiolate complexes is reported [2], the structure of protein-gold-selenolate complex is not known. However, the structural aspects of gold(I)-selenolate complexes are evidenced by the design, synthesis and single crystal X-ray structures of small-molecule gold(I)-selenolate complexes [10]. The gold(I)-selenolate complexes could be synthesized by the reduction of diselenides either by using sodium borohydride or by using suitable thiols to generate selenol intermediates followed by the reaction with trialkyl/arylphosphine gold(I) chlorides, auranofin (AUR) or any other electrophilic Au(I)-based anti-arthritic compound [10,11]. While the first method of reduction might not be compatible in the cellular

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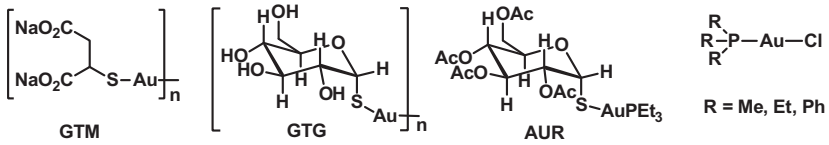


Fig. 1. Chemical structures of some representative gold(I) compounds.

environment, the later method is justified as such reductive cleavage of diselenide/disulfide bonds often takes place by cellular and activated thiols during many enzymatic processes. This is further supported by the recent reports on inhibition of the thiol-mediated antioxidant activity of native GPx as well as some functional mimics by anti-arthritic gold(I) compounds [11]. Considering the catalytic cycle, it is observed that only the selenol intermediate reacts with conventional gold(I) compounds during the inhibition leading to the formation of gold-selenolate complexes (Scheme 1) [11]. Therefore, the overall formation of gold-selenolate from diselenide is dependent on the feasibility of *in situ* generation of selenol from corresponding diselenides in the presence of thiol. It should be noted that the presence of N/O-containing coordinating groups are necessary for an efficient cleavage of Se–Se bonds in diselenides but such groups interferes on the generation of selenols from selenenyl sulfide intermediates due to the ligand exchange (thiol) reactions at Se-centers [12,13]. Therefore, any condition that prevents the ligand exchange (thiol) reaction and effectively generate selenol intermediate from diselenide, would lead to the formation of gold(I)-selenolate complexes. In the present report, we have considered a series of diaryl diselenides **1**–**8**, with/without *ortho*-coordinating amine/amide groups (Fig. 2). The structural aspects of selenenyl sulfides and gold(I)-selenolates are investigated both experimentally and theoretically to understand the role of intramolecular interactions, oxidation state on Se-center and geometrical features towards the feasibility of ligand exchange reactions and overall stabilities. Finally a number of special conditions are proposed for minimizing the unwanted thiol exchange reactions in selenenyl sulfide stage for an exclusive synthesis of gold(I)-selenolates from diaryl diselenides.

2. Results and discussion

2.1. Formation of gold-selenolates from diselenides 1–8

Considering the presence of selenocysteine (Sec) residue at the active site of native GPx enzyme, a number of organoselenium compounds have been developed since last few decades as

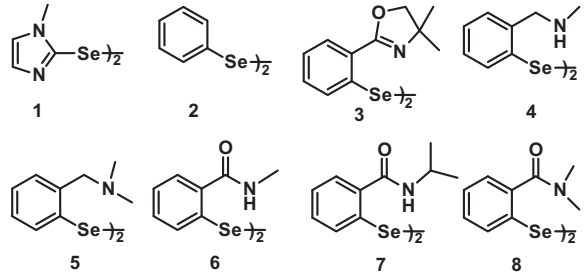
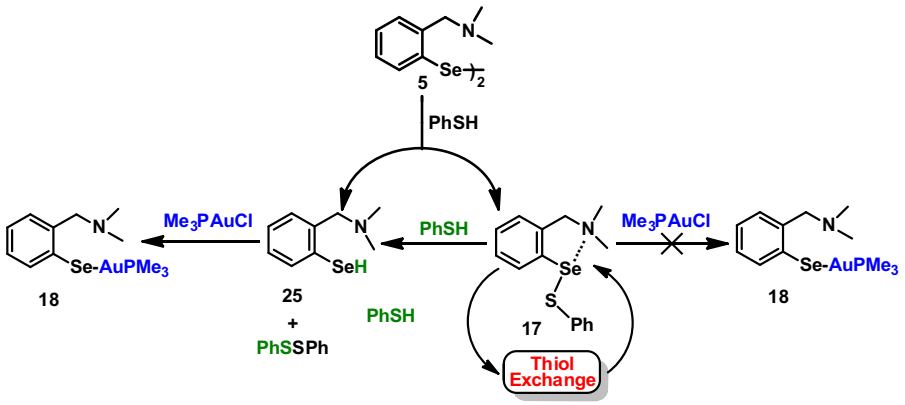


Fig. 2. Chemical structures of some representative diaryl diselenides **1**–**8** as synthetic GPx mimics.

functional mimics of GPx [12,14]. As shown in Fig. 2, a series of symmetrical diaryl diselenides **1**–**8** are chosen as representative synthetic mimics of GPx in the present study and the chemical structures of selenenyl sulfides and gold(I)-selenolate complexes are shown in Fig. 3. While diselenides **3**–**8** contain a coordinating group with N/O heteroatom at the *ortho*-position to the Se-center, diselenides **1** and **2** do not have such a coordinating group. It has been shown previously that the Se–Se bond in most diselenides can be cleaved by thiols such as glutathione (GSH) or aryl/benzyl thiols in the presence/absence of peroxide and the cleavage is further assisted by the presence of *ortho*-coordinating groups [12,14]. As depicted in Scheme 1, nucleophilic attack of one equivalent of PhSH to Se–Se bond of diselenide **5** having *ortho*-coordinating *N, N*-dimethylamino group produces a mixture of selenol **25** and selenenyl sulfide **17**. While the produced selenenyl sulfide **17** is unreactive towards gold(I) compound (Me_3PAuCl), the generated selenol **25** promote nucleophilic attack at the Au(I)-center leading to the formation of gold(I)-selenolate complex **18** (Scheme 1). Although, the produced selenenyl sulfide **17** can further be converted to the corresponding selenol in the presence of an additional amount of PhSH, the process is hampered by unwanted thiol exchange reaction at the Se-center of selenenyl sulfide [12,13]. A similar scenario also arises in the presence of other amine/amide-based coordinating groups. However, a nucleophilic



Scheme 1. Schematic representation to the formation of gold(I)-selenolate complex **18** upon the thiophenol-mediated cleavage of diselenide **5**. Similar scenario also prevails in the presence of other *ortho*-coordinating groups.

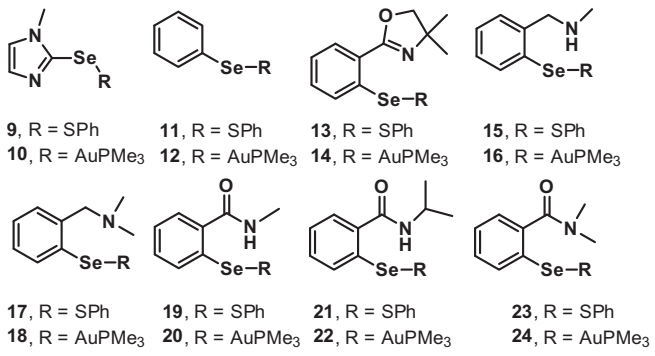


Fig. 3. Chemical structures of selenenyl sulfides and gold(I)-selenolates corresponding to diselenides **1**–**8**.

attack of thiol at the S-center of Se-S bond in selenenyl sulfide is rather necessary for the generation of selenol. Thus, although the presence of Se···N/O non-bonded interactions are beneficial for the cleavage of Se–Se bond in diselenides, this has negative influence for the generation of selenol from the corresponding selenenyl sulfide intermediate.

2.2. Important structural features of selenenyl sulfides and gold(I)-selenolate complexes

Upon the development of different series of synthetic mimics of GPx, a number of selenenyl sulfides were synthesized and characterized by spectroscopic methods as reported earlier [14b] To the best of our knowledge, crystallographic data on selenenyl sulfides was not available except three imine-based selenenyl sulfides (compounds **13**, **26** and **27**) having intramolecular Se···N interactions (Fig. 4) [15]. Non-bonded interactions in other selenenyl sulfides having different *ortho*-substitutions were mainly speculated based on the energy optimized geometries as calculated using density functional theory (DFT) [12–14]. In the present study, for the first time, we describe the single crystal X-ray structure of a sec-amide-based selenenyl sulfide **21** having strong Se···O non-bonded interaction (Fig. 4). The non-bonded donor-acceptor interactions in selenenyl sulfides are expected due to the presence of electron donating heteroatoms at the *ortho*-position of electrophilic Se-center (oxidation state of Se-center: -1). The selenenyl sulfide **21** was synthesized almost in a quantitative yield from the corresponding cyclic selenenylamide by the reaction with PhSH

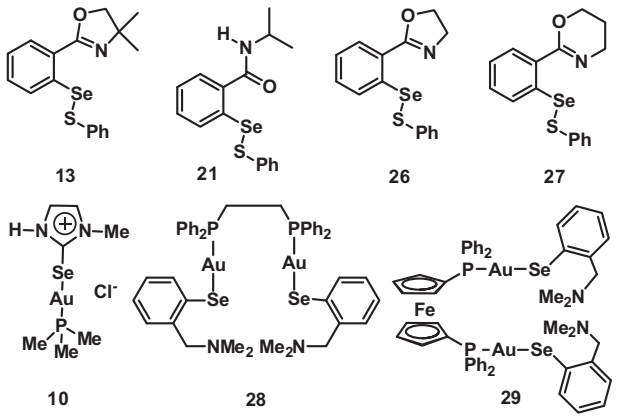


Fig. 4. Chemical structures of some selenenyl sulfides (**13** [15b], **21**, **26** [15c] & **27** [15a]) and gold(I)-selenolate complexes (**10**, **28** & **29**) [10], whose X-ray structures are known in the literature. X-ray data of compound **21** is described in the present study and is not reported earlier.

following the method as reported earlier (Scheme S1, Supporting Information) [16]. The crude compound **21** was obtained as white solid, which was recrystallized from dichloromethane to afford needle-shaped crystals. The pure compound was thoroughly characterized by NMR spectroscopic and Mass spectrometric analyses along with single crystal X-ray diffraction studies. On the other hand, although the X-ray crystal structure of protein-gold(I)-selenolate was not reported, the single crystal X-ray structures of several small-molecule gold(I)-selenolates such as compounds **10**, **28** and **29** were reported in the literature (Fig. 4) [10].

The ORTEP diagram of compound **21** as shown in Fig. 5 exhibits certain structural features. The carbonyl oxygen atom of amide group is found to interact with the electron deficient Se-center (dSe···O = 2.639 Å) and owing to this interaction, the O···Se–S moiety in the selenenyl sulfide aligns itself almost in a linear fashion with an angle of 175.6° (near 180°). This is in well agreement with the already reported imine-based selenenyl sulfides as shown in Table 1 [15]. Indeed such donor-acceptor non-bonded interactions in selenenyl sulfides are quite expected as the Se-center is electron deficient in nature (oxidation state of Se-center: -1). Apart from this intramolecular non-bonded Se···O interactions, the selenenyl sulfide **21** exhibits intermolecular H-bonding interactions. The free N–H group of sec-amide functionality of one molecule interacts with the carbonyl oxygen of amide group of another molecule with the formation of N–H···O linkages. Extrapolation of this intermolecular H-bonding led to the formation of network-like structural pattern (dN–H···O = 2.105 Å; θN–H···O = 160.7°) as shown in Fig. 6. The presence of similar Se···N/O non-bonded interaction is also observed in amine- and amide-based diselenides as reported earlier in their X-ray crystal structures [12,14].

Similar to selenenyl sulfides, single crystal X-ray structures of several gold(I)-selenolate complexes were reported in the literature [10]. To understand the importance and alignments of coordinating groups near Se-center (electron rich) on the structure and overall stability of gold-selenolate complexes, X-ray structures of three already reported gold-selenolate complexes such as **10**, **28** and **29** are considered in the present study (Fig. 7). Some important structural features of compounds **10**, **28** and **29** are presented in Table 1. While compound **10** does not contain any coordinating group, compounds **28** and **29** possess *N,N*-dimethylaminomethyl group at the *ortho*-position of Se-center. As expected, irrespective of the presence of any coordinating group, the Se–Au–P moiety in gold(I)-selenolates adopt almost linear geometries with bond angles ranging from 171° to 178°, which is the characteristic pattern of gold(I) complexes (Table 1). Owing to the selenolate character (electron rich center, oxidation state of Se-center: -2)

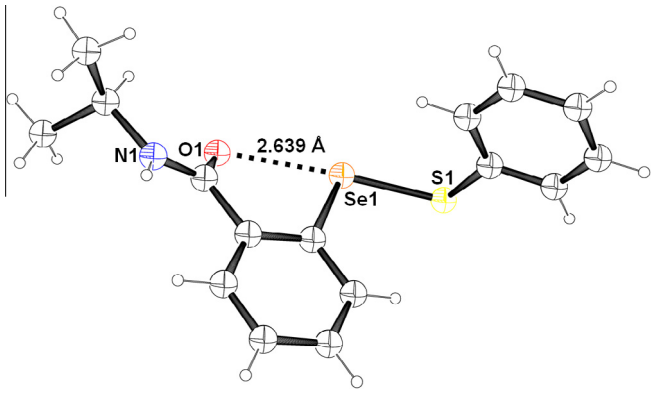


Fig. 5. X-ray crystal structure of selenenyl sulfide **21**. Displacement ellipsoids are drawn at 50% probability level and hydrogen atoms are shown as small spheres of arbitrary radii.

Table 1
Some of the representative structural parameters of selenenyl sulfides (**13**, **21**, **26** & **27**) and gold(I)-selenolate complexes (**10**, **28** & **29**) as obtained from their single crystal X-ray structures.

Compound	$d_{Se\cdots N/O}$ (Å)	$d_{Se\text{-}S/Au}$ (Å)	$d_{Au\text{-}P}$ (Å)	$\theta_{N/O\cdots Se\text{-}S/Au}$ (°)	$\theta_{Se\text{-}Au\text{-}P}$ (°)	Refs.
Selenenyl sulfides						
13	2.617	2.218	–	176.6	–	[15b]
21	2.639	2.197	–	175.5	–	Present
26	2.636	2.213	–	178.4	–	[15c]
27	2.458	2.249	–	176.4	–	[15a]
Gold(I)-selenolate complexes						
10	–	2.440	2.266	–	176.0	[10b]
28	4.600	2.404	2.262	102.9	173.1	[10a]
29	4.579, 3.265	2.425	2.268, 2.273	150.9, 169.6	170.6, 177.9	[10a]

of the Se-center in compounds **28** and **29**, the electron donating *ortho*-coordinating groups align themselves away from Se–Au–P moieties. This is in contrast to the alignment of sec-amide group in selenenyl sulfide **21** and imino groups in selenenyl sulfides **13**, **26** and **27** that exhibit significant intramolecular Se···O/N interactions. The absence of any Se···N non-bonded interaction in gold(I)-selenolates **28** and **29** is also reflected in the values of bond distances and angles as shown in Table 1. These observations indicate that the relative oxidation state of Se-center in diselenides (oxidation state of Se-center: -1) [16b], selenenyl sulfides (oxidation state of Se-center: -1) [15], and gold(I)-selenolates (oxidation state of Se-center: -2) [10a] play crucial roles for the non-bonded donor-acceptor interactions with the *ortho*-coordinating groups.

2.3. Ligand exchange reactions

It is now well established that ligand exchange reactions take place at the Se-center in selenenyl sulfides in the presence of thiols [12,13]. The extent of this exchange is amplified further in the presence of *ortho*-coordinating groups to the Se-center. The similar observation was also noticed for the sec-amide based selenenyl sulfide **21** as shown in Scheme 2. When the pure crystals of **21** was treated with another thiol such as 4-methylthiophenol, formation of a new selenenyl sulfide **30** was detected as monitored by ^{77}Se NMR spectroscopic method (Scheme 2). The process of thiol exchange with compound **21** using ^{77}Se NMR spectroscopic method has been reported earlier [16a]. The crude compound was purified by column chromatography and characterized by spectroscopic methods.

In contrast to selenenyl sulfides, the Se-centers in gold(I)-selenolates do not favor the nucleophilic attack of thiols for a ligand exchange reaction. This is mainly due to relatively higher electron density of Se-center in gold(I)-selenolates even as compared to the adjacent Au-center. However, ligand exchange reactions were observed in gold(I)-selenolate complexes in the presence of trialkyl/arylphosphine or selenol compounds as detected by ^{31}P, ^{77}Se NMR spectroscopic and ESI-MS spectrometric methods [10a,11]. For example, as reported earlier, treatment of *N, N*-dimethylbenzylamine-based gold(I)-selenolate **18** with an excess amount of triphenylphosphine led to the phosphine exchanged gold-selenolate **31** *via* intermediate formation of mixed phosphine-gold(I) complexes. This observation indicates that the incoming phosphine attacks at Au(I)-center rather than Se-center to generate new gold(I)-selenolate complex **31** with the elimination of trimethylphosphine that undergone aerial oxidation to the corresponding phosphine oxide (Scheme 3) [11]. Similarly, when the same gold-selenolate **18** was treated with selenol **25**, the bis-selenolato gold(I) complex **32** was detected as predominant species with the release of phosphine unit. These observations indicate that Au(I)-center in gold(I)-selenolates is the electrophilic center for possible ligand exchange reactions in the presence of nucleophiles.

To understand the reactivity of gold selenolate **18** with thiols such as DTT or PhSH, we have studied, the interactions of complex **18** with thiols. As indicated by ^{31}P and ^{77}Se NMR spectroscopic experiments some ligand displacement reactions take place in the presence of thiols. When the reaction of selenol **25** as produced *in situ* by the treatment of diselenide **5** with DTT followed by Ph_3PAuCl, the formation of triphenylphosphine selenide (Ph_3PSe) was detected and the intensity of this compound was found to increase with increasing concentration of DTT in the reaction mixture. However, the ligand exchange by PhSH was found ti be very negligible [11]. At this point, it is worth mentioning that, although the ligand exchange reaction (thiol exchange) in selenenyl sulfide intermediate has negative influence for both of the GPx-like antioxidant activity of diselenide or selenenylamides and towards the formation of gold(I)-selenolate complexes, the ligand exchange reaction at Au(I)-center of gold(I)-selenolate has positive/neutral impact regarding the interaction of therapeutic gold(I) compounds

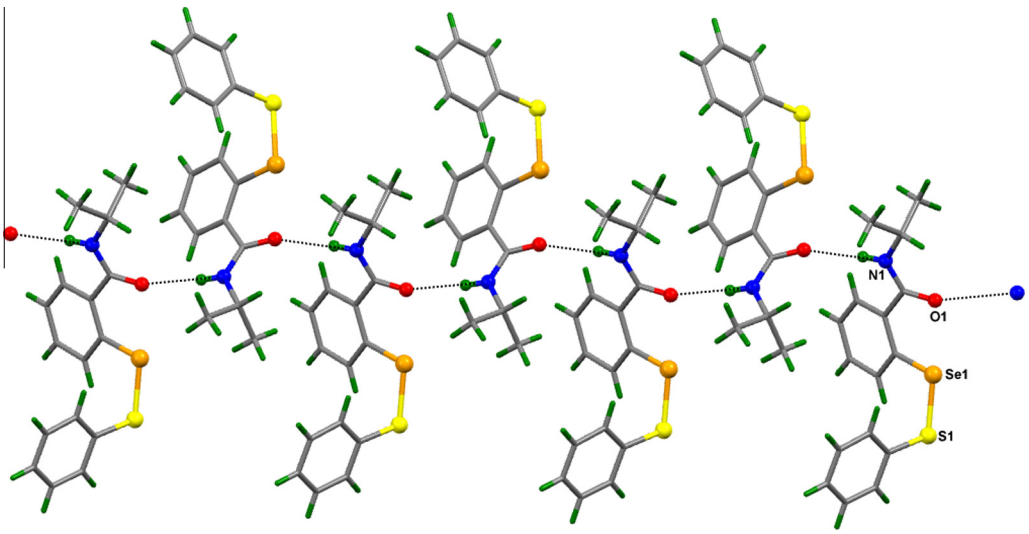


Fig. 6. Intermolecular H-bonding network in selenenyl sulfide **21** consisting of N–H···O moieties of amide functionality.

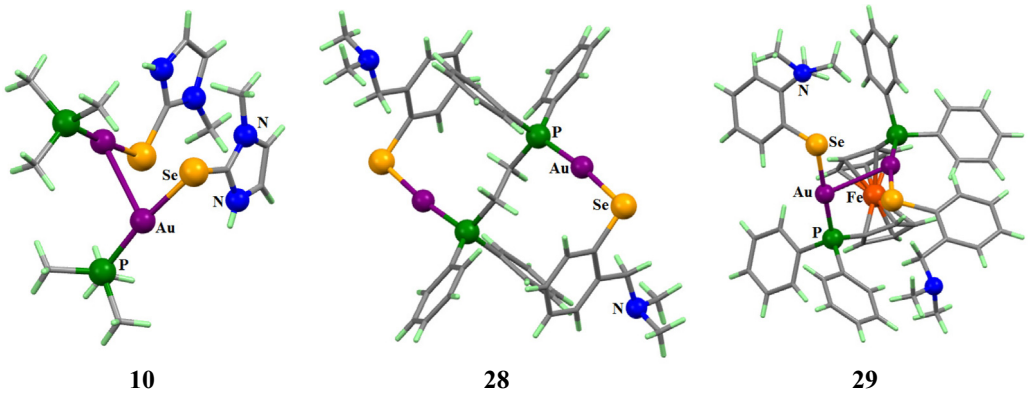
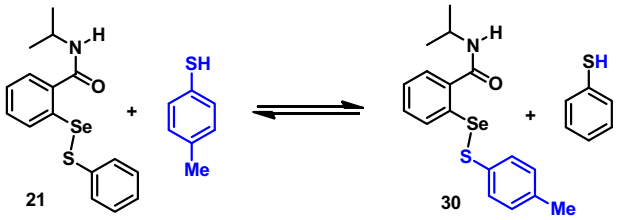


Fig. 7. X-ray crystal structures of gold(I)-selenolates **10** [10b], **28** [10a] and **29** [10a]. The heteroatoms are represented with ball and stick model. All these structures are taken from the reported crystal structural data (CIF) [10].



Scheme 2. Reaction of selenenyl sulfide **21** with a new thiol (4-methylthiophenol) with the formation of new selenenyl sulfide **30** by thiol exchange reaction (present work).

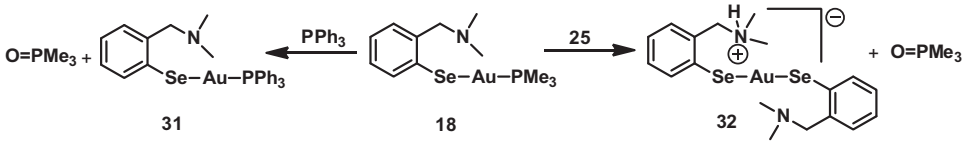
with cysteine- or selenocysteine-containing proteins. This is because such exchange with any other reactive thiol or selenol group would lead to produce bis-thiolato gold(I), bis-selenolato gold(I) or mixed gold(I) complexes without freeing the previous selenol/thiol.

Table 2
Some representative structural parameters on the energy optimized geometries of selenenyl sulfides and gold(I)-selenolates corresponding to diselenides **1**–**8**. The DFT calculation was performed at B3LYP/LANL2DZ level of theory.

Compounds	$d_{Se\cdots N/O}$ (Å)	$\theta_{N/O\cdots Se\text{-}S/Au}$ (°)	$\theta_{Se\text{-}Au\text{-}P}$ (°)	q_{Se}	$q_{S/Au}$
9	–	–	–	0.260	0.006
10	–	–	178.2	−0.215	0.252
11	–	–	–	0.236	−0.005
12	–	–	179.1	−0.222	0.185
13	2.515	175.7	–	0.388	−0.109
14	3.010	175.6	175.5	−0.088	0.149
15	2.539	174.5	–	0.304	−0.095
16	3.393	156.4	178.3	−0.185	0.167
17	2.529	175.7	–	0.326	−0.017
18	3.400	155.2	178.1	−0.179	0.167
19	2.453	173.9	–	0.410	−0.088
20	4.053	155.3	177.5	−0.185	0.183
21	2.476	173.0	–	0.402	−0.080
22	4.033	149.1	177.7	−0.186	0.180
23	2.500	172.7	–	0.394	−0.074
24	4.003	146.5	178.3	−0.189	0.180

2.4. Theoretical studies

To gather more generalized views and also to further support the experimental observations about the effect of Se···N/O non-bonded interactions on selenenyl sulfides and gold-selenolates, we have carried out detailed density functional theory (DFT) calculations on all the selenenyl sulfides and corresponding gold (I)-selenolate complexes of diselenides **1**–**8**. The calculations were performed using Gaussian03 package at B3LYP level of theory and the LANL2DZ basis set was chosen due to the presence of heavier Au-atom. All the geometries were optimized in gas phase and non-bonded interactions were determined by carrying out natural bond orbital (NBO) theory analysis on the energy optimized geometries. Some important structural parameters of these compounds are shown in Table 2 and the optimized geometries of some selected compounds are shown in Fig. 8. As observed from Fig. 8 and/or Table 2, significant Se···N/O non-bonded interactions are present in imine/amine/amide-based selenenyl sulfides and in agreement with our expectations, such interactions are almost absent or very weak in the corresponding gold(I)-selenolates. For example, while dSe···N distance in selenenyl sulfide **17** was 2.529 Å, the distance was significantly increased in the corresponding gold-selenolate **18** (3.400 Å). Reduction in strength of non-bonded Se···N interaction is also associated with the significant deviation from linearity of N···Se–S/Au angles on going from selenenyl sulfides to gold-selenolates (compound **17**: θN···Se–S = 175.7°; compound **18**: θN···Se–Au = 155.2°). A quite similar scenario is also observed when the amino group was replaced with the corresponding amide counterpart. A significantly high increase in Se···O distance was observed on going from amide-based selenenyl sulfides to amide-based gold-selenolate complexes. Deviation from the linear arrangement of amide moiety with Se-Au-P unit of the molecule is also evident from much lower values of O···Se–Au angles of amide-based gold(I)-selenolate complexes. Interestingly, similar to the results obtained from single crystal



Scheme 3. Schematic representations for ligand exchange reactions in gold-selenolate **18** in the presence of phosphine and selenol compounds (our own previously reported work) [11].

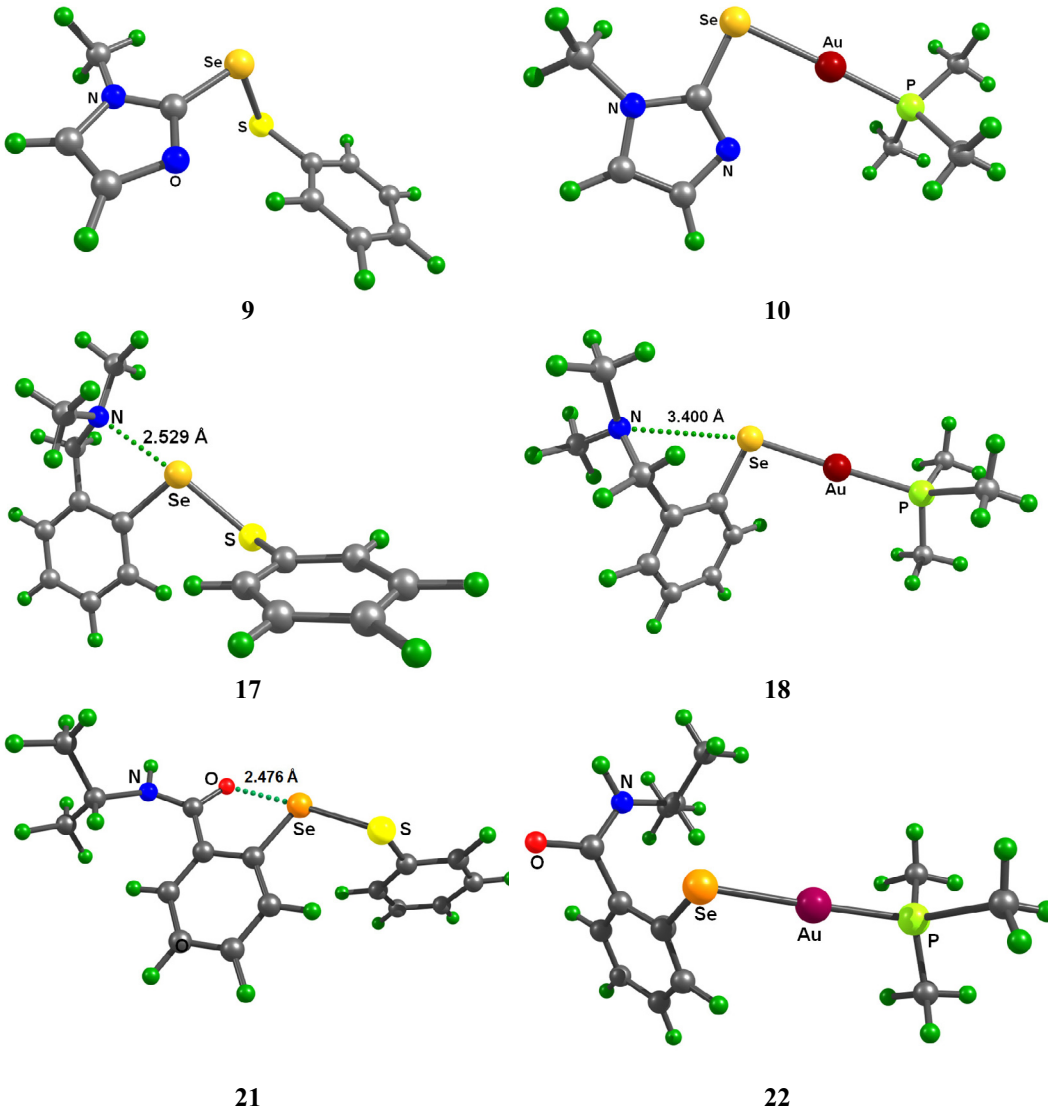


Fig. 8. Energy optimized geometries of some representative selenenyl sulfides and corresponding gold-selenolate complexes.

X-ray structures of gold(I)-selenolate complexes **10**, **28** and **29**, theoretical studies on all gold-selenolates reveal that Se–Au–P moiety adopt almost linear arrangement, which is the characteristics of Au(I) complexes. Unlike in selenenyl sulfides, very weak or the absence of non-bonded Se···N/O interaction in gold-selenolate complexes can be ascribed to the presence of a relatively electron rich Se-center (selenolate character) linked with Au(I)-center that prevents the electronic contribution from the *ortho*-substituted coordinating groups. To validate this assumption, natural charges on the heteroatoms were calculated using NBO analysis. Interestingly, both Se- and S-centers in selenenyl sulfides **9** and **11** were positively charged (Table 2) and the positive charge density (electron deficiency) on Se-center was found to be higher than that on S-centers in those selenenyl sulfides, indicating the feasibility of nucleophilic attack at Se-center. In contrast, the Se-centers in the corresponding gold-selenolates **10** and **12** are negatively charged (Table 2) and Au(I)-centers rather have positive charge. These observations support the lack of any intramolecular donor-acceptor interactions of the *ortho* coordinating groups with the Se-centers in gold(I)-selenolates. Furthermore, such interactions with the relatively positively charged Au(I)-centers are very less likely due to discrepancies with hard-hard and soft-soft interaction principle. As expected a significant increase in positive charge density or the electron deficiency at Se-center in selenenyl sulfides is observed in the presence of amine- or amide-based coordinating groups, indicating the transfer of electron density from coordinating groups to the anti-bonding molecular orbital of Se–S bond (Table 2) [12,13]. These observations clearly indicate that, the nucleophilic attack of thiols at Se-centers in selenenyl sulfides becomes more feasible in the presence of *ortho*-substituted coordinating groups, which is not a desired pathway for the generation of gold(I)-selenolates. Assumptions from these theoretical calculations are in well agreement with the experimentally observed (X-ray crystal structures) results on representative selenenyl sulfides **13**, **21**, **26**, **27** and gold-selenolate complexes **10**, **28** and **29** as discussed above.

The feasibility of ligand exchange reactions and the extent of intramolecular donor-acceptor interactions in selenenyl sulfides and gold(I)-selenolates can be well investigated by understanding the frontier molecular orbitals (FMOs) of these compounds. An electronic interaction/transition is basically a transition of electrons from ground state to first excited state. It is generally described as a transition of electron from highest occupied molecular orbital (HOMO) to lowest unoccupied orbital (LUMO).

Therefore, the HOMOs are the orbitals that have the ability to donate an electron and LUMOs are the ones that can accept an electron. They are often referred to as frontier molecular orbitals (FMOs). According to the Koopmans theorem, the energy of the HOMO is related to the ionization potential, while the energy of LUMO is related to the electron affinity [17] and therefore, these molecular orbitals mainly determine the stability or the reactivity of a molecule. The energy gap between HOMOs and LUMOs is related to the biological activity of the molecule [18,19] and a large HOMO–LUMO energy gap represents the high kinetic stability. The high energy gap indicates that the transfer of an electron from higher occupied molecular orbitals (HOMO) to lower unoccupied molecular orbitals (LUMO) is energetically unfavorable. Generally, the atom or fragment occupied by more densities of HOMOs should have stronger ability to detach an electron whereas; the atom with more occupation of LUMOs should have ability to gain an electron. In the present study, we have calculated the energetics of frontier orbitals of some representative selenenyl sulfides (**9** and **17**) and their corresponding gold(I)-selenolates (**10** and **18**). The 3D surfaces of HOMOs and LUMOs of these compounds are represented in Fig. 9 along with their corresponding energies and HOMO-LUMO energy gap. The positive and negative phases are represented in red and green colors, respectively. In the present context, the mode as well as the site of ligand exchanges in the presence of external nucleophiles can be satisfactorily justified using the 3D HOMO-LUMO surfaces of selenenyl sulfides and gold(I)-selenolates (Fig. 9). As seen in the surface views of HOMOs of selenenyl sulfides, major charge density is localized on thiophenol component (S-center and phenyl ring) and relatively smaller density on Se-centers, indicating that the electrons in HOMO are mainly delocalized over the -SPh moiety of selenenyl sulfides. A part of charge density is also localized on the coordinating heteroatom in case of *ortho*-coordinated derivatives. Whereas, in LUMOs, the charge density is distributed over Se–S units. Unlike in HOMOs of selenenyl sulfides, the electronic distribution in LUMOs is more diffused on Se-center than that on S-centers, indicating that the molecular orbital has more of Se-character. These observations further implies that the Se-center has relatively higher tendency of accepting electron density from an external nucleophile as well as coordinating donor groups, which is in well agreement with the experimental mode of ligand exchange in selenenyl sulfides in the presence of nucleophile such as thiophenol [12,13].

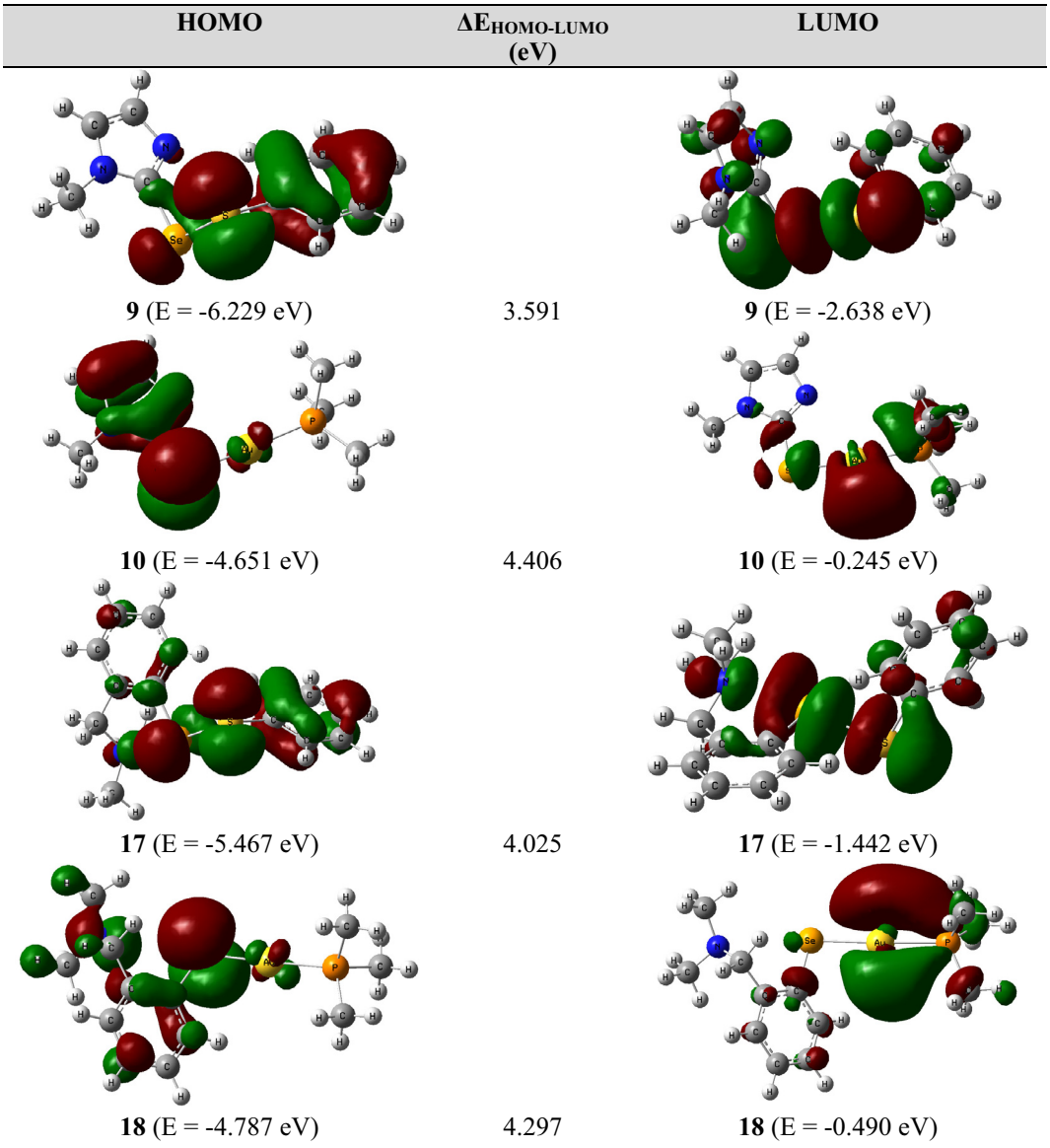


Fig. 9. 3D surfaces of Frontier Molecular Orbitals (FMOs) of some representative selenenyl sulfides and their corresponding gold(I)-selenolates. Values in the parentheses represent energies of HOMOs and LUMOs. An isovalue of 0.03 was used for visualizing the molecular orbital surfaces in Gaussview.

A similar and rather a better picture is reflected in the HOMOs and LUMOs of gold(I)-selenolates (Fig. 9). While the electron density of HOMOs are localized mainly on Se-center, a localized electron density diffused over Au(I)-center is observed in the corresponding LUMOs, supporting that Au(I)-center as the site for nucleophilic attack (ligand exchange). A very high electron density on Se-center in HOMOs of gold(I)-selenolates represents that Se-center is electron rich. The energies of HOMO and LUMO and HOMO–LUMO energy gap for these compounds as shown in Fig. 9 are also important for their overall reactivity/stability. In general, the calculated HOMO-LUMO energy gap of selenenyl sulfides and gold(I)-selenolates are small indicating their general reactivity. However, relatively lower energy gap for selenenyl sulfides as compared to the corresponding gold(I)-selenolates reveals the higher reactivity of selenenyl sulfides.

Although thiol exchange reactions were found to be relatively dominant in selenenyl sulfides than the generation of selenols as shown in Schemes 1, the unwanted thiol exchange could be overcome using few logical strategies that were established and evidenced earlier for the enhancement of antioxidant activities of synthetic GPx mimics [12,14a]. Therefore, selenols can effectively be synthesized from selenenyl sulfides under certain conditions such as (a) by using very high concentration of thiol [13a]; b) by weakening of Se···N/O non-bonded interactions [16b]; c) by introducing suitable substituent at 6-position of aromatic ring [16b]; d) by using a dithiol such as DTT or Lipoic acid [13b] or e) by introducing some strong coordinating group near to S-center [13a]. Under these conditions treatment of trialkyl/arylphosphine gold(I) chlorides in the reaction mixture would lead to an exclusive formation of phosphine gold(I)-selenolate complex from the corresponding selenenyl sulfide. Indeed the minimization of thiol exchange reaction in the presence of a dithiol was observed and this was utilized for the synthesis of gold(I)-selenolates in our earlier report [11]. While a treatment of two equivalents of PhSH to diselenide **5** led to a mixture selenol **25** and selenenyl sulfide **17** as evidenced by ^{77}Se NMR spectroscopic method, an exclusive formation of selenol **25** was detected when diselenide **5** was treated with two equivalents of dithiothreitol (DTT). Therefore, later method was followed for the preparation of gold-selenolates from diselenide **5** using different phosphine gold(I) chlorides [11]. These observations indicate that, although the treatment of thiol to diselenide produces a mixture of selenol and selenenyl sulfide, the produced selenenyl sulfide could efficiently be converted to the corresponding selenol under certain conditions for an effective generation of gold(I)-selenolate even in the presence of Se···N/O non-bonded interactions. Furthermore, some of the above conditions might fit under cellular environment for the formation of protein gold(I)-selenolate complexes. For example, the reactive multiple cysteine residues in proteins may serve the functions of dithiols with the formation of internal protein disulfide linkages. The thiol concentration can be supplemented by the significantly high intracellular concentration of glutathione and the coordinating groups to S-center in selenenyl sulfide stage might be possible by some proximal amino acid residues under special circumstances. Therefore, it is unsurprising to assume the formation of protein-gold(I)-selenolate complexes but warrants the crystallographic evidences for a solid proof.

3. Conclusion

In summary, in the present study we describe the synthetic methodology to gold(I)-selenolate complexes using *ortho*-substituted diaryl diselenides and electrophilic anti-arthritic gold (I)-compounds in the presence of thiol such as PhSH or DTT. As selenenyl sulfides do not directly produce gold(I)-selenolates and leads to unwanted thiol exchange reaction, an exclusive generation of selenol from diselenide is crucial for an effective formation of gold(I)-selenolate. As observed from experimental as well as computational methods that moderate to strong intramolecular Se···N/O interactions are present in most diselenides and selenenyl sulfides but such interactions are absent in gold(I)-selenolates. This absence is mainly due to different nature and oxidation state of Se-centers (electron rich) as well as typical characteristics of Au (I)-centers in gold(I)-selenolates. Furthermore, the observed ligand exchange reactions at Au(I)-center instead of electron rich Se-center in gold(I)-selenolates as supported by NBO charges and FMO surface views, would be beneficial for an stability of Se–Au bond and probably for an effective inhibition of selenoproteins by electrophilic anti-arthritic gold(I) compounds with possible formation of protein-gold(I)-selenolate complexes in the presence of high cellular concentration of thiols.

4. Experimental

4.1. General procedure

Thin layer chromatographic (TLC) analyses were carried out on pre-coated silica gel on aluminum sheets. The product was purified by Flash chromatographic system (Biotage) using pre-loaded silica gel cartridges. ^{1}H (400 MHz), ^{13}C (100.5 MHz), ^{31}P (161.9 MHz) and ^{77}Se (76.3 MHz) NMR spectra were obtained on a Bruker 400 MHz NMR spectrometer. Chemical shifts are cited with respect to Me_4Si (^{1}H and ^{13}C) as internal standard and H_3PO_4 (^{31}P) and Me_2Se (^{77}Se) as external standards. Mass spectral studies were carried out on a Bruker Daltonics Esquire 6000plus mass spectrometer with ESI-MS mode analysis. Crystal structures of selenenyl sulfides **13** [15b], **26** [15c] and **27** [15a] are taken from earlier reports for a comparative study with compound **21** (present work). Similarly, the crystal structures of gold(I)-selenolates **10** [10b], **28** [10a] and **29** [10a] were taken from previously reported literatures for a comparative study.

4.2. Synthesis of selenenyl sulfide 30

Method 1: To a CH_2Cl_2 (5 mL) solution of selenenyl sulfide **21** (30 mg, 0.12 mmol), 4-methylthiophenol (15.5 mg, 0.12 mmol) was added at room temperature and the reaction mixture was stirred for 30 min. The solvent was evaporated and the solid obtained was washed with petroleum ether (4 × 20 mL) to remove the unreacted 4-methylthiophenol and the eliminated PhSH. The residue was then dried *in vacuo* to obtain the corresponding selenenyl sulfide **30** in almost quantitative yield.

Method 2: 4-Methylthiophenol (15.5 mg, 0.125 mmol) was added to a CH_2Cl_2 (5 mL) solution of cyclic selenenylamide derivative [16a] (30 mg, 0.125 mmol, Mol wt: 240), at room temperature and the reaction mixture was stirred for 30 min. The solvent was evaporated and the solid obtained was washed with petroleum ether (4 × 20 mL) to remove the unreacted thiol and the corresponding disulfide impurities. The residue was then dried in vacuum to obtain the selenenyl sulfide **30** in quantitative yield.

^{1}H NMR ($CDCl_3$) δ (ppm): 1.27-1.28 (d, 6H, J = 4.0 Hz), 2.28 (s, 3H), 4.25-4.33 (m, 1H), 6.10 (br, 1H), 7.02–7.04 (d, 2H, J = 8.0 Hz), 7.22-7.25 (t, 1H, J = 8.0 Hz), 7.39-7.51 (m, 4H), 8.19-8.21 (d, 1H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.9, 22.8, 42.3, 125.8, 126.2, 128.5, 129.2, 129.6, 130.8, 131.8, 133.3, 136.4 and 137.2. ^{77}Se NMR ($CDCl_3$) δ (ppm): 599. ESI-MS m/z calcd. for $C_{17}H_{19}NOSSe$ $[M+Na]^+$ 388.0250; found: 388.0248.

4.3. Synthesis of gold-selenolate 18

The synthesis was done following our previously reported method [11]. To the solution of diselenide **5** in CDCl3, DTT was

added (2 equiv) and the formation of selenol **25** was confirmed by ^{77}Se NMR spectroscopy (δ = 37 ppm). To the solution was added stoichiometric amount of Ph_3PAuCl in $CDCl_3$ in an NMR tube. The yellow solution of selenol turned almost colorless immediately upon the addition of gold(I) chloride. The formation of triphenylphosphinegold(I) selenolate species **18** was characterized by ^{31}P and ^{77}Se NMR spectroscopy and mass spectrometric techniques. ^{31}P NMR ($CDCl_3$, ppm): δ 37.50. ^{77}Se NMR ($CDCl_3$, ppm): δ 74. ESI-MS. Calcd [(M+H)$^+$]: *m*/*z* 674.0790. Found: *m*/*z* 673.9761.

4.4. Crystallography

Single crystal X-ray diffraction data was collected on a Bruker AXS SMART APEX CCD diffractometer at room temperature (293 K). The X-ray generator was operated at 50 kV and 35 mA using Mo-Kα radiation (λ = 0.71073 Å). The data was collected using SMART software package [20]. The data were reduced by SAINTPLUS [20], an empirical absorption correction was applied using the package SADABS [20,21] and XPREP [20] were used to determine the space group. The crystal structure was solved by direct methods using SIR92 [22] and refined by full-matrix least-squares method using SHELXL97 [23]. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were assigned at idealized locations [24].

4.5. Computational methods

All calculations were performed using Gaussian 03 suite of quantum chemical program [25]. The hybrid Becke 3-Lee-Yang-Parr (B3LYP) exchange correlation functional was applied for DFT calculations [26]. Geometries were fully optimized at B3LYP level of theory using the LANL2DZ basis set. Orbital interactions were analyzed using natural bond orbital (NBO) theory at B3LYP/LANL2DZ level and charges were calculated using natural population analysis (NPA) [27]. The frontier molecular orbitals of the energy optimized compounds were visualized using Gaussview 3.09 program.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2016.06.022.

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