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Synthesis and characterization of some gold(I)-thiolate complexes having N-methylimidazole moiety

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Antithyroid drugs inhibit the thyroid hormone synthesis by inactivating the thyroid peroxidase and/or iodothyronine deiodinase, which are involved in iodination and deiodination reactions. Gold(I) compounds also inhibit the thyroid hormone synthesis by interacting with the selenocysteine residue of iodothyronine deiodinase. However, the chemical reactions between these two different classes of compounds have not been studied. In this paper, we describe the interaction of therapeutic gold(I) compounds with the commonly used thiourea-based antithyroid drug, methimazole. It is observed that the gold(I) phosphine complexes (R_3PAuCl, where R = Me, Et, Ph) react with methimazole only upon deprotonation to produce the corresponding gold(I)-thiolate complexes. Addition of PPh_3 to the gold(I)-thiolates produces $(R_3PAuPPh_3)^+$ (R = Me or Et), indicating the possibility of ligand exchange reactions.

Keywords: Gold thiolate, Thiolates, Antithyroid drugs, Antiarthritic drugs, Methimazole, Ligand exchange, Rheumatoid arthritis

Gold(I)-based complexes have been used for the treatment of rheumatoid arthritis (RA) for many years along with the treatment of some other diseases such as tuberculosis, endocarditis and syphilis.[1] Particularly, the use of gold(I) complexes for the treatment of RA (chrysotherapy) has attracted considerable research attention as these compounds have been shown to effectively slow down or even stop the progress of RA. Although the exact biochemical mechanism for the therapeutic action of these gold(I) drugs has not been well-understood, considerable amount of experimental evidences suggest that these Au(I)-based complexes exert their therapeutic effects by inhibiting certain enzyme activities or affecting the functions of inflammatory cells.[1,2] The gold(I) compounds, which have been used earlier for the treatment of RA, are generally the oligomeric gold(I)-thiolates such as gold thiomalate (**1**, GTM), gold thiopropanol sulfonate (**2**, GTPS) and gold thioglucose (**3**, GTG) (Fig. 1).[3] In 1985, a monomeric phosphine-based gold(I) compound, auranofin (**4**, AUR) with improved pharmacokinetic profile and reduced side effects has been developed (Fig. 1).[4]

As gold(I) has a high affinity towards sulfur and selenium, the interaction of gold(I) complexes with several cysteine (Cys)- and selenocysteine (Sec)-containing proteins has been extensively studied.[5] Serum albumin (Alb-SH), the most abundant plasma protein, has been shown to bind rapidly with the gold(I) drugs to produce the corresponding protein-gold(I)-thiolate complexes.[6-8] The interaction of gold(I) complexes with other Cys-containing proteins such as human glutathione reductase (hGR)[9] and protein tyrosine phosphatases (PTPs)[10] has also been studied. Furthermore, gold(I) complexes have been shown to inhibit a number of selenoproteins such as glutathione peroxidase (GPx),[11] thioredoxin reductase

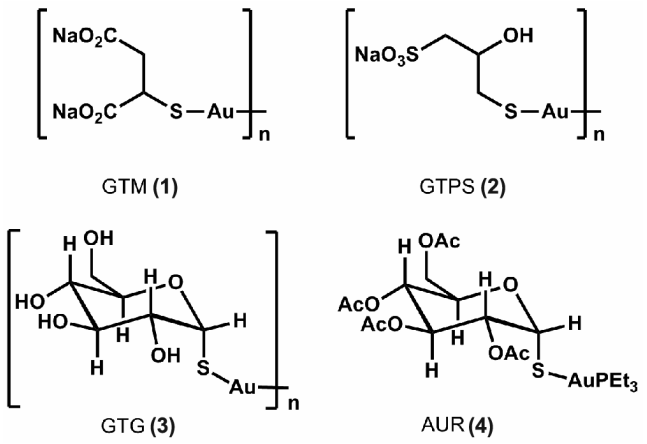


Fig. 1 – Chemical structures of some anti-arthritic Au(I) drugs.

(TrxR)[12,13] and type-I iodothyronine deiodinase (ID-I)[14] by forming gold(I)-selenolate complexes at the active sites of these enzymes. The gold-thiolate/selenolate complexes generally undergo ligand exchange reactions with other nucleophiles. Such ligand exchange reactions alter the inhibitory properties of gold(I) complexes. As the formation of stable gold(I)-thiolate/selenolate complexes affect the enzyme activity, the inhibition of such enzymes by gold(I) compounds may have implications in the treatment of RA. The chemistry of gold(I) complexes toward cysteine/selenocysteine has been studied by using synthetic thiolate and selenolate ligands. Recently, we have shown that gold(I) compounds effectively inhibit the GPx activity of the *N,N*-dimethylbenzylamine-based selenol (**5**).[15] The efficient inhibition of the GPx activity of (**5**) is due to the formation of gold(I)-selenolate complexes such as (**6**) – (**8**).[15] Similarly, the reactions of thiols/thiolates with gold(I) complexes generally produce the corresponding gold(I)-thiolates (e.g. **9-12**).[16] In this paper, we describe the synthesis and characterization of gold(I)-thiolate complexes bearing the antithyroid drug, methimazole, moiety. We also report on the nature of ligand exchange reactions in the presence of nucleophiles such as phosphines and thiols.

Materials and Methods

Trimethylphosphine gold(I) chloride, triethylphosphine gold(I) chloride and triphenylphosphine gold(I) chloride were purchased from Aldrich. Most of the experiments were carried out under dry and oxygen free nitrogen using standard Schlenk techniques for the synthesis. ^{1}H (400 MHz), ^{13}C (100 MHz) and ^{31}P (162 MHz) NMR spectra were obtained on a Bruker 400 MHz NMR spectrometer. Chemical shifts are cited with respect to Me_4Si as internal (^{1}H and ^{13}C) and H_3PO_4 (^{31}P) as external standard. Mass spectral studies were carried out on a Bruker Daltonics Esquire 6000plus mass spectrometer with ESI-MS mode analysis.

Synthesis of gold-thiolates (14) – (16)

To a methanolic solution of MMI (**13**) (20.0 mg, 0.175 mmol), was added sodium hydroxide (7.0 mg, 0.175 mmol) to generate the corresponding thiolate. After stirring for 5 min at room temperature, appropriate phosphine gold(I) chloride (0.175 mmol) was added and the reaction mixture was stirred for 1 h. The solvent was evaporated *in vacuo* and the yellowish semi-solid product was obtained almost in quantitative yield. As the products were essentially pure, no further purification was required.

Compound (**14**): ^{1}H NMR ($CDCl_3$) δ (ppm): 1.52 (d, J = 12.0 Hz, 9H), 3.54 (s, 3H), 6.71 (d, J = 1.6 Hz, 1H), 6.74 (d, J = 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 16.2, 16.6, 34.8, 121.1, 126.6, 147.8. ^{31}P NMR ($CDCl_3$) δ (ppm): -2.8. ESI-MS (*m/z*): Calcd for $C_7H_{14}N_2AuPS$ $[M+H]^+$: 387.0; Found :387.0.

Compound (**15**): ^{1}H NMR ($CDCl_3$) δ (ppm): 1.16-1.25 (m, 9H), 1.82-1.90 (m, 6H), 3.63 (s, 3H), 6.79 (d, J = 1.2 Hz, 1H), 6.81 (d, J = 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 9.4, 18.2, 18.5, 34.8, 121.1, 127.4, 147.0. ^{31}P NMR ($CDCl_3$) δ (ppm): 35.9. ESI-MS (*m/z*): Calcd for $C_{10}H_{20}N_2AuPS$ $[M+H]^+$: 429.0; Found: 429.1.

Compound (**16**): ^{1}H NMR ($CDCl_3$) δ (ppm): 3.64 (s, 3H), 6.80 (d, J = 1.2 Hz, 1H), 6.87 (d, J = 1.2 Hz, 1H), 7.28-7.45 (m, 10H), 7.46-7.60 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm): 34.8, 121.3, 127.7, 129.6, 129.7, 130.2, 132.1, 134.7, 134.9, 146.6. ^{31}P NMR ($CDCl_3$) δ (ppm): 37.6. ESI-MS (*m/z*): Calcd for $C_{22}H_{20}N_2AuPS$ $[M+H]^+$: 573.0; Found: 573.0.

Results and Discussion

In recent years, several gold(I)-thiolate and -selenolate complexes have been reported in the literature.[15-17] As selenols are much better nucleophiles than thiols, the formation of gold(I)-selenolates is more favored than the formation of gold(I)-thiolates. Complexes (**6**) – (**8**) shown in Fig. 2 were synthesized in reasonably good yields by treating phosphine gold(I) chlorides (R_3PAuCl, where R = Me, Et or Ph) with the selenol (**5**).[15] The selenol (**5**) could be generated by reducing the corresponding

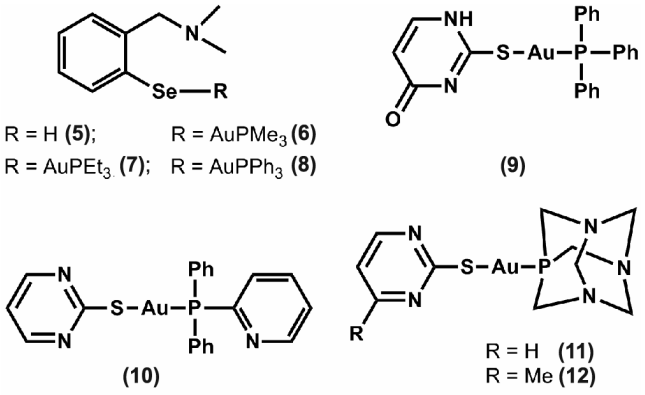
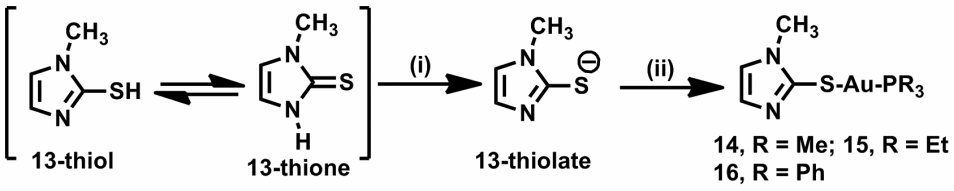


Fig. 2 – Chemical structures of selenol (**5**) and some representative gold-selenolates (**6**) – (**8**) and gold-thiolates (**9**) – (**12**).



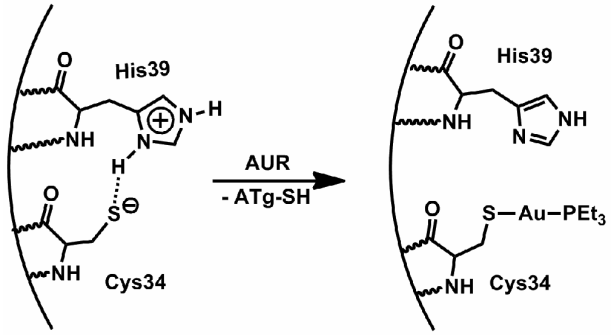
(i) NaOH, MeOH, 5 min; (ii) R_3PAuCl (R = Me, Et or Ph), MeOH, 1 h

Synthesis of gold-thiolate complexes (**14**) – (**16**)

Scheme 1

diselenide in the presence of thiols.[18] In contrast, the reactions of methimazole (**13**) with (R_3PAuCl, where R = Me, Et or Ph) did not produce the expected gold(I)-thiolate complexes, although the thione moiety in compound (**13**) can act as a strong nucleophile. In these reactions, only the starting materials were recovered after stirring the reaction mixtures for 24 h at room temperature. However, in the presence of a base such as NaOH, the reactions afforded the expected complexes (**14**) – (**16**) almost in quantitative yields (Scheme 1). This is due to the fact that MMI exists predominantly in its thione form, which does not allow a direct reaction between this compound and gold(I) chlorides.[19] In the presence of sodium hydroxide, the deprotonation of MMI leads to the formation of a more reactive thiolate, which can readily react with the phosphine gold(I) chlorides (Scheme 2). All the gold(I)-thiolate complexes were characterized by NMR (^1H, ^{13}C and ^{31}P) spectroscopic and ESI-MS spectrometric analyses. A downfield chemical shift was observed in the ^{31}P NMR experiments upon the formation of gold-thiolates (**14**) – (**16**) as compared to the corresponding gold(I) chlorides. For example, the ^{31}P NMR signals for R_3PAuCl (R = Me, Et and Ph) were observed at -10.10, 31.50 and 33.30 ppm, respectively. In comparison, the signals for the gold(I)-thiolate complexes (**14**) – (**16**) were observed at 2.80, 35.90 and 37.60 ppm, respectively, indicating a significant downfield shift in the signals. A similar downfield shift in the ^{31}P NMR chemical shift values was observed for the *N,N*-dimethylbenzylamine-based gold-selenolates.[15]

Interestingly, the reactivity of (**13**)-thiolate with gold(I) compounds appears to be similar to the reactivity of Cys residues in serum albumin (Alb-SH), which is activated by histidine residues. It is known that Alb-SH is the most abundant plasma protein and the main extracellular source of thiol groups in the circulatory systems. As the main function of Alb-SH is the transport of various substrates such as metal

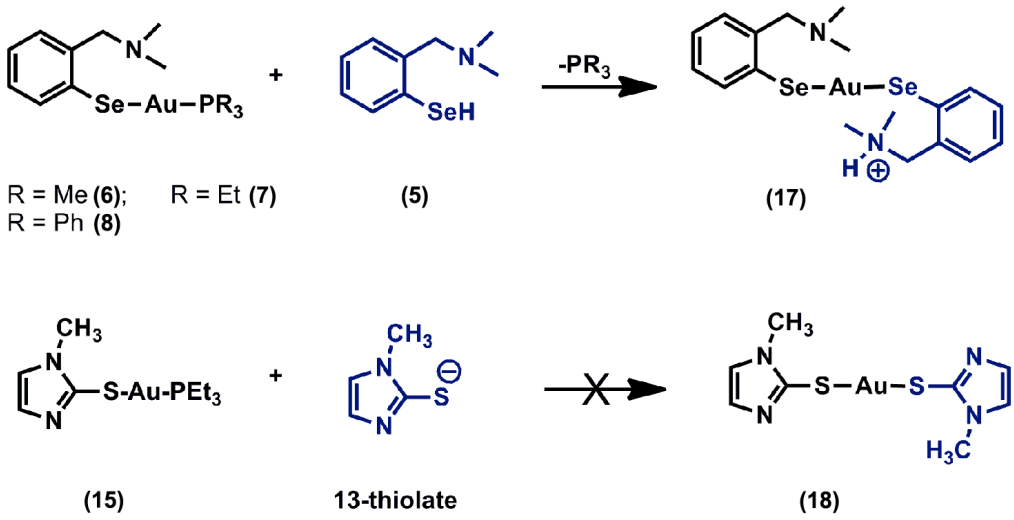


Reaction of Cys34 residue of serum albumin with auranofin.

The proximal His39 residue activates the thiol group of Cys34 to produce a more reactive thiolate[5]

Scheme 2

ions, amino acids, medicinal drugs etc from the site of adsorption to the site of action, the interaction of gold(I) drugs with serum albumin has been extensively studied.[6-8] It has been shown that AUR reacts with Cys34 residue in albumin to produce a gold(I)-thiolate complex.[6-8] Although albumin contains 35 cysteine residues, only Cys34 reacts with gold(I) as the remaining cysteines are present in disulfide form. It should be noted that the thiol group in Cys34 exists predominantly as thiolate due to the presence of a proximal histidine residue (His39), which deprotonates the thiol moiety to form a thiolate-imidazolium ion pair (Scheme 2).[20,21] As the *pK*a of albumin thiolate anion is much lower (~5) than the free cysteine anion (8.15) at physiological *p*H, a rapid nucleophilic attack of Cys34 at the gold(I) center in AUR leads to the formation of the corresponding gold(I)-thiolate complex.[22] Therefore, the generation of thiolate appears to be important for a facile synthesis of gold(I)-thiolate complex. It should be noted that several Cys-containing proteins such as Alb-SH, hGR and PTP effectively interact with the anti-arthritic gold(I) compounds as one or more Cys residues in these proteins are activated by His-mediated deprotonation.[6-10]



Nucleophilic attack of the selenol (**5**) at the Au(I)-center in gold-selenolates (**6**) –(**8**) to produce the bis-selenolate-gold complex (**18**). No spectral change was observed when (**13**)-thiolate was added to complex (**15**)

Scheme 3

The stability of gold(I)-thiolate complexes is generally altered by ligand exchange reactions. Such ligand exchange reactions have been frequently observed in protein-gold(I)-phosphine complexes due to the nucleophilic attack of proximal Cys residues at the Au(I)-center. The incoming nucleophile can either replace the thiolate or the phosphine moiety in the protein-gold(I)-phosphine complexes depending upon the strength of Au(I)-S and Au(I)-P bonds. Coffer *et al.*[6(b, c)] have previously shown that the nucleophilic attack of the Cys-34 residue of the Alb-SH at the Au(I)-center of AUR leads to the formation of protein-gold(I)-phosphine (Alb-S-AuPEt$_3$) complex by the replacement of thioglucose moiety. This suggests that the replacement of thiolate group in gold(I)-thiolates is more favored than the replacement of the phosphine ligand attached to the Au(I) center.[2a] In contrast, in the presence of selenol (**5**), the removal of phosphine ligand was found to be more favored than the selenolate exchange in the gold(I)-selenolate complexes (**6**) – (**8**) (Scheme 3).[15] This is probably due to the presence of non-bonded Se···N interactions in complexes (**6**) – (**8**), which can weaken the Au(I)-P bond, leading to the formation of bio-selenolate-gold(I) complex (**17**) with the removal of phosphine moiety upon the nucleophilic attack of selenol (**5**). As the imidazole-based gold-thiolates (**14**) – (**16**) do not exhibit any such non-bonded interactions, the reactivity of these complexes toward Cys residues may lead to the formation of protein-gold(I)-phosphine complexes by eliminating the *N*-methylimidazole thiolate moiety. To understand the ligand exchange reactions in complexes (**14**) – (**16**), we treated complex (**15**) with an equimolar amount of *N*-methylimidazole thiolate (**13**)-thiolate and followed the reaction by ^{31}P NMR spectroscopy. The signal for compound (**15**) at 37.1 ppm was unchanged upon treatment with (**13**)-thiolate, indicating that the thiolate does not replace the Et$_3$P moiety to produce complex (**18**) (Scheme 3). A similar reactivity of gold(I)-thiolate was observed when AUR was treated with serum albumin (Alb-SH). It should be mentioned that the formation of gold(I)-thiolates may be possible upon the administration of anti-arthritic gold(I) compounds to the patients undergoing treatment for hyperthyroidism with thiourea-based drugs. Therefore, the chemical reactions between the two entirely different classes of drugs should be considered while designing new antithyroid agents.

In addition to the replacement of phosphine ligands in complexes (**6**) – (**8**) by selenol (**5**), phosphine interchange reactions were also observed upon treatment with PPh$_3$. The non-bonded Se···N interactions in complexes (**6**) – (**8**) weaken the Au(I)-P bonds and this '*trans* directing effect' facilitates the removal of phosphine ligands. In contrast, the replacement of *N*-methylimidazole thiolate moiety was observed upon treatment of complexes (**14**) and (**15**) with PPh$_3$. The nucleophilic attack of PPh$_3$ at the Au(I) centers in complexes (**14**) and (**15**) produces the corresponding phosphine complexes $(R_3PAuPPh_3)^+Cl^-$ (R = Me or Et). In the

presence of an excess amount of PPh_3, further exchange of phosphine ligands takes place, leading to the formation of $Au(PPh_3)_2^+ Cl^-$ as the final product.

Conclusions

The therapeutic gold(I) compounds react with the commonly used thiourea-based antithyroid drug, methimazole, to produce the corresponding gold(I)-thiolate complexes. Although these gold(I)-thiolates can inhibit enzymes similar to the anti-arthritic gold drugs, extensive ligand exchange reactions may alter the inhibitory effects of these complexes. The ligand exchange reactions take place at the Au(I) center by an attack of the incoming nucleophile. The exchange of the thiolate or phosphine ligands in the phosphine-gold(I)-thiolate complexes depends on the relative strengths of Au(I)-S or Au(I)-P bonds. The effect of gold(I) compounds on the enzymatic activity of cysteine- or selenocysteine-containing proteins may have medicinal implications for the treatment of rheumatoid arthritis.

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