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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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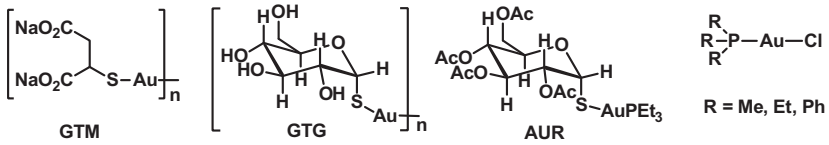


Fig. 1. Chemical structures of some representative gold(I) compounds.

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

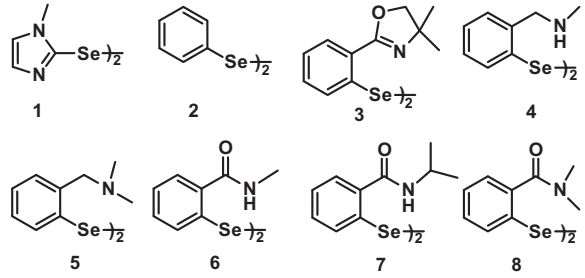
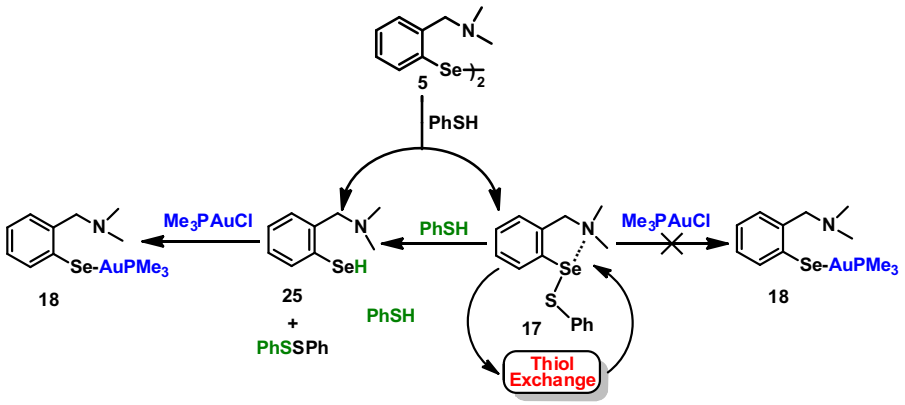


Fig. 2. Chemical structures of some representative diaryl diselenides **1**–**8** as synthetic GPx mimics.

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.