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Gold(III) Assisted C-H activation of 1,4,7-trithiacyclononane : Synthesis and Spontaneous Resolution of a Bicyclic Chiral Sulfonium Salt

Cite this: DOI: 10.1039/x0xx00000x

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/x0xx00000x

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Reaction of [9]aneS$_3$ (1,4,7-trithiacyclononane) with KAuCl$_4$ in nitromethane yields the complex [Au([9]aneS$_3$)Cl$_2$][AuCl$_4$]. Heating of this salt yields the bicyclic sulfonium [9]aneS$_3^+$ (4,7-dithia-1-thioniabicyclo[4,3,0]nonane) as a racemic [AuCl$_4$]$^-$ salt. Further reaction produces [[9]aneS$_3^+$][AuCl$_2$], which undergoes spontaneous resolution upon crystallization. Each enantiomer of [[9]aneS$_3^+$][AuCl$_2$] was crystallographically characterized as well as the racemic [AuCl$_4$]$^-$ salt.

The coordination chemistry of the trithiacrown macrocycle [9]aneS$_3$ (1,4,7-trithiacyclononane) has been explored with a range of transition metals. However, the unique mismatch of the ideally facial tridentate bonding of [9]aneS$_3$ with the preferred square planar geometry d^8 metals (both homoleptic and heteroleptic complexes) frequently leads to unusual optical and electrochemical properties as well as stabilization of rare oxidation states.[1-5] The common structural feature found in nearly all instances of d^8 complexes of [9]aneS$_3$ is an axial M...S interaction longer than a bond but shorter than van der Waals contact. These pseudo-five coordinate complexes serve as models in understanding ligand substitution reactions in d^8 systems that involve associative mechanisms.[6-9]

While the chemistry of [9]aneS$_3$ with Pt(II) and Pd(II) has been explored extensively, much less work has focused on Au(III). With a growing range of organic transformations using Au(I) and Au(III) catalysts, insights into the bonding preferences of gold with [9]aneS$_3$ and the potential importance of stabilized Au(II) complexes may ultimately aid in improved catalyst design. To date, the most notable published examples of gold [9]aneS$_3$ chemistry include Schröder's reports of the homoleptic Au(III) species [Au([9]aneS$_3$)$_2$]$^{3+}$ and the related Au(II) complex [Au([9]aneS$_3$)$_2$]$^{2+}$.[10-11] The two axial Au...S distances in [Au([9]aneS$_3$)$_2$]$^{3+}$ are 2.926(4)Å, while [Au([9]aneS$_3$)$_2$]$^{2+}$ exhibits two Au...S interactions at 2.839(5) Å. Remarkably, the [Au([9]aneS$_3$)$_2$]$^{2+}$ complex is air stable as a solid.

Our group has recently accessed a series of cyclometallated gold complexes of the form [Au(C^N)([9]aneS$_3$)]$^{2+}$ (C^N = cyclometallating ligand) in an effort to better understand ancillary ligand effects on the axial M...S interactions present in these complexes.[12] During the course of our work, while focused on a synthetic scheme that involved introducing the [9]aneS$_3$ ligand prior to the ancillary cyclometallating ligand, we accessed a simple heteroleptic Au(III) complex of [9]aneS$_3$ with unique reactivity. Addition of [9]aneS$_3$ to a solution of KAuCl$_4$ (1:2 molar ratio) in nitromethane at room temperature yields a red-brown precipitate of [Au([9]aneS$_3$)Cl$_2$][AuCl$_4$] (**1**) in high yield. The X-ray structure of the cation of **1** is shown in Fig. 1.

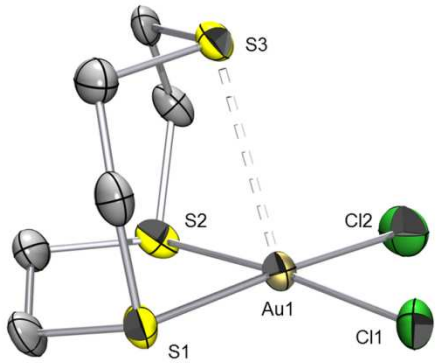


Fig. 1 Anisotropic thermal ellipsoid diagram of the cation of [Au([9]aneS$_3$)Cl$_2$][AuCl$_4$] (**1**) (50% probability ellipsoids).

The cation of **1** shows two equatorial Au-S bonds (2.301(3) Å, 2.313(2) Å) as well as an axial Au...S interaction at 2.999(3) Å (Au/S VDW radii sum = 3.46 Å). As the strong π-donor chloride ligands supply significant electron density to the gold center, the axial Au...S interaction lengthens in response. This long Au...S axial distance fully supports the assignment of the oxidation state as Au(III). The axial interaction of the unbonded sulfur of [9]aneS$_3$ responding to ancillary ligand effects has been previously observed in Pt(II) and Pd(II)

complexes[9,13,14] and more recently in Au(III) complexes.[12] The axial Au...S interaction of **1** is the longest observed in any Au(III) complex of [9]aneS$_3$, consistent with prior work regarding the electronic effects in these d^8 complexes. The ambient temperature NMR spectra of **1** demonstrate that the ligated [9]aneS$_3$ is fluxional on the NMR timescale as indicated by the AA'BB' splitting pattern in the ^{1}H spectrum and the single ^{13}C resonance observed. (Fig. 2) This is the first report of a fluxional [9]aneS$_3$ ligand on Au(III).

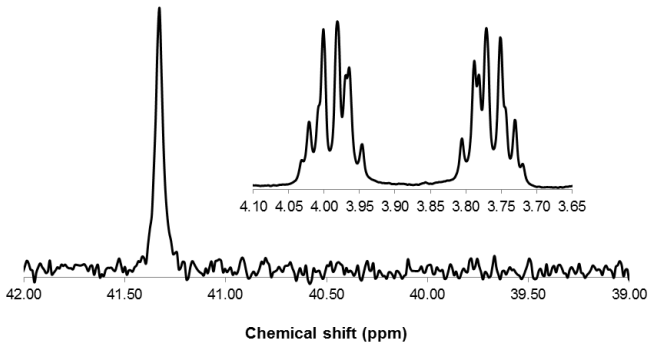


Fig. 2. ^{13}C and ^{1}H (inset) NMR spectra of [Au([9]aneS$_3$)Cl$_2$][AuCl$_4$] (**1**) in CD_3NO_2.

As we explored the stability of complex **1** to heat, we discovered an unexpected product. Heating of a nitromethane solution of **1** at 90°C for 2h results in the formation of the red-orange sulfonium salt [[9]aneS$_3^+$][AuCl$_4$] (**2**) ([9]aneS$_3^+$ =4,7-dithia-1-thioniabicyclo[4,3,0]nonane). The X-ray structure of **2** is shown in Fig. 3.

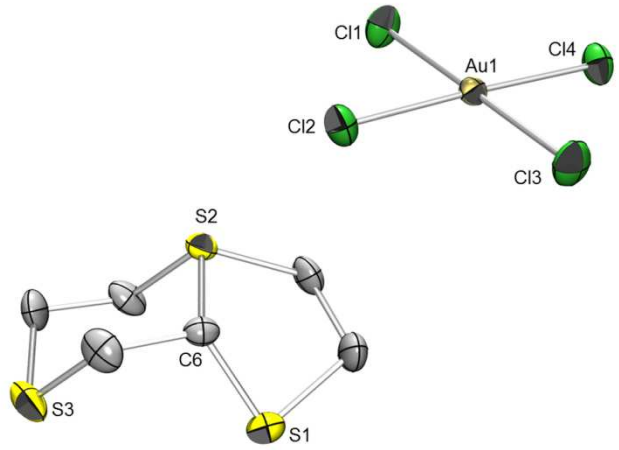
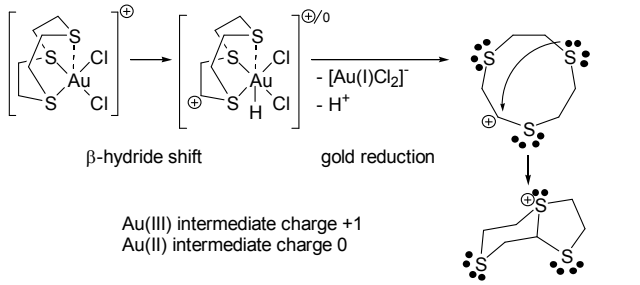


Fig. 3. Anisotropic thermal ellipsoid diagram of [[9]aneS$_3^+$][AuCl$_4$] (**2**) showing the C6(*S*),S2(*R*) enanantiomer (50% probability ellipsoids).

The structure consists of a bicyclic chiral sulfonium cation with chiral centers of opposite configuration at C6 and S2 within one molecule. Since **2** crystallizes in the centrosymmetric space group P$_{bca}$, the crystal is a racemic mixture of the enantiomeric pair C6-*R*, S2-*S* and C6-*S*, S2-*R*. The conformation of the 6-membered and 5-membered rings of the sulfonium cation can be described as chair and envelope, respectively. The lone pair of S2 is *trans* to the methine hydrogen of C6. The ^{13}C DEPT 135 NMR spectrum of **2** confirms the inequivalence of all carbons in the [9]aneS$_3^+$ cation as well as the presence of one unique methine carbon. (ESI Fig. S1). Though the ^{1}H NMR spectrum (ESI Fig. S2) is complicated, a highly deshielded doublet of doublets at 5.32 ppm is consistent with the proton attached to the chiral methine carbon and the total integration of all protons equals 11. Two other racemic salts of this [9]aneS$_3^+$ cation have been reported previously; one with the [TeBr$_6$]$^{2-}$ anion[15] and another with the [BF$_4$]$^-$ anion.[16] Each of these salts exhibit the same chiral configurations as that observed in **2**. Though few bicyclic sulfonium salts have been previously characterized by X-ray crystallography, a *p*-tosylate salt of the closely related two-sulfur analog 9S2$^+$ (5-thia-1-thioniabicyclo[4,3,0]nonane) has been reported.[17] Chiral sulfoniums are optically stable[18] and are widely used as ylide precurors for C-C bond forming reactions including the Corey–Chaykovsky reaction.[19] Chiral sulfoniums are of particular interest as targets for therapeutic use as inhibitors of glycosidase enzymes.[20-22]

The transformation of **1** to **2** can be explained by a mechanism that includes both the unique coordination geometry of [9]aneS$_3$ at d^8 metals as well as the propensity for Au(III) reduction (Scheme 1).



Scheme 1. Mechanism of formation of [9]aneS$_3^+$.

The first step in the proposed mechanism for the formation of **2** from **1** likely involves a β-hydride shift from the [9]aneS$_3$ ligand to the highly electrophilic Au(III) center which has an open coordination site opposite the Au...S axial interaction. This gold-hydride intermediate could be a pseudo six-coordinate Au(III) center that retains an axial Au...S interaction of the coordinated [9]aneS$_3$ or a six-coordinate Au(II) center with three genuine Au-S bonds to [9]aneS$_3$. These types of intermediates are supported by work that has shown the stabilization of Au(II) with [9]aneS$_3$ ligands[11] and that Au(III) hydrides have been postulated as intermediates in many gold-catalyzed organic reactions[23] including computational support[24] as well as a recent report a stable isolated Au(III) hydride.[25] In either case, with sufficient electron density provided by the hydride and additional [9]aneS$_3$ interaction (or bond), the gold then undergoes a reduction to Au(I) with concomitant loss of the unstable monocyclic [9]aneS$_3$ ligand cation and a proton. The ease of reduction of Au(III) to Au(I) in the presence of thioethers[26] supports this mechanism. The d^{10} Au(I) center retains the chloride ligands and adopts the preferred linear two-coordinate geometry. An intramolecular nucleophilic attack by a transannular sulfur atom completes the formation of the bicyclic sulfonium [9]aneS$_3^+$. C-H activation of [9]aneS$_3$ coordinated to an electrophilic metal center (Co^{3+}, Rh^{3+}, Ir^{3+}) has been previously observed.[27] In these cases however, as the metal center was

coordinatively saturated with two [9]aneS$_3$ ligands, the resulting C-H activation induced by addition of base yielded a ring-opened vinyl-thiother. In the case of **1**, the presence of the open coordination site *trans* to the Au...S interaction and the ease of Au(III) reduction are likely important to this difference in reactivity. The heated reaction to form **2** was monitored by ^{1}H NMR (ESI Fig. S3) and indicated no significant buildup of reaction intermediates.

Solutions of **2** undergo a slow decomposition to form the pale-yellow Au(I) salt [[9]aneS$_3^+$][AuCl$_2$] (**3**). Upon obtaining a crystal structure of **3**, it was observed that the space group determined was the noncentrosymmetric group $P2_12_12_1$. As the Flack parameter[28] indicated the absolute structure was well determined and the [9]aneS$_3^+$ cation possessed two chiral centers, the structure was required to be a single enantiomer. This structure (**3a**, Fig. 4) shows the same [9]aneS$_3^+$ ring conformations as **2**, as well as one of the enantiomeric configurations observed in **2**. In the case of **3a**, the structure exhibits only the enantiomer with configurations C6-*R* and S2-*S*. As a spontaneous resolution of these enantiomers should yield an equal amount of crystals with the opposite configurations at C6 and S2, a closer examination of the crystals was made. While crystals of **3** were not enantiomorphous in morphology, the crystals of each unique enantiomer are required to respond in an opposite fashion to extinction of polarized light. A microscope with cross-polarizers was used to identify crystals that behaved as **3a** under polarized light, as well as crystals that responded in an opposite fashion (ESI Fig. S4). In this way, a crystal of **3b** was identified and the structure was determined. The structure of **3b** (Fig. 4) was determined to be isomorphous with **3a**, except with opposite configurations of the chiral centers in the [9]aneS$_3^+$ cation (C6-*S*, S2-*R*). The Flack parameter of this structure also verified the correct absolute structure was obtained. To our knowledge, this is the first report of a pair of structurally characterized single enantiomer sulfonium salts.[29]

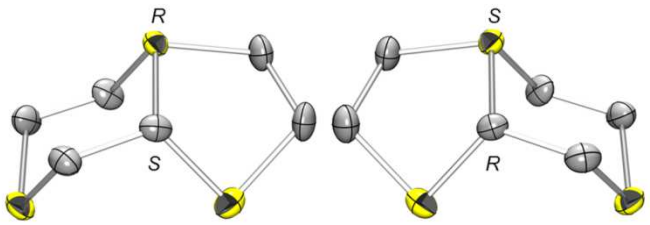


Fig. 4. Anisotropic thermal ellipsoid diagrams of the cation of C6(*S*),S2(*R*) [[9]aneS$_3^+$][AuCl$_2$] (**3a**) (left) and C6(*R*),S2(*S*) [[9]aneS$_3^+$][AuCl$_2$] (**3b**) (right) (50% probability ellipsoids, hydrogens and anions omitted).

Conclusions

We have synthesized a heteroleptic fluxional Au(III) [9]aneS$_3$ complex that undergoes a thermal reaction to form a racemic two-chiral center sulfonium salt derived from [9]aneS$_3$. The mechanism likely involves both the unique *fac*-tridentate coordination of [9]aneS$_3$ as well as redox of the Au(III) template. We observed the spontaneous resolution of the enantiomers of [[9]aneS$_3^+$][AuCl2] and obtained crystal structures of each enantiomer. The study of Au(III) templated cyclization of other related macrocycles such as [9]aneS$_2$O (1-oxa-4,7-dithiacyclononane) and [12]aneS$_3$ (1,5,9-trithiacyclononane) to form chiral sulfonium salts is underway.

Acknowledgements

The authors wish to acknowledge the National Science Foundation: Major Research Instrumentation award #1125975 "MRI Consortium: Acquisition of a Single Crystal X-ray Diffractometer for a Regional PUI Molecular Structure Facility". This work was funded through the St. Catherine University School of Humanities, Arts, and Sciences through the Endowed Chair in the Sciences.

Notes and references

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Electronic Supplementary Information (ESI) available: synthetic procedures, analytical data, detailed X-ray structural information, NMR spectra, and images of crystals. See DOI: 10.1039/c000000x/

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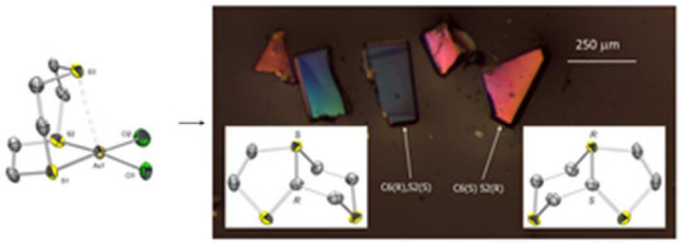

A trithiamacrocyclic ligand complex of Au(III) undergoes a redox-mediated thermal reaction to form a chiral bicyclic sulfonium salt.
29x10mm (300 x 300 DPI)