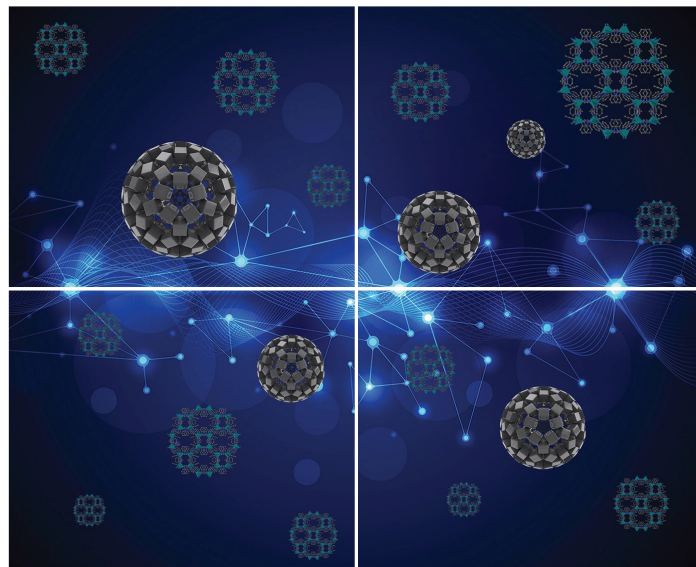


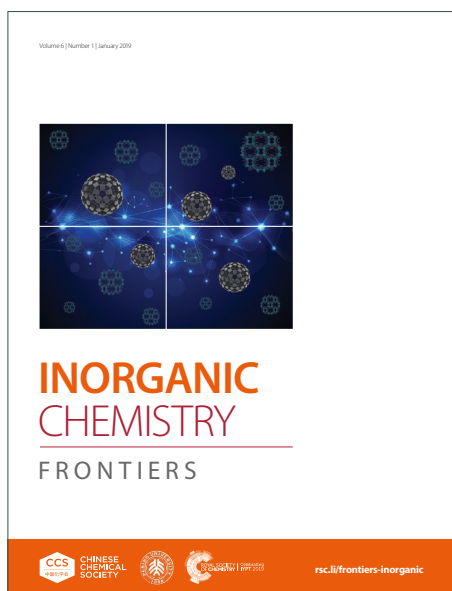
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ARTICLE

Conversion of a double-tetranuclear cluster silver helicate into a dihelicate *via* a rare desulfurization process

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We present the first example of a silver double-tetranuclear cluster helicate $[\text{Ag}_4\text{L}_2]$ obtained from a bithiosemicarbazone ligand using electrochemical synthesis. This cluster helicate undergoes a rare desulfurization process in chloroform giving rise to a cationic silver dihelicate $[\text{Ag}_2(\text{H}_2\text{L})_2]\text{SO}_4$. This is the first silver mediated desulfurization reaction.

Introduction

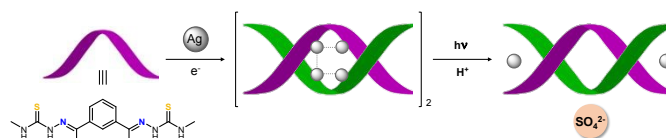
Helicity is a common feature in the natural world. Since ancient times helical motifs have been inspiration source for humans, including chemists. Thus, in the last decades a big effort has been made for obtaining artificial helical architectures. Between them, metallohelicates¹ are considered functional metal platforms with top applications in different areas of nanoscience related to biomedicine,^{1,2} catalysis,³ and magnetic materials.⁴

In 2005 our group presented for the first time a new type of helicates, the cluster helicates.⁵ These cluster helicates combine the inherent properties of metal clusters with the singular arrangement of metallohelicates. Our route to cluster helicates demonstrated that the use of pentadentate or tetradentate thiosemicarbazone ligands in combination with monovalent metal ions led to stable tetranuclear or hexanuclear cluster helicates.^{6,7} Since then several nice examples of cluster helicates have been presented in the literature, together its potential applications in fields like catalysis and nanomedicine.⁸

Thiosemicarbazone ligands have been used during a long time for the preparation of biological active metal compounds.⁹ More recently they were demonstrated to be suitable precursors of metallosupramolecular architectures due to its

great coordinative versatility, being possible to obtain cluster helicates,^{5,6} helicates¹⁰ or mesocates¹¹ with different metal ions and to predict their supramolecular structure.¹²

In this work, we present the first case of a double $\text{Ag}(\text{I})$ tetranuclear cluster helicate and its conversion into a sulfate dihelicate *via* a desulfuration process occurred during recrystallization. The tetradentate thiosemicarbazone ligand H_2L used in this work possesses two flexible bidentate $[\text{NS}]$ domains separated by a rigid aromatic spacer (Scheme 1), thus fulfilling the requirements generally established to assemble helical or meso-helical structures. It has been synthesised by the reaction of 1,3-diacetylbenzene and the corresponding 4-*N*-methyl-thiosemicarbazide precursor, as published before.⁶



Scheme 1. Conversion of the cluster helicate into a sulfate dihelicate *via* desulfurization process presented in this work.

Results and discussion

Electrochemical oxidation¹³ of a silver plate in a conducting acetonitrile solution of the ligand H_2L resulted in a yellow solution from which a yellow solid precipitated upon concentration under reduced pressure. The analytical and mass data agreed with an octanuclear $[\text{Ag}_8\text{L}_4]$ stoichiometry. Mass spectra show the octanuclear peak at 2200.7 m/z but also other lower fragments attributable to cluster degradation (Figure S1). NMR data demonstrates coordination of silver to deprotonated ligands in the octanuclear complex (Figure S2). Moreover the ^1H NMR spectrum shows a single set of signals revealing that the two arms of the ligands are equivalent upon coordination to the metal centres, which is indicative of a helical arrangement (Figure S2).^{5,6}

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Recrystallization of the acetonitrile mother liquors provided single crystals of the octanuclear complex $[\text{Ag}_4\text{L}_2]_2$ which were characterized by X-ray diffraction (Figure 1). The octanuclear crystal structure consists of two double-linked tetranuclear cluster helicates. Each cluster helicate comprise two dianionic ligand strands (L^{2-}) wrapped around a central tetranuclear $\text{Ag}(\text{I})$ core in a helical mode. Each ligand thread is bound to a couple of silver ions by means of the imine nitrogen and the thioamide sulfur atoms, the latter acting as bridge between two silver ions. The connection between the two tetranuclear clusters is achieved by means of two long N–Ag bonds $\text{Ag}3\text{--N}5$ 2.758 Å (Figures S3 and S4 in Supporting Information). The tetrahedral coordination geometries of the eight metal centres are much distorted, as illustrated by the range of angles between the N, S and Ag atoms (76.49–142.16°).

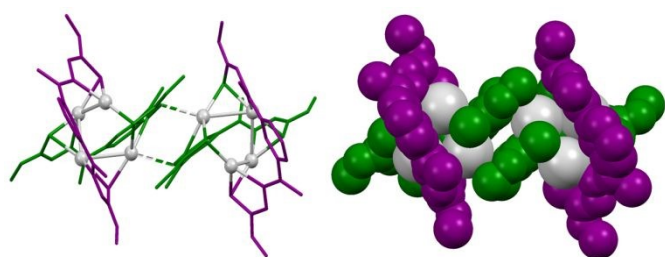


Figure 1. Stick and spacefill representation of the double-linked tetranuclear cluster helicate $[\text{Ag}_4\text{L}_2]_2$.

The four $\text{Ag}(\text{I})$ ions in each cluster form a distorted tetrahedron (Figures S3 and S4). The intermetallic Ag–Ag distances range from 3.006 to 3.111 Å between the sulfur-bridged Ag^{I} ions and from 3.315 to 4.247 Å between the unbridged Ag^{I} ions. These distances are significantly shorter than the sum of the van der Waals radii for two silver atoms (van der Waals radius for Ag = 3.44 Å)¹⁴ and may suggest the existence of metal–metal interactions.⁵ The possible existence of these interactions implies that the coordination number of the Ag^{I} ions should increase from 3 to 5 or 6, which is unusual for this metal ion. To the best of our knowledge this would be the first case of a double-tetranuclear cluster helicate.

Recrystallization of the silver cluster in chloroform in the presence of light affords yellow crystals suitable for X-ray diffraction studies. Surprisingly, the structure does not correspond to the cluster but consists of a cationic dinuclear bishelicate which contains one sulfate molecule as counterion, $[\text{Ag}_2(\text{H}_2\text{L})_2]\text{SO}_4 \cdot \text{H}_2\text{O}$ (Figure 2 and Figures S5 and S6). Herein, we must point out that despite of the two metal ions and the thiosemicarbazone chains present some disorder the crystal structure possess quality enough for the complete dihelicate crystallographic characterization.

In this dihelicate each neutral ligand is coordinated to both $\text{Ag}(\text{I})$ ions. The silver atoms adopt a distorted tetrahedral N_2S_2 kernel by coordination with the imine nitrogen and the thioamide sulfur atoms belonging to two intertwined neutral ligand threads H_2L (Figure S5). Both enantiomers are present in the unit cell in 50% yields. The existence of a distorted tetrahedral environment is confirmed by the values of the

metal–donor set bond angles (between 75.54–155.1°). The bond distances Ag–N and Ag–S are in the order to those found in the literature for $\text{Ag}(\text{I})$ complexes derived from thiosemicarbazone ligands and do not merit further mention. The long Ag–Ag bond distance, 5.497 Å, precludes any argentophilic interaction.

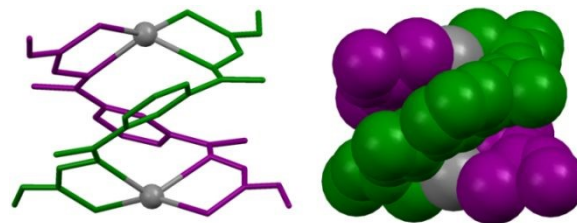


Figure 2. Stick and spacefill representation of the dinuclear bishelicate $\Delta\Delta\text{-}[\text{Ag}_2(\text{H}_2\text{L})_2]\text{SO}_4 \cdot \text{H}_2\text{O}$.

Considering the absence of any sulfur source in the reaction or in the crystallization media, this sulfate ion must be generated in a desulfurization process experienced by some thiosemicarbazone cluster molecules. This process can be explained as an oxidative elimination reaction, which gives rise to the loss of the thioamide sulfur atom. Wide thiosemicarbazones's literature offer several examples of desulfurization processes that produce different sulfur products like octasulfur S_8 , carbonitrile, sulfide, sulfona, hydrogen sulfate or sulfate.¹⁵ Different factors have been probed to induce desulfurization processes like strong oxidant agents, acidic and basic medium or coordination to metal ions. Regarding to the latter, to date metals with accessible oxidation states like manganese, copper and iron [e.g. $\text{Cu}(\text{I})/\text{Cu}(\text{II})$, $\text{Fe}(\text{II})/\text{Fe}(\text{III})$ and $\text{Mn}(\text{II})/\text{Mn}(\text{III})$] have been probed to promote thiosemicarbazone desulfurization processes whereas other like zinc, lead and cobalt did not undergo these reactions. According to these precedents, a silver promoted desulfurization is an unexpected result. As far as we are aware, silver-promoted desulfurization processes have not been described in thiosemicarbazones to date. However, these reactions have been reported for related thiosemicarbazides.¹⁶ We have performed a detailed study of the factors involved in the recrystallization of the cluster helicate and subsequently to the formation of the sulfate ion in the resulting dihelicate complex. Three are the main factors that may affect to this desulfurization process: solvent, light and time.

We have performed the recrystallization of the silver cluster in different solvents (acetonitrile mother liquors, methanol, ethanol, chloroform...) and in the presence or absence of light. We must point out that only those recrystallizations performed in chloroform in the presence of light lead to the formation of the sulfate helicate crystals. Concerning to the time factor, the appearance of the sulfate crystals takes place after a long crystallization period of 3–4 weeks. Herein we must note that the isolation of the sulfate crystals is a reproducible process, which precludes serendipity.

The fact that the desulfurization process takes place in chloroform only, leads us to think about the possible role of this solvent in the desulfurization process. It is well-known that

chloroform is an unstable solvent. For that reason, to enhance product shelf life it is combined with a variety of stabilizers (eg. ethanol or amylene), scavenging free radicals such as chloride or acid media from chloride acid. In order to propose a mechanism for the conversion of the double-linked tetranuclear cluster helicite into a dinuclear sulfate dihelicate in chloroform, ^1H NMR studies were performed by mimicking the crystallization conditions. The deuterated chloroform used for this purpose was not stabilized and hence it decomposed to a small amount of hydrochloric acid, as it had been exposed to light for a long period of time. All the spectra were acquired with presaturation for chloroform suppression at 7.26 ppm (Figure 3). The ^1H NMR spectrum of a freshly prepared solution of crystals of $[\text{Ag}_4\text{L}_2]_2$ in CDCl_3 was recorded and its evolution was monitored overtime. A single set of aromatic signals from the benzene spacer in the silver helicite was observed in the range 7.0-8.4 ppm (Figure 3a). A broad singlet assigned to the NH thioamide proton is partially overlapped with the suppressed chloroform signal at ca. 7.2 ppm. Moreover, an unexpected broad singlet at ca. 11.8 ppm suggests the protonation of the hydrazine NH in this complex.

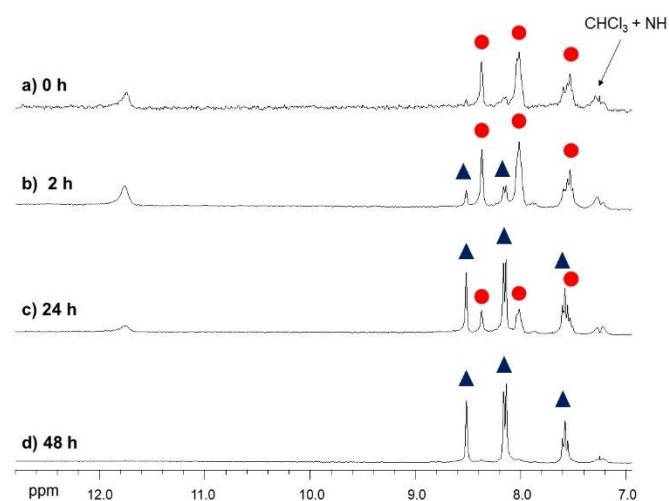


Figure 3. Evolution of the ^1H NMR spectrum (aromatic region) of the octanuclear helicite $[\text{Ag}_4\text{L}_2]_2$ (red dots) and formation of $[\text{Ag}_2(\text{H}_2\text{L})_2]^{2+}$ (blue triangles) in CDCl_3 .

Hence, the first step of the desulfurization and conversion mechanism may start with the protonation of the hydrazine NH groups in the acidic medium. This protonate cluster helicite was immediately formed in solution and rapidly evolved to a new species, as further signals were observed after 2 and 24 h (Figure 3b and 3c, respectively). After 48 h, a new symmetric silver complex, that might be attributed to the dinuclear dihelicate $[\text{Ag}_2(\text{H}_2\text{L})_2]^{2+}$, was detected as the only species in solution (Figure 3d). We must point out that in the case of NMR spectra of the dihelicate the NH signals could not

be observed due to deuterium intercalation processes (Figure 3d). The formation of $[\text{Ag}_2(\text{H}_2\text{L})_2]^{2+}$ was further supported by mass spectrometry, as the deuterated dihelicate peak was detected in the MALDI-TOF spectrum performed to the resulting NMR solution (Figure S7). These studies confirmed that the protonation of the hydrazide group and the formation of the silver dihelicate trigger the later desulfurization process.

Another point that must be considered is the formation of side-products after the hydrolysis. The isolation of the sulfate crystals is always accompanied by the appearance of a black solid that has been separated for identification purposes. Addition of a dilute 50% (v/v) solution from commercial chloride acid to that solid gave rise to disappearance of the dark particles after 5-6 hours whereas if commercial chloride acid (36% v/v) was added this solid was dissolved immediately. The analytical data of this solid show that it contains sulfur. All these results clearly indicate that this dark insoluble residue is not silver metal and contains sulfur in the form of silver hydrogen sulfide and/or silver sulfide. The formation of the final sulfate can be feasibly explained by partial oxidation of the silver hydrogen sulfide/silver sulfide by moisture oxygen, as it was previously reported.^{15e}

To identify all the species involved, we have also investigated the presence of desulfurization organic side-products in the chloroform recrystallization solution. In both, -ESI spectra could be observed a peak at 336 m/z corresponding to the *b*sthiosemicarbazone H_2L ligand but also another peak at 304 m/z, which corresponds to the semicarbazone side-product released from the oxidative desulfurization (Figure S8). The formation of semicarbazone moieties is a well-known process that has been proposed to be involved in the *in vitro* biological activity of thiosemicarbazone compounds.¹⁷ So, this result confirm that the ligand H_2L is the source of sulfur for the formation of the SO_4^{2-} anion.

With all the above facts in mind, we have tried to formulate a possible mechanism to account the formation of the sulfate dihelicate from the double-tetranuclear cluster helicite. The first step would start with the cluster helicite dissolved in the acidic media generated by the light-degradation of chloroform. This pH causes the protonation of the hydrazine moiety (**1**). Because of this, a partial demetallation of the Ag-cluster takes place, giving rise to the cationic dinuclear silver compound (**2**) (Figure 4). In a second instance, some of these molecules undergo a nucleophilic attack by a water molecule^f which triggers ligand desulfurization with the formation of a semicarbazone fragment (**3**) and the releasing of hydrogen sulfide and/or silver sulfide (**4**). Then in a slower process, silver hydrogen sulfide and/or silver sulfide converts to sulfate in the presence of moisture oxygen. Finally, the remaining dinuclear complex combines with the sulfate thus generating the final crystallised sulfate dihelicate $[\text{Ag}_2(\text{H}_2\text{L})_2]\text{SO}_4$.

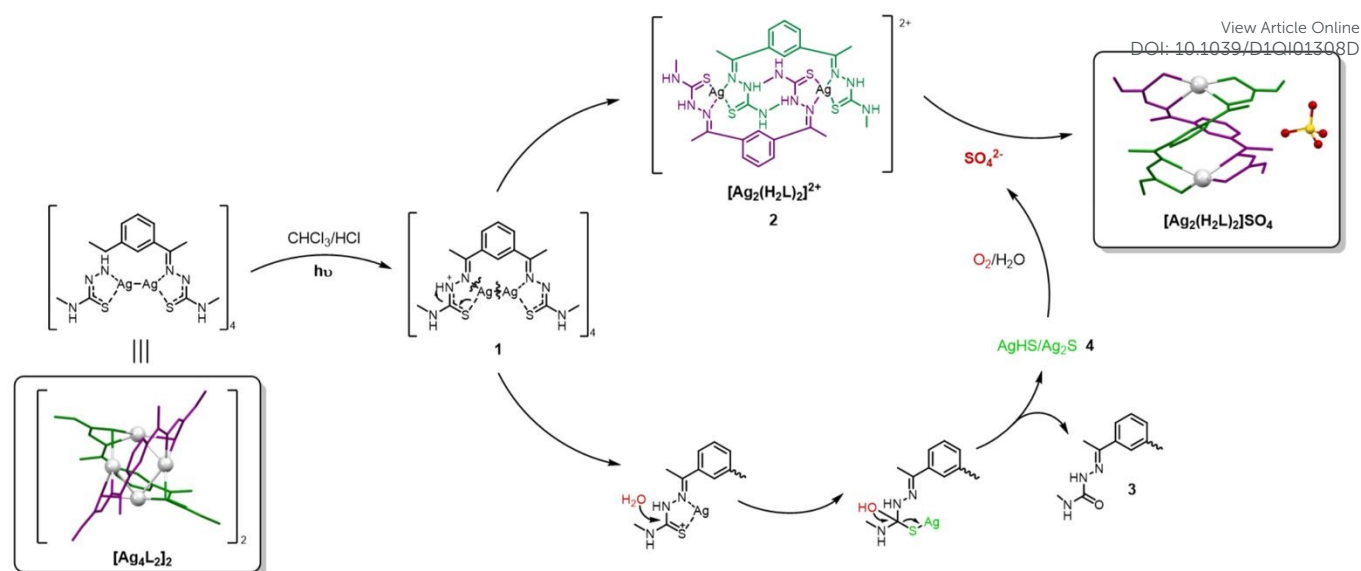


Figure 4. Conversion of the double-tetranuclear cluster helicate $[Ag_4L_2]_2$ via desulfurization and the later formation of the dinuclear helicate $[Ag_2(H_2L)_2](SO_4)$.

Conclusions

In conclusion, a novel silver double-tetranuclear cluster helicate from a bithiosemicarbazone ligand using electrochemical synthesis has been obtained. The conversion of this cluster helicate into a dinuclear dihelicate by means of a desulfurization occurred during recrystallization has been studied in detail. To the best of our knowledge, this is the first example of a desulfurization reaction mediated by silver ions.

This finding provides valuable information for understanding new desulfurization processes and we believe it could open new routes for the interconversion of helical architectures.

Author Contributions

The research was equally conceived by M. M. C., A. M. G.-N. and R. P. Compounds were synthesized and characterized by S. F.-F, M. J. R., L. M. G.-B. and M. M.-C. The desulfurization mechanism was rationalised by J. M. S. and J. G.-T. M. M. was involved in the global analysis of the experimental results. Crystallographic work was performed by G. Z. All authors have contributed during the paper writing and all of them have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Innovación y Universidades, METALBIO (CTQ2017-90802-REDT) and NANOMETDRUGS (RED2018-102471-T).

Notes and references

‡ Crystal data for $[Ag_4L_2]_2$: Formula: $C_{56}H_{72}Ag_8N_{24}S_8$; Volume: $3544.1(3) \text{ \AA}^3$, MW, 2200.82 $\text{g}\cdot\text{mol}^{-1}$; Crystal size: $0.18 \times 0.07 \times 0.06 \text{ mm}^3$; Z= 2; Spatial Group: $Pnn2$; D: 2.062 mg m^{-3} ; Crystal System: Orthorhombic; Interval θ : $3.1\text{--}30.0^\circ$; $a = 10.7941(5) \text{ \AA}$; $b = 17.6381(9) \text{ \AA}$, $c = 18.6154(9) \text{ \AA}$; $\alpha = 90^\circ$; $\beta = 90^\circ$; $\gamma = 90^\circ$; $\mu = 2.45 \text{ mm}^{-1}$; $F(000) = 2160$; Radiation $\lambda(\text{Mo-K}\alpha) = 0.7107 \text{ \AA}$, Measured/unique reflexions: 83075/11795 (Rint= 0.060); R= 0.027; wR= 0.044; GOF= 1.041; Residues: 0.73/-0.59 e \AA^{-3} .

§ Crystal data for $[Ag_2(H_2L)_2](SO_4)\cdot H_2O$: Formula: $C_{28}H_{42}Ag_2N_{12}O_5S_5$; Volume: $3743.5(5)$, MW, 1002.78 $\text{g}\cdot\text{mol}^{-1}$; Crystal size: $0.08 \times 0.06 \times 0.06 \text{ mm}^3$; Z= 4; Spatial Group: $I2/a$; D: 1.779 mg m^{-3} ; Crystal System: Monoclinic; Interval θ : $1.9\text{--}25.4^\circ$; $a = 16.3978(16) \text{ \AA}$; $b = 13.1041(7) \text{ \AA}$, $c = 17.5038(10) \text{ \AA}$; $\alpha = 90^\circ$; $\beta = 95.561(2)^\circ$; $\gamma = 90^\circ$; $\mu = 1.38 \text{ mm}^{-1}$; $F(000) = 2032$; Radiation $\lambda(\text{Mo-K}\alpha) = 0.7107 \text{ \AA}$, Measured/unique reflexions: 17775/3413 (Rint= 0.1); R= 0.055; wR= 0.143; GOF= 1.016; Residues: 1.46/-0.62 e \AA^{-3} .

† The crystallization of $[Ag_2(H_2L)_2](SO_4)\cdot H_2O$ has been achieved in an open to air vial and the $CHCl_3$ used for that purpose has not been dried, so the water molecules can come from both the air moist or/and water content of the $CHCl_3$ bottle.

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