

Synthesis, reaction and structure of a highly light-stable silver(I) cluster with an $\text{Ag}_4\text{S}_4\text{N}_4$ core having a tridentate 4N -morpholyl 2-acetylpyridine thiosemicarbazone ligand: Use of water-soluble silver(I) carboxylates as a silver(I) source†

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A novel neutral tetrameric silver(I) cluster $[\text{Ag}(\text{mtsc})_4]$ was obtained from reactions of a tridentate 4N -morpholyl 2-acetylpyridine thiosemicarbazone ligand (N' -[1-(2-pyridyl)ethylidene]morpholine-4-carbothiohydrazide, Hmtsc) and silver(I) sources containing Ag–O bonds (Ag_2O , $\text{Ag}(\text{OAc})$, silver(I) 2-pyrrolidone-5-carboxylate $\infty\{[\text{Ag}(\text{Hpyrrld})]_2\}$, silver(I) 5-oxo-2-tetrahydrofurancarboxylate $\infty\{[\text{Ag}(\text{othf})]_2\}$, and silver(I) complexes with camphanic acid $\infty\{[\text{Ag}(\text{ca})]\}$ and $\infty\{[\text{Ag}(\text{ca})(\text{Hca})]\}$). The cluster was characterized by elemental analysis, TG/DTA, FTIR and single-crystal X-ray analysis in the solid state. The solution properties of the complexes were investigated using solution molecular weight measurement, ESI-MS and solution (^1H , ^{13}C and ^{31}P) NMR spectroscopy. The obtained cluster is a novel example of a light-stable Ag^{I} cluster with a tridentate thiosemicarbazone ligand and the second report of a crystal structure of a thiosemicarbazone silver(I) complex. The reaction of the tetramer with a large excess of PPh_3 gave dimeric complexes, namely, $[\text{Ag}(\mu(\text{S})\text{-mtsc})(\text{PPh}_3)_2]_2$ and $[(\text{PPh}_3)_2\text{Ag}(\mu(\text{S})\text{-mtsc})_2\text{Ag}]$. The chloroform solution of the tetrameric complex showed modest and effective activities against selected bacteria (*Bacillus subtilis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*) and yeasts (*Candida albicans* and *Saccharomyces cerevisiae*), respectively, but it did not inhibit the growth of any selected microorganisms in a water-suspension system.

Introduction

Thiosemicarbazones have attracted considerable interest because of their chemistry and potentially beneficial biological activities such as antitumor, antibacterial, antiviral and antimalarial activities. These biological activities are considered to be due to their ability to form chelates with heavy metals.¹ The biological activities of the metal complexes differ from those of either the ligand or the metal ion, and increased and/or decreased biological activities have been reported for several transition metal complexes such as copper(II) and nickel(II).^{1c–e,g,h,k,l} Thiosemicarbazones are versatile ligands because they can coordinate to the metal either as a neutral ligand or as a deprotonated ligand through the S, N, N atoms and also structural isomers (*E*-, *E'*- and *Z*-forms) are often seen.^{1e,j,2}

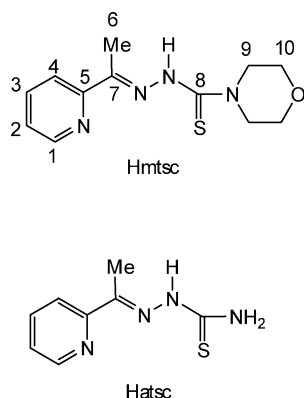
We investigated the relationship between structure and antimicrobial activity in the transition and non-transition metal complexes with multidentate 2-acetylpyridine thiosemicarbazone and semicarbazone ligands.³ The results obtained thus far have led to the conclusion that structural factors, which govern antimicrobial activities, are strongly dependent on the central metal ion. It is known that several silver(I) thiolates are pharmaceutically active

and their structural analyses show that they are complicated oligomeric or polymeric silver(I) complexes with μ -S bridging atoms.⁴ Although silver(I) complexes with thiosemicarbazones were reported more than 20 years ago,⁵ the first structural report showing a hexameric silver(I) cluster with 2-salicylaldehyde thiosemicarbazone was published only in 2004,⁶ probably due to their light-unstable properties.

In this study, a light-stable tetrameric silver(I) cluster ($[\text{Ag}(\text{mtsc})_4]$) was prepared from reactions of N' -[1-(2-pyridyl)ethylidene]morpholine-4-carbothiohydrazide (Hmtsc) with several silver(I) sources containing only Ag–O bonds, such as Ag_2O , $\text{Ag}(\text{OAc})$, silver(I) 2-pyrrolidone-5-carboxylate $\infty\{[\text{Ag}(\text{Hpyrrld})]_2\}$, silver(I) 5-oxo-2-tetrahydrofurancarboxylate $\infty\{[\text{Ag}(\text{othf})]_2\}$ and silver(I) complexes with camphanic acid $\infty\{[\text{Ag}(\text{ca})]\}$ and $\infty\{[\text{Ag}(\text{ca})(\text{Hca})]\}$. This crystalline cluster was characterized by elemental analysis, thermogravimetric (TG) and differential thermal analysis (DTA), FTIR, ^{31}P NMR spectroscopy and single-crystal X-ray analysis in the solid state. The behavior of the complex in solution was investigated by solution molecular weight measurement, electrospray ionization (ESI) mass spectrometry and ^1H , ^{13}C and ^{31}P NMR spectroscopy. In order to examine the reactivity of the cluster, the tetramer was allowed to react with PPh_3 . Moreover, the antimicrobial activities of the well-characterized cluster were evaluated by minimum inhibitory concentration (MIC: $\mu\text{g mL}^{-1}$) in a water-suspension and CHCl_3 solution.

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Results and discussion

Compositional characterization of $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$ in the solid and in solution

A reaction of the Hmtsc and $\infty\{[\text{Ag}(\text{Hpyrrld})_2]\}$ in a 4 : 1 CH_2Cl_2 –EtOH solvent, followed by crystallization from CHCl_3 , produced orange crystals of $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$, whose structure was determined by crystallography, as described later. TG/DTA measurements of the compound showed that it was isolated with two CHCl_3 solvated molecules and its decomposition began at around 240 °C. Further, the formula $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$ was consistent with the results of elemental analysis (shown in the Experimental section).

Even if an excess amount of Hmtsc or $\infty\{[\text{Ag}(\text{Hpyrrld})_2]\}$ was mixed, the isolated product was always $[\text{Ag}(\text{mtsc})]_4$. When water-soluble and light-stable silver(I) sources ($\infty\{[\text{Ag}(\text{othf})_2]\}$, $\infty\{[\text{Ag}(\text{ca})]\}$ and $\infty\{[\text{Ag}(\text{ca})(\text{Hca})]\}$) were used instead of $\infty\{[\text{Ag}(\text{Hpyrrld})_2]\}$ during the preparation, the carboxylate and carbonyl groups of the ligands (Hpyrrld, othf, ca) disappeared in 30 min. These four water-soluble silver(I) complexes with Ag–O bonds produced the tetramer quantitatively over a short period of reaction time at room temperature, the resulting product was easily purified by washing with water. When a light-unstable silver material ($\text{Ag}(\text{OAc})$) which was sparingly soluble in water was used, the reaction also completed within 30 min. When water-insoluble Ag_2O was used in the reaction, more than several hours were required to produce the tetramer quantitatively. When AgNO_3 was used in the reaction, complicated mixtures containing silver(I), mtsc[−] ligand and NO_3^- were observed, and we could not isolate the light-stable silver(I) complex after numerous trials.

The orange colour of this tetramer did not change for three months at room temperature, this indicates that the silver(I) cluster was extremely light-stable in the solid state. In contrast to the present silver(I) cluster, the colour of the Ag_6 cluster with 2-salicylaldehyde thiosemicarbazone prepared according to the literature⁶ began to change after it was allowed to stand for 1 d at room temperature in the solid state. When 2-acetylpyridine thiosemicarbazone (Hatsc) was used during the preparation, instead of Hmtsc, a light-unstable product was formed that contained both H_2pyrrld and Hatsc ligands. These preparations indicated that the 4-*N*-morpholine group in mtsc[−] played an important role in the formation of the light-stable cluster.

The ^1H NMR spectrum of the compound in CDCl_3 showed that the seven protons of the silver(I) complexes were shifted to a higher

field in comparison to those of the free Hmtsc ligand due to the coordinating mtsc[−] ligand. The signals of the ^1H NMR spectrum of the compound in CDCl_3 were broad. The ^{13}C NMR spectrum of the complex in CDCl_3 consisted of ten lines arising from signals of the ligand, whose spectrum did not change after it was allowed to stand for 1 d. This indicated that no structural isomerization of the mtsc[−] ligand (*E*, *E'* and *Z*-forms) occurred in solution. The chemical shift of C8 in the C=S group of the silver(I) complex was shifted more than 10 ppm to higher field as compared to that of the free ligand, Hmtsc. Surprisingly, neither precipitation nor colour change was observed for CH_2Cl_2 or CDCl_3 solutions of this silver(I) cluster for three months at room temperature.

The positive ion ESI-MS spectrum showed several peaks assigned to $[\text{AgL} + \text{H}]^+$, $[\text{AgL}(\text{HL}) + \text{H}]^+$ and $[\text{Ag}_n(\text{mtsc})_{n-1}]^+$; m/z (relative intensity) = 372 (74) $\{[\text{Ag}(\text{mtsc})] + \text{H}^+\}^+$, 636 (59) $\{[\text{Ag}(\text{mtsc})(\text{Hmtsc})] + \text{H}^+\}^+$, 743 (33) $\{[\text{Ag}_2(\text{mtsc})_2] + \text{H}^+\}^+$, 850 (43) $\{[\text{Ag}_3(\text{mtsc})_3]\}^+$, 1114 (15) $\{[\text{Ag}_5(\text{mtsc})_5] + \text{H}^+\}^+$, 1221 (54) $\{[\text{Ag}_4(\text{mtsc})_4]\}^+$, 1593 (68) $\{[\text{Ag}_5(\text{mtsc})_4]\}^+$, 1964 (71) $\{[\text{Ag}_6(\text{mtsc})_5]\}^+$, 2333 (91) $\{[\text{Ag}_7(\text{mtsc})_6]\}^+$, 2704 (100) $\{[\text{Ag}_8(\text{mtsc})_7]\}^+$, 3076 (31) $\{[\text{Ag}_9(\text{mtsc})_8]\}^+$, 3448 (4) $\{[\text{Ag}_{10}(\text{mtsc})_9]\}^+$ and 3820 (1) $\{[\text{Ag}_{11}(\text{mtsc})_{10}]\}^+$. The intensity of the tetramer is high, but not extremely high. The intensity of the other species ($[\text{Ag}(\text{mtsc})_n]$) is also obviously observed.

The solution molecular weight measurements of the crystalline or powder $[\text{Ag}(\text{mtsc})]_4$ in CHCl_3 or CH_2Cl_2 solutions indicated that the molecular weight was in the range 950 to 1160, which was higher than the molecular weight of the dimeric species ($[\text{Ag}(\text{mtsc})_2]$) but lower than that of the tetramer. The broad signals of the ^1H NMR spectrum, solution molecular weight measurement and ESI-MS indicated the existence of another $[\text{Ag}(\text{mtsc})]_n$ species in solution (where *n* is a number other than four). Under the ESI-MS measurement conditions, higher orders of multinuclear species up to nonamer were also observed in addition to the tetramer. The low solubility of the tetramer and the ease of packing would be reasons why the isolated product was always $[\text{Ag}(\text{mtsc})]_4$. These results indicated that the mtsc[−] coordination to Ag^{I} (*i.e.* coordination of guideline N and S donor atoms and maybe Ag–Ag van der Waals contacts) and not the number of $[\text{Ag}(\text{mtsc})]$ units in the cluster played an important role in the light-stable properties of the silver(I) complex.

Crystal and molecular structures of $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$

The molecular structure of the silver(I) complex with the atom numbering scheme is shown in Fig. 1(a) and the geometry around the silver(I) atoms is shown in Fig. 1(b). Selected bond distances and angles are listed in Table 1.

The X-ray structure analysis revealed that the silver(I) complex with the tridentate thiosemicarbazone bearing a 2-pyridine ring was a tetrameric cluster, $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$. To date, this is the second reported example of a structural study of silver(I) complex with thiosemicarbazone ligands. The first structural report of a silver(I) complex with thiosemicarbazone was published in 2004, which reported the hexamer with the thiosemicarbazone bearing a phenol moiety.⁶ We think that both the donor atom difference (NNCS coordination of the tetramer *vs* NS coordination of the hexamer⁶) as well as the *N*-morpholyl substituent of thiosemicarbazone ligand made the structural difference between the two clusters.

Table 1 Selected bond distances (Å) and angles (°) for [Ag(mtsc)]₄·2CHCl₃, [Ag(μ(S)-mtsc)(PPh₃)₂]₂ and [(PPh₃)₂Ag(μ(S)-mtsc)₂Ag]^a

[Ag(mtsc)] ₄ ·2CHCl ₃			
Ag1–N1	2.528(2)	N2–Ag1–N1	67.07(7)
Ag1–N2	2.329(2)	N2–Ag1–S1	74.64(5)
Ag1–S1	2.5614(9)	N1–Ag1–S1	135.64(5)
Ag1–S2 ⁱ	2.4568(10)	N1–Ag1–S2 ⁱ	99.18(5)
Ag2–N5	2.443(2)	S1–Ag1–S2 ⁱ	124.00(3)
Ag2–N6	2.387(2)	N6–Ag2–N5	67.54(7)
Ag2–S1	2.4537(12)	N6–Ag2–S1	130.68(5)
Ag2–S2	2.7109(10)	N5–Ag2–S1	109.73(5)
Ag1–Ag2 ⁱ	2.9027(12)	N6–Ag2–S2	70.36(5)
Ag2–Ag2 ⁱ	3.2111(11)	N5–Ag2–S2	127.35(5)
		S1–Ag2–S2	121.48(2)
		Ag1–S1–Ag2	106.61(2)
		Ag2–S2–Ag1 ⁱ	68.14(3)
[Ag(μ(S)-mtsc)(PPh ₃) ₂] ₂			
Ag1–N1	2.6198(14)	N2–Ag1–N1	64.83(4)
Ag1–N2	2.4252(13)	N2–Ag1–S1	72.60(3)
Ag1–S1	2.6397(4)	P1–Ag1–N1	95.09(3)
Ag1–P1	2.4203(4)	S1–Ag1–S1 ⁱⁱ	109.548(11)
Ag1–S1 ⁱⁱ	2.6402(4)	P1–Ag1–S1	111.737(15)
Ag1...Ag1 ⁱⁱ	3.046(3)	P1–Ag1–S1	120.910(14)
[(PPh ₃) ₂ Ag(μ(S)-mtsc) ₂ Ag]			
Ag1–S1	2.481(3)	S1–Ag1–S2	114.43(6)
Ag1–S2	2.640(3)	S1–Ag1–N2	75.61(12)
Ag1–N2	2.462(4)	S1–Ag1–N5	105.31(11)
Ag1–N5	2.588(5)	S1–Ag1–N6	128.39(12)
Ag1–N6	2.356(4)	S2–Ag1–N2	122.34(9)
Ag2–S1	2.690(3)	S2–Ag1–N5	135.57(12)
Ag2–S2	2.707(4)	S2–Ag1–N6	73.46(10)
Ag2–P1	2.470(2)	N2–Ag1–N5	85.39(14)
Ag2–P2	2.481(2)	N2–Ag1–N6	146.12(12)
Ag1...Ag2	3.012(3)	N5–Ag1–N6	66.48(13)
		S1–Ag2–P1	114.31(8)
		S1–Ag2–P2	99.76(6)
		S1–Ag2–S2	105.85(6)
		S2–Ag2–P1	102.99(10)
		S2–Ag2–P2	112.64(8)
		P1–Ag2–P2	120.81(4)

^a Symmetry operations: i = −x, 1 − y, 1 − z; ii = −x, 1 − y, 2 − z.

The complex crystallized in the space group $P\bar{1}$ and one tetramer was located in the unit cell. There was an inversion centre in the complex and an asymmetric unit contained one-half of [Ag(mtsc)]₄·2CHCl₃. Two solvated CHCl₃ molecules were disordered. The pyridine ring and the connecting azomethine moiety of four tridentate ligands were almost parallel. The ligand that contained the N1, N2 and S1 atoms was almost planar with Ag1 located at 0.707(2) Å from the plane. In contrast, the mtsc[−] that contained the N5, N6 and S2 atoms was twisted, the N5, N6 and Ag2 atoms were on a plane, however, S2, C20 and the successively connecting morpholine moiety were not on the plane.

As shown in Fig. 1(b), the geometry around the Ag1 atom was a distorted tetrahedron composed of the N1, N2 and S1 atoms of one mtsc[−] and the S2ⁱ atom of another mtsc[−]. Four atoms (N5, N6, S2 and S1) are also coordinated to Ag2. Each sulfur atom (S1, S2, S1ⁱ and S2ⁱ) bridges the two Ag(i) atoms. The Ag1–S1–Ag2 and Ag2–S2–Ag1ⁱ angles were 106.61(2) and 68.14(3)°, respectively. The Ag1–Ag2ⁱ and Ag2ⁱ–Ag2 distances were 2.9027(12) and 3.2111(11) Å, respectively, which are longer than the Ag–Ag separation of metallic silver (2.88 Å)^{7a} but shorter than twice the van der Waals radius for silver (3.44 Å).^{7b} These Ag–Ag distances indicated the existence of three van der Waals contacts in the tetramer (dotted line in Fig. 1(b)). Six atoms (Ag1,

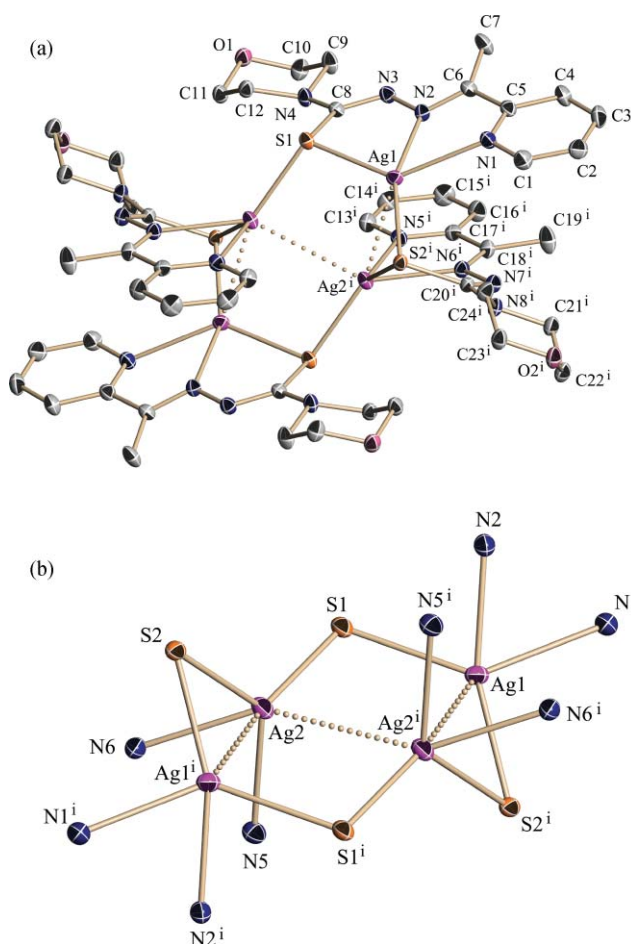


Fig. 1 (a) Molecular structure of [Ag(mtsc)]₄·2CHCl₃ in the solid-state with 50% probability ellipsoids. Atoms labeled 'i' are inversion-related equivalents at (−x, 1 − y, 1 − z). Solvent molecules are omitted for clarity. (b) The 8-membered Ag₄S₄N₈ framework.

Ag2ⁱ, S1ⁱ, Ag1ⁱ, Ag2 and S1) were almost on the plane and two sulfur atoms (S2 and S2ⁱ) were outside the plane. The torsion angles Ag2–Ag2ⁱ–Ag1–S1 and Ag2–Ag2ⁱ–Ag1–S2ⁱ were −13.384(14) Å and 120.10(2)°, respectively. During the preparation of various silver(I) complexes with thiol ligands, such as 2-mercaptobenzoic acid (H₂mmba), mercaptonicotinic acid (H₂mna) and thiomalic acid (H₃tma), we found that the silver(I) complexes produced with both thiol and carboxylate groups tended to form light-stable oligomeric and polymeric silver(I) complexes.^{4b,d} Among several structural reports of silver(I) thiolates containing an Ag₄S₄ core,^{4d,8} the framework of the Ag₄S₄N₈ core of [Ag(mtsc)]₄ is unique.

Reaction of [Ag(mtsc)]₄ with PPh₃

In order to investigate the reactivity of the tetramer, it was allowed to react with PPh₃. When [Ag(mtsc)]₄ was reacted with PPh₃ in the molar ratio 1 : 4, the solubility of the isolated powder was similar to that of the tetrameric starting material. More PPh₃ was added to the solution containing the tetramer and ³¹P NMR spectra of the products were measured. Two signals were observed when 8 equiv. of PPh₃ was added. The intensity of the lower-field signal increased with the amount of PPh₃ and finally became a single peak when 40 equiv. of PPh₃ were added to the tetramer. Slow evaporation

produced light-stable single crystals of two dimers, whose colour and behavior were very similar. Their molecular structures were determined by X-ray crystallography, as shown in Fig. 2 and 3.

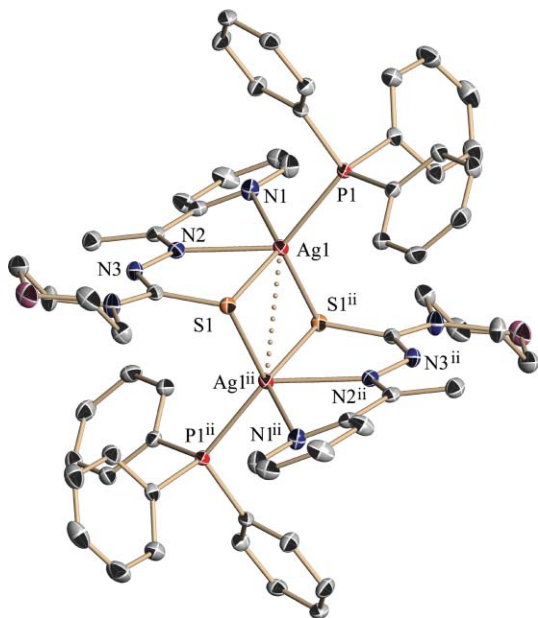


Fig. 2 Molecular structure of $[\text{Ag}(\mu(\text{S})\text{-mtsc})(\text{PPh}_3)_2]_2$ in the solid-state with 50% probability ellipsoids. Atoms labeled 'ii' are inversion-related equivalents at $(-x, 1-y, 2-z)$.

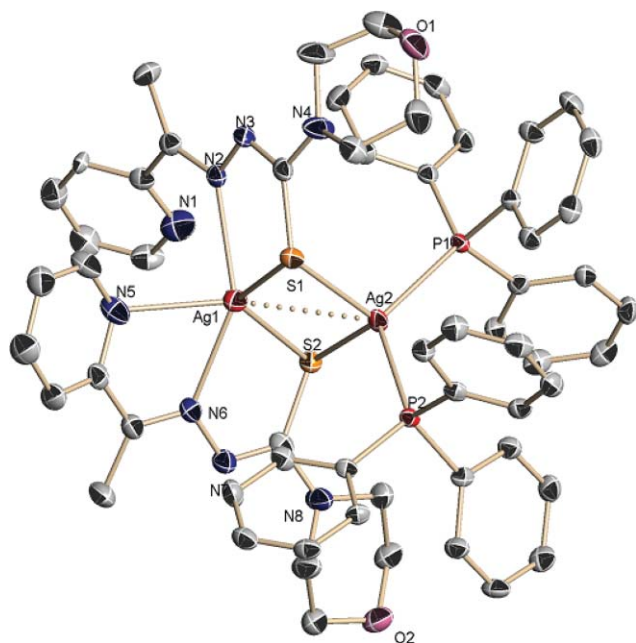


Fig. 3 Molecular structure of $[(\text{PPh}_3)_2\text{Ag}(\mu(\text{S})\text{-mtsc})_2\text{Ag}]$ in the solid-state with 50% probability ellipsoids.

The X-ray structure analysis revealed that one silver(I) complex was a symmetrical dimer, $[\text{Ag}(\mu(\text{S})\text{-mtsc})(\text{PPh}_3)_2]_2$. This silver(I) complex crystallized in the space group $P\bar{1}$ and one dimer molecule was located in the unit cell. Hence, there was an inversion centre in the dimer. As shown in Fig. 2, five atoms (the N1, N2 and S1 atoms

of one mtsc^- , the S1ⁱⁱ atom of the other mtsc^- and the P1 atom) are coordinated to Ag1. The sulfur atom bridges two Ag^I atoms. The P1–Ag1–S1 and P1–Ag1–S1ⁱⁱ angles were 111.737(15)° and 120.910(14)°, respectively. The Ag1–Ag1ⁱⁱ distance was 3.046(3) Å, which also indicated the existence of a van der Waals contact in this dimer (dotted line in Fig. 2).

The second dimer was $[(\text{PPh}_3)_2\text{Ag}(\mu(\text{S})\text{-mtsc})_2\text{Ag}]$. The space group of this second complex was also $P\bar{1}$. However, two molecules of the dimer were present in the unit cell because the two Ag^I atoms were not equivalent. As shown in Fig. 3, two mtsc^- ligands and two PPh_3 are coordinated to Ag1 and Ag2, respectively, and sulfur atoms bridge the two Ag^I atoms. Therefore, five atoms (N2, N5, N6, S1 and S2) are coordinated to Ag1 and four atoms (P1, P2, S1 and S2) are coordinated to Ag2. The Ag1–N1 distance was 3.186(5) Å, indicating that N1 was too far away for coordination to Ag2. The Ag1...Ag2 distance was 3.012(3) Å, which also indicated the existence of a van der Waals contact in this dimer.

In order to investigate the solution behavior, the isolated crystals were re-dissolved in CD_2Cl_2 in order to measure the ^1H , ^{13}C , ^{31}P and ^{109}Ag NMR spectra. The ^1H NMR signals were relatively broad. Splits in the signals due to two isomers were not observed in the ^{13}C NMR spectrum at ambient temperature. The ^{109}Ag NMR spectrum showed only one signal at 1021 ppm. At ambient temperature, the two isomers were not distinguishable in solution and the existence of fast equilibria of at least two isomeric species were suggested. As the temperature decreased, the single ^{31}P NMR peak shifted to higher field and divided into two broad peaks at -60°C (Fig. 4). When the solution was heated to ambient temperature, the two broad signals recombined into a single signal at almost the same place as before cooling. Two sets of doublets whose integrals were almost the same were observed at -0.33 and 5.46 ppm in the solid-state ^{31}P NMR spectrum. The ^{31}P spectrum in the solid state indicated that two species containing

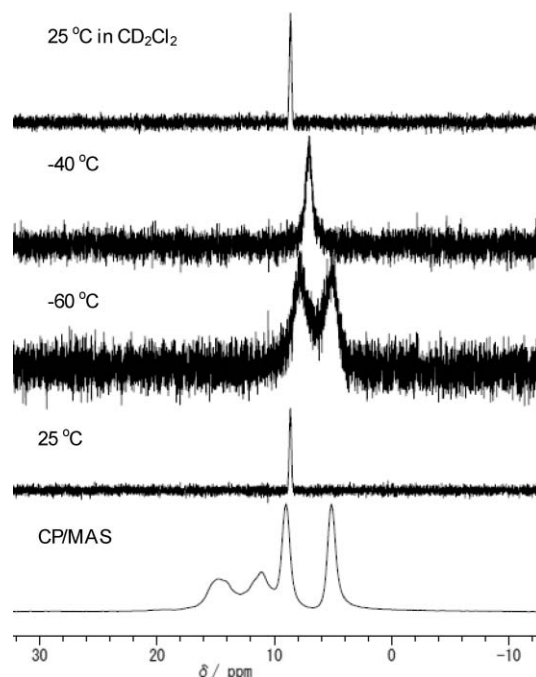


Fig. 4 VT and CP MAS ^{31}P NMR spectra of silver(I) complex with PPh_3 .

PPh_3 ($[\text{Ag}(\mu(S)\text{-mtsc})(\text{PPh}_3)]_2$ and $[(\text{PPh}_3)_2\text{Ag}(\mu(S)\text{-mtsc})_2\text{Ag}]$) co-existed in the single crystals grown in the mother liquor.

The solution molecular weight measurement in CHCl_3 indicated that the molecular weight of the dimer was *ca.* 641, which is close to the molecular weight of $[\text{Ag}(\text{mtsc})(\text{PPh}_3)]$ (M_w 633). This result supports the fact that equilibrium between the dimer and the monomer and/or PPh_3 dissociation from the dimer occurs in solution.

Antimicrobial activity of $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$

The antimicrobial activities of the water-insoluble complex were evaluated by minimum inhibitory concentration (MIC; $\mu\text{g mL}^{-1}$) in a water-suspension system and in CHCl_3 solution (see Table 2). A high MIC showed the material did not inhibit the growth of microorganisms, while a small MIC indicated that the material showed effective antimicrobial activity. The free ligand (Hmtsc) showed a wide spectrum of moderate to effective antimicrobial activities against the test organisms (*Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, *Saccharomyces cerevisiae*, *Aspergillus niger* and *Penicillium citrinum*), particularly, against yeasts (*C. albicans* and *S. cerevisiae*)³ and water-soluble starting materials, *i.e.* Ag–O bonded complexes, showed superior antimicrobial activities against all the selected microorganisms.⁹ However, the MIC values of the tetrameric cluster for the selected bacteria, yeasts and molds in water suspension were larger than 1000, which indicated no antimicrobial activity. When the tetramer was dissolved in CHCl_3 and added to the test culture, it showed modest activities for bacteria and was effective against yeasts, but showed no activity against molds. The blank test adding CHCl_3 alone to the culture cells did not have any effect on the selected microorganisms. The different antimicrobial spectral patterns between the ligand and the CHCl_3 solution of the tetramer indicates that some of the $[\text{Ag}(\text{mtsc})]_n$ species yielded by the equilibrium in solution would interact with the biomolecules of the microorganisms. The tetramer did not inhibit the selected microorganisms when contacted in the solid state. The lack of activity in the water-suspension system could be attributed to the extraordinary stability or the low solubility of this complex.

Conclusion

A reaction of a ⁴N-substituted tridentate thiosemicarbazone ligand with NNS donor atoms and silver(I) sources with only relatively weak Ag–O bonds ($\infty\{[\text{Ag}(\text{Hpyrrld})]_2\}$,

$\infty\{[\text{Ag}(\text{othf})]_2\}$, $\infty\{[\text{Ag}(\text{R,S-ca})]\}$, $\infty\{[\text{Ag}(\text{ca})(\text{Hca})]\}$, $\text{Ag}(\text{AcO})$ and Ag_2O) successfully produced a unique neutral tetrameric cluster, $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$, which was characterized by FTIR, TG/DTA, elemental analysis and X-ray crystallography. Solution NMR spectroscopy, ESI-MS and solution molecular weight measurement indicated that fast equilibrium of the $[\text{Ag}(\text{mtsc})]_n$ species occurred in solution. Interestingly, the silver(I) complex was remarkably light-stable and neither colour change nor precipitation was observed for a few months at room temperature in the solid state and in solution. This water-insoluble silver(I) tetramer did not show antimicrobial activity against the selected microorganisms in a water-suspension system but did show effective antimicrobial activity against two yeasts in CHCl_3 solution. The reaction of the tetramer with a large excess of PPh_3 produced two dimeric species in the form of single crystals, $[\text{Ag}(\mu(S)\text{-mtsc})(\text{PPh}_3)]_2$ and $[(\text{PPh}_3)_2\text{Ag}(\mu(S)\text{-mtsc})_2\text{Ag}]$. Solution NMR spectroscopy and solution molecular weight measurement indicated that fast equilibrium occurred for the dimer, and that it was dissociated in solution.

Experimental

Instrumentation/analytical procedures

CHN elemental analyses were performed using a Perkin Elmer PE2400 series II CHNS/O Analyzer (Kanagawa University). TG/DTA measurements were carried out using a Rigaku Thermo Plus2 TG 8120 instrument under air with a temperature ramp of 4°C min^{-1} between 30°C and 500°C . Infrared spectra were recorded on a Jasco FTIR 4100 spectrometer in KBr disks at room temperature. ^1H NMR, $^{13}\text{C}\{^1\text{H}\}$ NMR and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra in solution were recorded on a JEOL JNM-EX 400 or ECP500 using tubes with an outer diameter of 5 mm. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of the complexes were measured in CDCl_3 solution with reference to internal TMS. The assignment of the proton and carbon signals were primarily performed by HMQC and HMBC. The ^{31}P NMR spectrum was referenced to an external standard of 85% H_3PO_4 by a substitution method. The ^{109}Ag NMR (18.45 MHz) spectra in solution were recorded at 20.2°C on a JEOL EX-400 FT-NMR spectrometer equipped with a low-frequency tunable probe using tubes with an outer diameter of 10 mm. The ^{109}Ag NMR spectra of the complexes were measured in CD_2Cl_2 with reference to an external standard of saturated $\text{AgNO}_3\text{-D}_2\text{O}$ solution by the substitution method. Chemical shifts are reported on the δ scale by considering resonances downfield of AgNO_3 (δ 0) as positive. The solid-state

Table 2 Antimicrobial activities of the tetramer (water-suspension and CHCl_3 solution), free ligand, Ag_2O and CHCl_3 evaluated by minimum inhibitory concentration (MIC; $\mu\text{g mL}^{-1}$)

Compound	$[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$		Hmtsc	Ag_2O	
	H_2O	CHCl_3	H_2O	H_2O	CHCl_3
<i>Escherichia coli</i>	> 1000	125	250		>1000
<i>Bacillus subtilis</i>	> 1000	62.5	125	500	>1000
<i>Staphylococcus aureus</i>	> 1000	1000	250	1000	>1000
<i>Pseudomonas aeruginosa</i>	> 1000	500	125		>1000
<i>Candida albicans</i>	> 1000	31.3	31.3		>1000
<i>Saccharomyces cerevisiae</i>	> 1000	31.3	31.3		>1000
<i>Aspergillus niger</i>	> 1000	> 1000	125		>1000
<i>Penicillium citrinum</i>	> 1000	> 1000	125		>1000

^{31}P NMR (121 MHz) spectrum was measured using a JEOL JNM-ECP 300 FT-NMR spectrometer equipped with a cross-polarization (CP)/magic angle spinning (MAS) accessory. The solid-state ^{31}P NMR chemical shifts were indirectly calibrated through external $(\text{NH}_4)_2\text{HPO}_4$ as 1.6 ppm. Positive electrospray ionization (ESI) mass spectrometry measurements were performed on a JEOL JMS-T100LC spectrometer equipped with an Agilent 1100 (HPLC) using MeOH as a mobile phase with an m/z range of 100–4000. 1 mg of $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$ was dissolved in 1 mL of a 1 : 1 mixture of CH_2Cl_2 –MeOH solvent and was further diluted with MeOH to obtain a 100 ppb solution. The electrospray interface was heated to *ca.* 250 °C, the needle voltage was 2 kV. The sheath N_2 gas pressure was 488 kPa, and 10 μL of the $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$ solution was infused into the ESI source at a flow rate of 0.2 mL min^{-1} . Solution molecular weight measurements based on vapor pressure osmometry were performed by Mikroanalytisches Labor Pascher (Remagen, Germany). The results of these measurements in CHCl_3 and CH_2Cl_2 contained an error of *ca.* 10% because of the low solubility of the complexes.

Antimicrobial activity

Antimicrobial activities were estimated by the minimum inhibitory concentration (MIC: $\mu\text{g mL}^{-1}$) in heterogeneous aqueous media and CHCl_3 solution as shown elsewhere.^{4c}

Materials

The ligands (Hmtsc¹⁰ and Hatsc¹¹) and achiral silver sources $\infty\{[\text{Ag}(\text{Hpyrrld})_2]\}$,^{9a} $\infty\{[\text{Ag}(\text{othf})_2]\}$,^{9b} $\infty\{[\text{Ag}(\text{ca})]\}$ and $\infty\{[\text{Ag}(\text{ca})(\text{Hca})]\}$ ^{9c} were prepared according to the literature. All chemicals were of reagent grade and were used as received: DMSO, EtOH, Et₂O, CHCl_3 , CH_2Cl_2 , MeOH, EtOAc, CH_3CN , acetone, benzene, Ag(OAc) and Ag₂O from Wako, PPh₃ from Aldrich, and CD_2Cl_2 and CDCl_3 from Isotec.

Synthesis

$[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$. Hmtsc (0.26 g, 1 mmol) was added to a suspension of 0.24 g (0.5 mmol) of $\infty\{[\text{Ag}(\text{Hpyrrld})_2]\}$ in 50 mL of a mixed solvent (CH_2Cl_2 –EtOH = 4 : 1), followed by stirring for 30 min at room temperature. The white suspension changed to a clear orange solution, and it was filtered through a folded filter paper (Whatman No.5). The filtrate was concentrated to *ca.* 4 mL by a rotary evaporator at 30 °C. The deep-yellow powder thus formed was collected on a membrane filter (JG 0.2 μm) and was washed with water, EtOH, EtOAc, and diethyl ether (30 mL each) (0.29 g of $[\text{Ag}(\text{mtsc})]_4$, 77.2% yield). After drying *in vacuo* for 2 h, 0.17 g of the powder was re-dissolved in 200 mL of CHCl_3 at 30 °C and filtered through a folded filter paper (Whatman No.5). The solution was concentrated to 80 mL and placed in a 100 mL vial. Vapor diffusion of the concentrated solution (in the vial)/200 mL of a hexane (outer solvent) system at room temperature produced orange rod-shaped crystals. They were collected on a membrane filter (JG 0.2 μm), washed with hexane (100 mL), and dried *in vacuo*. The light-stable and thermally stable complex $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$ was obtained, it was soluble in CHCl_3 and CH_2Cl_2 ; sparingly soluble in DMSO, MeOH and acetone, and insoluble in hexane, water, EtOAc, diethyl ether and EtOH. Yield 0.12 g, 70.6% (Found: C, 34.84; H, 3.64;

N, 12.84. Calc. for $\text{C}_{50}\text{H}_{62}\text{Ag}_4\text{Cl}_6\text{N}_{16}\text{O}_4\text{S}_4$ or $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$: C, 34.84; H, 3.63; N, 13.00%). TG/DTA data: 14.11% weight loss under 195 °C (calc. for $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$ = 13.85% weight loss). Decomposition began at around 240 °C with an exothermic peak at 243 °C. Some predominant IR bands in the 1800–400 cm^{-1} region (KBr disc): 1629 w, 1585 m, 1552 w, 1483 m, 1454 m, 1427 vs, 1354 m, 1300 m, 1282 m, 1265 m, 1217 m, 1205 s, 1158 w, 1140 m, 1114 m, 1067 m, 1030 m, 997 w, 976 m, 930 w, 883 m, 838 w, 802 w, 780 m, 756 m, 742 m, 719 w, 658 w, 631 w, 599 w, 559 w, 465 w and 406 w. δ_{H} (CDCl_3 , 22.9 °C) 2.09 (3H, broad, H6), 3.58 (4H, broad, H10/H11), 3.79 (4H, broad, H9/H12), 7.19 (1H, broad, H2), 7.50 (1H, broad, H4), 7.69 (1H, broad, H3) and 8.47 (1H, broad, H1). δ_{C} (CDCl_3 , 25.6 °C) 14.15 (C7), 47.69 (C9/C12), 66.83 (C10/C11), 121.33 (C4), 122.94 (C2), 136.89 (C3), 149.73 (C1), 150.08 (C6), 153.60 (C5) and 171.50 (C8). m/z (relative intensity) (positive ESI) 372 (74) $\{[\text{Ag}(\text{mtsc})] + \text{H}^+\}^+$, 636 (59) $\{[\text{Ag}(\text{mtsc})(\text{Hmtsc})] + \text{H}^+\}^+$, 743 (33) $\{[\text{Ag}_2(\text{mtsc})_2] + \text{H}^+\}^+$, 850 (43) $\{[\text{Ag}_3(\text{mtsc})_3] + \text{H}^+\}^+$, 1114 (15) $\{[\text{Ag}_4(\text{mtsc})_4] + \text{H}^+\}^+$, 1221 (54) $\{[\text{Ag}_5(\text{mtsc})_5] + \text{H}^+\}^+$, 1593 (68) $\{[\text{Ag}_6(\text{mtsc})_6] + \text{H}^+\}^+$, 1964 (71) $\{[\text{Ag}_7(\text{mtsc})_7] + \text{H}^+\}^+$, 2333 (91) $\{[\text{Ag}_8(\text{mtsc})_8] + \text{H}^+\}^+$, 2704 (100) $\{[\text{Ag}_9(\text{mtsc})_9] + \text{H}^+\}^+$, 3076 (31) $\{[\text{Ag}_{10}(\text{mtsc})_{10}] + \text{H}^+\}^+$, 3448 (4) $\{[\text{Ag}_{11}(\text{mtsc})_{11}] + \text{H}^+\}^+$ and 3820 (1) $\{[\text{Ag}_{12}(\text{mtsc})_{12}] + \text{H}^+\}^+$. λ_{max} (CH_2Cl_2)/nm ($\epsilon/\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$): 305 (4.5×10^4) and 366 (4.5×10^4). Solution molecular weight measurement: 5.47 mg of $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$ in 0.8436 g of CH_2Cl_2 produced M_w 1160, 6.618 mg of $[\text{Ag}(\text{mtsc})]_4$ in 1.277 g of CHCl_3 showed M_w 950.

When Ag₂O and Hmtsc were reacted on the scale of 0.5 mmol, $[\text{Ag}(\text{mtsc})]_4$ was obtained in less than 40% after 30 min stirring, however, it was obtained in 82% yield with 24 h stirring. When Ag(OAc) was used in the reaction, a powder was afforded quantitatively after 30 min stirring (0.32 g, 82%). When $\infty\{[\text{Ag}(\text{othf})_2]\}$, $\infty\{[\text{Ag}(\text{ca})]\}$ or $\infty\{[\text{Ag}(\text{ca})(\text{Hca})]\}$ were reacted with Hmtsc on a scale of 0.25 mmol, $[\text{Ag}(\text{mtsc})]_4$ was produced in 0.12 g (63%), 0.12 g (63%) and 0.13 g (70%) yields, respectively. In the reaction of $\infty\{[\text{Ag}(\text{othf})_2]\}$ and Hmtsc, precipitation by adding acetone before recrystallization from CHCl_3 was necessary. The product $[\text{Ag}(\text{mtsc})]_4$ prepared from $\infty\{[\text{Ag}(\text{othf})_2]\}$, $\infty\{[\text{Ag}(\text{ca})]\}$, $\infty\{[\text{Ag}(\text{ca})(\text{Hca})]\}$, Ag(OAc) and Ag₂O was also characterized by elemental analysis, FTIR, ^1H NMR and ESI-MS.

$[\text{Ag}(\text{mtsc})(\text{PPh}_3)]_2$, $[\text{Ag}(\mu(\text{S})\text{-mtsc})(\text{PPh}_3)]_2$ and $[(\text{PPh}_3)_2\text{Ag}(\mu(\text{S})\text{-mtsc})_2\text{Ag}]$. EtOH (10 mL) was added to a solution of 0.20 g (0.135 mmol) of $[\text{Ag}(\text{mtsc})]_4$ dissolved in 300 mL of CH_2Cl_2 , followed by adding PPh₃ (1.4 g, 5.4 mmol). The mixture was stirred for 1 h at room temperature. The clear yellow solution was filtered through a folded filter paper (Whatman No.5) and the filtrate was dried using a rotary evaporator at 30 °C. 50 mL of diethyl ether was added to the orange oil formed and was stirred for 30 min. The yellow powder thus formed was collected on a membrane filter (JG 0.2 μm) and was washed with 50 mL of diethyl ether followed by drying *in vacuo* for 2 h (at this stage 0.18 g of $[\text{Ag}(\text{mtsc})(\text{PPh}_3)]_2$, 52.6% yield). 0.20 g of this powder was dissolved in 20 mL of a mixed solvent (CH_2Cl_2 –EtOH = 1 : 1) and filtered through a folded filter paper (Whatman No.5). The solution was slowly evaporated at room temperature in order to obtain yellowish-orange rod-shaped crystals. These crystals were collected on a membrane filter (JG 0.2 μm), washed with diethyl ether (50 mL), and dried *in vacuo*. The light-stable and thermally stable complexes $[\text{Ag}(\text{mtsc})(\text{PPh}_3)]_2$ which contain two isomers

were obtained, which were soluble in CHCl_3 , CH_2Cl_2 , EtOAc , DMSO , CH_3CN , MeOH and acetone, sparingly soluble in diethyl ether, but insoluble in water. Yield 0.11 g, 55% (Found: C, 56.83; H, 4.77; N, 8.83. Calc. for $\text{C}_{60}\text{H}_{60}\text{Ag}_2\text{N}_8\text{O}_2\text{P}_2\text{S}_2$ or $[\text{Ag}(\text{mtsc})(\text{PPh}_3)]_2$: C, 56.88; H, 4.77; N, 8.84%). TG/DTA data: no weight loss under ca. 180 °C. Decomposition began at around 180 °C with endothermic peaks at 196 and 219 °C and exothermic peaks at 199 and 235 °C. Some predominant IR bands in the 1800–400 cm^{-1} region (KBr disc): 1584 m, 1479 m, 1451 m, 1434 s, 1410 s, 1354 m, 1301 m, 1281 m, 1261 m, 1219 m, 1200 s, 1156 m, 1109 m, 1093 m, 1066 m, 1026 m, 995 m, 978 m, 921 m, 882 m, 836 m, 803 m, 780 m, 742 m, 721 m, 693 s, 628 m, 563 m, 516 m, 505 m and 492 m. δ_{H} (CDCl_3 , 20.6 °C) 2.42 (3H, s, H6), 3.67 (4H, t, H10/H11), 3.94 (4H, t, H9/H12), 6.77 (1H, t, H2), 7.23–7.40 (16H, t and m, PPh_3 and H3) and 7.66 (1H, d, H4), 8.02 (1H, d, H1). δ_{C} (CD_2Cl_2 , 17.6 °C) 15.86 (C7), 48.08 (C9/C12), 67.36 (C10/C11), 122.23 (C4), 122.81 (C2), 129.14 (PPh_3), 130.45 (PPh_3), 133.17 (PPh_3), 134.20 (PPh_3), 136.50 (C3), 149.46 (C1), 153.29 (C6), 157.03 (C5) and 177.87 (C8). δ_{P} (CD_2Cl_2 , 20.7 °C) 9.98. δ_{Ag} (CD_2Cl_2 , 20.2 °C) 1021.0. λ_{max} (CH_2Cl_2)/nm ($\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$): 230 (5.2×10^4), 253 (3.8×10^4) and 371 (2.1×10^4). Solution molecular weight measurement: 20.337 mg of $[\text{Ag}(\text{mtsc})(\text{PPh}_3)]_2$ in 1.4934 g of CHCl_3 showed M_w 950.

Crystallographic data collection and refinement of the crystal structures of the silver(I) complexes

A single-crystal of the silver(I) complexes ($0.20 \times 0.15 \times 0.05 \text{ mm}$ for $[\text{Ag}(\text{mtsc})]_4$, $0.16 \times 0.20 \times 0.36 \text{ mm}$ for $[\text{Ag}(\mu(\text{S})\text{-mtsc})(\text{PPh}_3)]_2$ and $0.39 \times 0.39 \times 0.34 \text{ mm}$ for $[(\text{PPh}_3)_2\text{Ag}(\mu(\text{S})\text{-mtsc})_2\text{Ag}]$ was mounted on 'a loop' and used for measurements of precise cell constants and intensity data collection on a Bruker Smart CCD or Rigaku Mercury CCD diffractometer (Mo- $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$). The structures were solved by direct methods followed by subsequent difference Fourier calculation and refined by a full-matrix least-squares procedure using SIR97, the WinGX and SHELXTL program packages.¹² Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed geometrically and treated with a riding model.

Crystal data for $[\text{Ag}(\text{mtsc})]_4 \cdot 2\text{CHCl}_3$. $\text{C}_{50}\text{H}_{62}\text{Ag}_4\text{Cl}_6\text{N}_{16}\text{O}_4\text{S}_4$, $M_r = 1723.6$, triclinic, space group $P\bar{1}$, $a = 9.997(4) \text{ \AA}$, $b = 11.983(5) \text{ \AA}$, $c = 13.481(6) \text{ \AA}$, $\alpha = 73.203(6)^\circ$, $\beta = 87.140(6)^\circ$, $\gamma = 85.074(6)^\circ$, $V = 1539.7(11) \text{ \AA}^3$, $Z = 1$, $T = 90 \text{ K}$, $\mu = 1.87 \text{ mm}^{-1}$, $F(000) = 860$. 20798 reflections collected, 7602 unique. Final agreement factors were $R1 = 0.0308$, $wR2 = 0.0814$ ($I > 2 \sigma(I)$) and GOF = 1.132 (all data). CCDC reference number 294754.

Crystal data for $[\text{Ag}(\mu(\text{S})\text{-mtsc})(\text{PPh}_3)]_2$. $\text{C}_{60}\text{H}_{60}\text{Ag}_2\text{N}_8\text{O}_2\text{P}_2\text{S}_2$, $M_r = 1266.99$, triclinic, space group $P\bar{1}$, $a = 11.005(11) \text{ \AA}$, $b = 11.477(11) \text{ \AA}$, $c = 12.859(13) \text{ \AA}$, $\alpha = 70.353(2)^\circ$, $\beta = 76.622(2)^\circ$, $\gamma = 65.256(2)^\circ$, $V = 1381(2) \text{ \AA}^3$, $Z = 1$, $T = 90 \text{ K}$, $\mu = 0.894 \text{ mm}^{-1}$, $F(000) = 648$. 18103 reflections collected, 6839 unique. Final agreement factors were $R1 = 0.0231$, $wR2 = 0.0638$ ($I > 2 \sigma(I)$) and GOF = 1.026 (all data). CCDC reference number 296440.

Crystal data for $[(\text{PPh}_3)_2\text{Ag}(\mu(\text{S})\text{-mtsc})_2\text{Ag}]$. $\text{C}_{60}\text{H}_{60}\text{Ag}_3\text{N}_8\text{O}_2\text{P}_2\text{S}_2$, $M_r = 1266.99$, triclinic, space group $P\bar{1}$, $a = 13.342(12) \text{ \AA}$, $b = 14.69(2) \text{ \AA}$, $c = 15.137(17) \text{ \AA}$, $\alpha = 105.03(3)^\circ$, $\beta = 102.17(3)^\circ$, $\gamma = 100.31(3)^\circ$, $V = 2714(5) \text{ \AA}^3$, $Z = 2$, $T = 113 \text{ K}$, $\mu = 0.910 \text{ mm}^{-1}$,

$F(000) = 1296$. 26421 reflections collected, 9872 unique. Final agreement factors were $R1 = 0.0462$, $wR2 = 0.1021$ ($I > 2 \sigma(I)$) and GOF = 1.070 (all data). CCDC reference number 637149.

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