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Syntheses, Structures, and Antimicrobial Activities of Remarkably Light-Stable and Water-Soluble Silver Complexes with Amino Acid Derivatives, Silver(I) *N*-Acetylmethioninates

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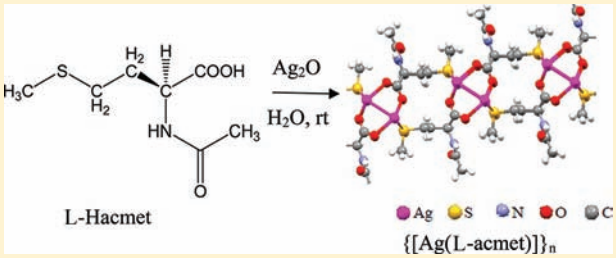
Supporting Information

ABSTRACT: Reaction of L- and DL-*N*-acetylmethionine (Hacmet) and Ag_2O in water at ambient temperature afforded the remarkably light-stable silver complexes $\{[Ag(L\text{-acmet})]\}_n$ (**1**) and $\{[Ag_2(D\text{-acmet})(L\text{-acmet})]\}_n$ (**2**), respectively. The color of the solids and aqueous solutions of **1** and **2** did not change for more than 1 month under air without any shields. The light stability of these two silver(I) complexes is much higher than that of silver(I) methioninate $\{[Ag_2(D\text{-met})(L\text{-met})]\}_n$ (**3**) (Hmet = methionine), silver(I) *S*-methyl-L-cysteinate $\{[Ag(L\text{-mecys})]\}_n$ (**4**), and silver(I) L-cysteinate $\{[Ag(L\text{-Hcys})]\}_n$ (**5**). X-ray crystallography of **1** obtained by vapor diffusion revealed that ladder-like coordination polymers with two O- and two S-donor atoms were formed. The acetyl group of acmet$^-$ prevents chelate formation of the ligand to the metal center, which is frequently observed in amino acid metal complexes, but allows for formation of hydrogen bonds between the ligands in the crystals of **1**. These two silver(I) *N*-acetylmethioninates showed a wide spectrum of effective antimicrobial activities against Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and yeasts (*Candida albicans* and *Saccharomyces cerevisiae*), the effectiveness of which was comparable to that of water-soluble Ag−O bonding complexes.



INTRODUCTION

Medicinal applications of coinage metal (Cu, Ag, and Au) complexes have been established for years,[1] and among them silver(I) complexes as well as silver clusters[2] have been known to show antimicrobial activity. It has been said that discovering new compounds that work against Gram-negative bacteria but simultaneously are not toxic to humans is difficult.[3] Fortunately, silver materials have been shown to exhibit low toxicity toward human skin,[4] and silver(I) histidinate formulated with some additives is a practical example.[5] Notably, silver(I) complexes have been reported to show a different antimicrobial spectrum against microorganisms compared to the activity of the ligand itself and the hydrated silver(I) ion.[1b,c,6] During investigation of the structural relationship of silver(I) complexes with their antimicrobial activities in aqueous media we noticed that silver(I) complexes with hard donor atoms (i.e., silver(I)−N and/or silver(I)−O bonds) exhibited an effective and a wide spectrum of antimicrobial activity,[1c,6a−e,h] whereas silver(I) thiolates were shown to have a narrower spectrum of antimicrobial activity.[6f,g] From these results we concluded that the nature of the atom that coordinates to the silver(I) center and its bonding properties (rather than the solubility, charge, chirality, or degree of polymerization of the complexes) and the ease of ligand replacement are the key factors that lead to a wide spectrum of antimicrobial activity. The primary targets for inhibition of bacteria and yeasts by the silver(I) complexes are proteins that function as sulfur donor ligands but not nucleic acids that act as N/O donors. Although Ag−O and Ag−N bonding silver(I) complexes are potential antimicrobial reagents with a wide spectrum of antimicrobial activities, many of them are not light-stable and/or poorly soluble in common solvents, as seen in $[Ag(Him)_2]NO_3$ (Him = imidazole),[7a] $\{[Ag(im)]\}_n$,[7b] and others, including the silver(I) complexes of amino acids, peptides, and proteins.[8] Therefore, their characterization, including structural studies, has not been easily carried out.

To investigate the interactions between biomolecules and metal complexes via transmission electron microscopy,[9] water-soluble coinage metal complexes are desired. However, there are only a few water-soluble silver(I) complexes that can be used as starting materials and are easy to handle. Typical commercial sources are $AgClO_4$ and $AgNO_3$, but use of $AgClO_4$ requires caution, especially in organic solvents, and the NO_3^- anion is in many cases hard to remove completely during the purification steps. We found that reaction of Ag_2O and acids containing the HOOC−C−X−C═O (X = N or O) moiety gave relatively light-stable (i.e., aqueous solutions containing the silver(I) complexes are stable for a few hours to days at ambient temperature without light shielding) and water-soluble silver(I) complexes, such as silver(I) aspartate,[6c] silver(I) 2-pyrrolidone-5-carboxylates,[6b,d] and silver(I) acetyl-

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glycinate.[6e] Addition of soft ligands, such as phosphines, to a solution containing Ag−O bonding complexes increases the light stability of silver(I) complexes but tends to decrease their antimicrobial activity.[10] Silver(I) thiolate complexes are more light stable, but as described above they exhibit a narrower spectrum of antimicrobial activity against Gram-negative bacteria, and their characterization is difficult, especially for silver(I) complexes with aliphatic thiolate ligands due to their oligomeric nature.[6f,g,i]

Herein, we report the synthesis, characterization, crystal and solution structures, and properties of novel silver(I) complexes derived from *N*-acetyl-L-methionine (L-Hacmet) and *N*-acetyl-DL-methionine (DL-Hacmet), i.e., $\{[Ag(L\text{-acmet})]\}_n$ (**1**) and $\{[Ag_2(D\text{-acmet})(L\text{-acmet})]\}_n$ (**2**), the aqueous solutions of which are stable under ambient conditions without shade for several weeks to months. Acetylmethionine was thought to be a potential candidate for forming a water-soluble, light-stable, and effective antimicrobial silver(I) complex for the following reasons: (i) compounds containing the O=C−N−C−COO partial moiety in the backbone have been found to form water-soluble silver(I) complexes (red circle in Figure 1);[6e] (ii) acetyl

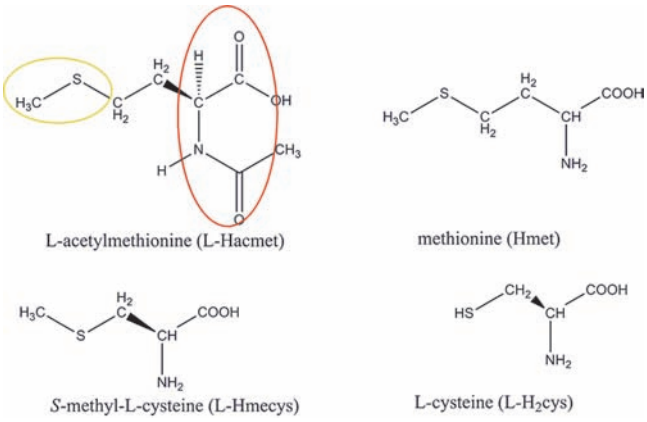

Figure 1. Chemical structure of *N*-acetyl-L-methionine and related ligands. Yellow and red circles show the thioether and O=C−N−C−COO partial moiety of L-Hacmet, respectively.

group substitution changes the zwitterionic nature of the methionine to an acid and also enables the ligands to make interunit hydrogen bonds; (iii) the interaction of the silver(I) ion and the soft S-donor atoms of the thioether groups would be less tight (yellow circle in Figure 1) compared with that of Ag−S (thiolate) bonding silver(I) complexes,[11] but it would stabilize silver(I) complexes in aqueous solution; and (iv) the ligand (L-Hacmet or DL-Hacmet) is a derivative of the amino acid methionine, which is easily obtained from natural products and expected to form complexes that are less toxic to human skin. The complexes were characterized using elemental analysis, thermogravimetric (TG) analysis, and differential thermal analysis (DTA), FT-IR, and solution ^{1}H, ^{13}C{^{1}H}, and ^{109}Ag NMR spectroscopies, and X-ray crystallography. The antimicrobial activities of complexes **1** and **2**, as well as related silver(I) complexes, evaluated by minimum inhibitory concentration (MIC, μg mL^{-1}) in a water or water−suspension system are also presented. The properties of these silver complexes, including light stability, solubility in water, and antimicrobial activity, are compared with those of silver(I) methioninate $\{[Ag(DL\text{-met})]\}_n$ (**3**), silver(I) *S*-methyl-L-cysteinate $\{[Ag(L\text{-mecys})]\}_n$ (**4**), and silver(I) L-cysteinate $\{[Ag(L\text{-Hcys})]\}_n$ (**5**) (Figure 1).

EXPERIMENTAL SECTION

Materials. The following reagent-grade chemicals were used as received: Ag_2O, dimethyl sulfoxide (DMSO), EtOH, Et_2O, $CHCl_3$, CH_2Cl_2, MeOH, EtOAc, CH_3CN, and acetone (Wako); *N*-acetyl-DL-methionine, *N*-acetyl-L-methionine, L-methionine, DL-methionine, *S*-methyl-L-cysteine, and L-cysteine (Tokyo Kasei); 4,4-dimethyl-4-silapentane-1-sulfonic acid (DSS) (Aldrich); and D_2O (99.9 D atom %, Isotec).

Instrumentation/Analytical Procedures. CHN elemental analyses were performed using a Perkin-Elmer PE2400 series II CHNS/O analyzer. Thermogravimetric (TG) and differential thermal analyses (DTA) were performed under air with a temperature ramp of 4 °C min^{-1} using a Rigaku Thermo Plus 2 TG 8120 instrument between 30 and 500 °C. Infrared spectra were recorded on a JASCO FT-IR 4100 spectrometer in KBr disks at room temperature. ^{1}H, ^{13}C{^{1}H}, and ^{109}Ag NMR spectra in solution were recorded at ambient temperature on a JEOL EX-400 NMR or a JEOL ECP500 NMR spectrometer. ^{1}H and ^{13}C{^{1}H} NMR spectra of the complexes were measured in a D_2O solution with reference to an internal DSS. The signals of the two methyl groups and the carbonyl in the acetyl and carboxylate moieties in the ^{1}H and ^{13}C NMR spectra were assigned using 2D NMR, heteronuclear multiple quantum coherence (HMQC), and heteronuclear multiple-bond connectivity (HMBC). ^{109}Ag NMR spectra of the complexes were measured in D_2O with reference to an external standard solution consisting of saturated $AgNO_3$−D_2O using a substitution method. Solid-state cross-polarization magic-angle-spinning (CPMAS) ^{13}C (75 MHz) NMR spectra were recorded in 6 mm o.d. rotors on a JEOL JNM-ECP 300 FT-NMR spectrometer with a JEOL ECP-300 NMR data processing system. These spectra were referenced to the methyl peak of hexamethylbenzene as an external standard (δ 17.37).

X-ray Crystallography. Crystallization of **1** and **4** was carried out by vapor diffusion of an internal aqueous solution of the silver(I) complex with an external solvent (acetone). Water-soluble colorless crystals of **1** and **4** suitable for single-crystal X-ray analysis were obtained. Colorless crystals of **3** suitable for single-crystal X-ray analysis were grown using a slow-evaporation method.

Each single crystal of the silver(I) complexes (**1**, **3**, and **4**) was mounted on a loop and used for measurements of precise cell constants and collection of intensity data at 90 K on a Bruker Smart APEX CCD diffractometer. Structures were solved by direct methods, followed by difference Fourier calculations; they were refined by full-matrix least-squares on F^2 using the SHELXTL program package.[12] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed geometrically or shown on a difference Fourier map and treated using a riding model. Crystal data and structure refinement of complexes **1**, **3**, and **4** are summarized in Table 1. Details of the crystal data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 842939, 842940, and 842941 for complexes **1**, **3**, and **4**, respectively.

Antimicrobial Activity. Antimicrobial activities were estimated based on the minimum inhibitory concentration (MIC, μg mL^{-1}) by adding an aqueous solution of the silver(I) complexes, as described elsewhere.[6f−h] Bacteria were inoculated into 5 mL of a liquid medium (soybean casein digest (SCD)) and cultured for 24 h at 35 °C. Yeast was inoculated into 5 mL of a liquid medium (glucose peptone (GP)) and cultured for 48 h at 30 °C. The cultured fluids were diluted, adjusted to a concentration of 10^6−10^7 mL^{-1}, and used for inoculation in the MIC test. As for the mold culture, the agar slant (potato dextrose (PD) agar medium), for 1-week cultivation at 27 °C, was gently washed with saline containing 0.05% Tween 80. The spore suspension obtained was adjusted to a concentration of 10^6 mL^{-1} and used for inoculation in the MIC test. The test materials were dissolved (silver complexes **1**−**4** and the "free" ligands) or suspended (complex **5**) in water. Such solutions were then diluted with an SCD medium for bacteria and with a GP medium for yeast and mold. Using these 2-fold-

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Table 1. Summary of Crystal Data and Structure Refinement Parameters for Crystals 1, 3, and 4[a]

	{[Ag(L-acmet)]}$_n$ (**1**)	{[Ag$_2$(D-met)(L-met)]·6H$_2$O}$_n$ (**3**)	{[Ag(L-mecys)]}$_n$ (**4**)
empirical formula	$C_7H_{12}NO_3SAg$	$C_{10}H_{32}N_2O_{10}S_2Ag_2$	$C_4H_8NO_2SAg$
fw	298.12	620.24	242.04
cryst syst	monoclinic	monoclinic	orthorhombic
space group	*C*2 (No. 5)	$P2_1/c$ (No. 14)	$P2_12_12_1$ (No. 19)
a/Å	16.124(5)	12.3891(9)	5.0463(4)
b/Å	4.7856(14)	7.3815(5)	5.6304(5)
c/Å	15.443(5)	11.7052(9)	23.2902(19)
α/deg	90	90	90
β/deg	117.911(9)	97.2720(10)	90
γ/deg	90	90	90
V/Å^3	1053.0(6)	1061.83(13)	661.74(10)
D_{calcd}/g·cm^{-3}	1.88	1.94	2.430
Z	4	4	4
μ/mm^{-1}	2.088	2.088	3.281
T/K	90	90	90
no. of total reflns	4188	8112	4923
no. of unique reflns	2463	2631	1641
no. of observations ($I > 2\sigma(I)$)	2342	2531	1638
R_{int}	0.0332	0.0214	0.0235
R_1	0.0361	0.0175	0.0190
wR_2	0.0990	0.0456	0.0446
GOF	1.069	1.102	1.227

[a] $R_1 = \Sigma\{|F_o| - |F_c|\}/\Sigma|F_o|$. $wR_2 = [\Sigma\omega(|F_o| - |F_c|)^2/\Sigma\omega F_o^2]^{1/2}$. GOF = $[\Sigma\omega(|F_o| - |F_c|)^2/(m - n)]^{1/2}$ where *m* = no. of reflections, *n* = no. of parameters.

diluted solutions, concentrations from 1000 to 2 μg mL^{-1} were prepared. Each 1 mL of a culture medium containing various concentrations of test materials was inoculated with 0.1 mL of the microorganism suspension prepared above. Bacteria were cultured for 24 h at 35 °C, yeast for 48 h at 30 °C, and mold for 1 week at 25 °C, and then growth of the microorganisms was observed. When no growth was observed in the medium containing the lowest concentration of test materials, the MIC was defined at this point of dilution.

Preparation of {[Ag(L-acmet)]}$_n$ (1). To a suspension of 0.348 g (1.50 mmol) of Ag$_2$O in 40 mL of water was added 1.15 g (6.02 mmol) of L-Hacmet. During 2 h of stirring, the black suspension changed to a clear pale-yellow solution. Unreacted black powder (Ag$_2$O) was filtered off through a folded filter paper (Whatman No. 5). The clear yellow filtrate was added dropwise to 500 mL of acetone. The white powder that formed was collected on a membrane filter (JG 0.2 μm), washed with acetone (50 mL × 2) and diethyl ether (100 mL × 2), and dried in vacuo. The light-stable and thermally-stable white powder (0.775 g, 87.6% yield) was soluble in water but insoluble in most organic solvents. Crystallization of the obtained powder was carried out by vapor diffusion of an internal aqueous solution of 100 mg of the powder in 10 mL of water with acetone as the external solvent, which gave water-soluble, colorless needle crystals (59.9 mg). The crystals obtained were characterized as below. Anal. Calcd for $C_7H_{12}NO_3SAg$ or [Ag(L-acmet)] as a monomer unit: C, 28.20; H, 4.06; N, 4.70. Found: C, 28.30; H, 4.29; N, 4.74. TG/DTA data: no weight loss was observed before the decomposition temperature. Decomposition began at around 192 °C with an endothermic peak at 211 °C. Prominent IR bands in the 1800−400 cm^{-1} region (KBr disk): 1635 vs, 1592 vs, 1442 m, 1399 s, 681 m, 599 m, 549 m cm^{-1}. ^{1}H NMR (D$_2$O, 17.1 °C): δ 2.03 (*CH*$_3$ in acetyl group, s, 3H), 2.06−2.11 and 2.23−2.25 (*CH*$_2$CH, two multiplets, 2H), 2.43 (*CH*$_3$S, s, 3H), 2.82 (*CH*$_2$S, t, 2H), 4.32 (*CH*, double doublet, 1H) ppm. ^{13}C NMR (D$_2$O, 25.7 °C): δ 20.62 (*SCH*$_3$), 24.62 (*CH*$_3$ in acetyl group), 34.78 and 35.40 (two *CH*$_2$), 56.57 (CH), 176.37 (C═O in acetyl group), 180.50 (COO) ppm. ^{109}Ag NMR (D$_2$O, 19.7 °C, pH 5): δ 352 ppm. No color change was observed for about 1 month in the solid state nor in an aqueous solution. Solubility in water at room temperature was approximately 50 mg mL^{-1}. Even when 4 equiv of L-Hacmet were added to Ag$_2$O in the reaction mixture instead of 2 equiv, the same silver(I) complex **1** was isolated by adding acetone (confirmed by IR, ^{1}H and ^{13}C NMR, and elemental analysis data). However, the reaction mixture using 4 equiv of L-Hacmet showed different signals in the ^{109}Ag NMR spectrum (538 ppm, pH 3.0) and was more light stable. The filtrate of the reaction mixture was also more light stable, and the color did not change for several months.

Preparation of {[Ag$_2$(D-acmet)(L-acmet)]}$_n$ (2). An achiral silver(I) complex, **2**, was obtained in a similar manner using 4 equiv of DL-Hacmet instead of L-Hacmet. Anal. Calcd for $C_{14}H_{24}N_2O_6S_2Ag_2$ or [Ag$_2$(D-acmet)(L-acmet)] as a monomer unit: C, 28.20; H, 4.06; N, 4.70. Found: C, 28.29; H, 3.80; N, 4.74. TG/DTA data: no weight loss was observed before the decomposition temperature. Decomposition began at around 183 °C with an endothermic peak at 201 °C. Prominent IR bands in the 1800−400 cm^{-1} region (KBr disk): 1637 vs, 1589 vs, 1119 vs, 1043 vs, 966 vs cm^{-1}. ^{1}H NMR (D$_2$O, 23.1 °C): δ 2.02 (*CH*$_3$ in acetyl group, s, 3H), 2.02−2.09 and 2.16−2.23 (*CH*$_2$CH, two multiplets, 2H), 2.42 (*CH*$_3$S, s, 3H), 2.83 (*CH*$_2$S, t, 2H), 4.32 (*CH*, dd, 1H) ppm. ^{13}C NMR (D$_2$O, 25.5 °C): δ 20.46 (*SCH*$_3$), 24.66 (*CH*$_3$ in acetyl group), 34.83 and 35.14 (two *CH*$_2$), 56.62 (CH), 176.43 (C═O in acetyl group), 180.62 (*COO*) ppm. ^{109}Ag NMR (D$_2$O, 22.0 °C, pH 5): δ 356 ppm. Solubility in water at room temperature was approximately 20 mg mL^{-1}, which is about one-half of that of **1**. No color change was observed for about 1 month in the solid state nor in an aqueous solution.

Preparation of {[Ag$_2$(D-met)(L-met)]}$_n$ (3). To a suspension of 0.580 g (2.50 mmol) of Ag$_2$O in 100 mL of water was added 0.745 g (5.00 mmol) of DL-Hmet. During 2 h of stirring, the black suspension changed to a clear solution. The unreacted black powder of Ag$_2$O was filtered off through a folded filter paper (Whatman No. 5). The clear filtrate was added dropwise to 1 L of ethanol, and the resulting mixture was allowed to stand for 1 day. The white powder formed was collected on a membrane filter (JG 0.2 μm), washed with ethanol (50 mL × 2) and diethyl ether (100 mL × 2), and dried in vacuo. The light-stable and thermally-stable white powder obtained in 1.15 g (89.8%) yield was soluble in water but insoluble in most organic solvents. The powder (0.300 g) was dissolved in 2.5 mL of warm water. Colorless granular crystals were grown in 1 day while standing at room temperature (0.215 g). Although the powder was soluble in water, the crystals were sparingly soluble in water and insoluble in common organic solvents. The water-soluble powder and crystals obtained were characterized as below. Anal. Calcd for $C_{10}H_{20}N_2O_4S_2Ag_2$ or [Ag$_2$(D-met)(L-met)] as a monomer unit: C, 23.45; H, 3.94; N, 5.47. Found: C, 23.41; H, 3.59; N, 5.46. TG/DTA data: no weight loss was observed before the decomposition temperature. Decomposition began at around 148 °C with an endothermic peak at 166 °C. Prominent IR bands in the 1800−400 cm^{-1} region (KBr disk): 1577 vs, 1442 s, 1427 s, 1404 s, 1326 m, 1305 s, 1275 m, 1254 m, 1032 m, 961 m, 620 m cm^{-1}. ^{1}H NMR (D$_2$O, 22.8 °C): δ 2.04−2.17 (*CH*$_2$CH, two multiplets, 2H), 2.45 (*CH*$_3$S, s, 3H), 2.90 (*CH*$_2$S, t, 2H), 3.58 (*CH*, t, 1H) ppm. ^{13}C NMR (D$_2$O, 25.1 °C): δ 20.36 (*SCH*$_3$), 34.98 (*CH*$_2$), 58.78 (CH), 182.25 (COO) ppm. ^{109}Ag NMR (D$_2$O, 25.5 °C, 0.08 M): δ 494 ppm. The color of the powder gradually changed to brown in a few days and that of the aqueous solution in a few hours. A chiral silver(I) complex {[Ag(L-met)]}$_n$ was also obtained in a similar manner using 2 equiv of L-Hmet instead of DL-Hmet; however, characterization was too difficult to perform because of its hygroscopic nature. Crystals of complex **3** suitable for X-ray crystallography contained 6 hydrated water molecules.

Preparation of {[Ag(L-mecys)]}$_n$ (4). A chiral silver(I) complex, **4**, was obtained in a manner similar to preparation of complex **3** using 2 equiv of L-Hmecys instead of L-Hmet. Crystallization was also carried out by vapor diffusion of an internal aqueous solution of 100 mg of the

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Scheme 1. Synthetic Scheme of Silver(I) Complexes 1−5

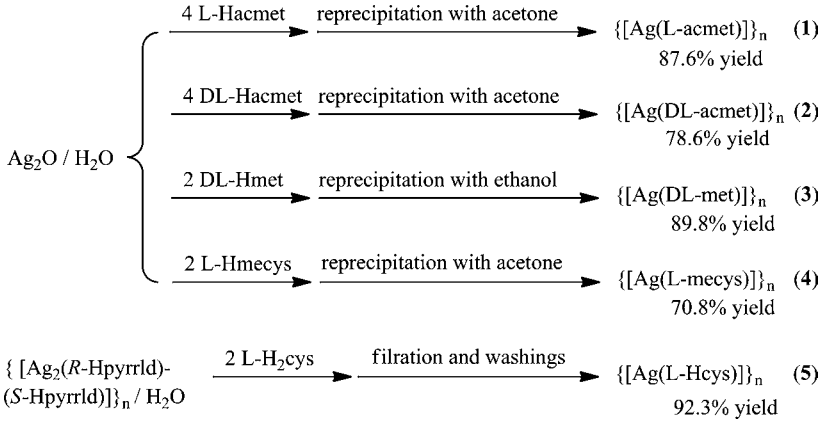

Table 2. Selected Distances (Angstroms) and Angles (degrees) of Crystals 1, 3, and 4[a]

{[Ag(L-acmet)]}$_n$ (1)		{[Ag$_2$(D-met)(L-met)]·6H$_2$O}$_n$ (3)		{[Ag(L-mecys)]}$_n$ (4)	
Ag1−S1	2.4969(13)	Ag1−S1	2.3953(4)	Ag1−S1	2.8436(7)
Ag1−S1^{i}	2.9940(14)	Ag1−O1^{vii}	2.4530(11)	Ag1−O1^{i}	2.590(2)
Ag1−O1^{ii}	2.345(3)	Ag1−O2^{viii}	2.5848(11)	Ag1−O2^{X}	2.188(2)
Ag1−O2^{iii}	2.209(4)	Ag1 N1^{vii}	2.2408(13)	Ag1−N1	2.212(2)
Ag1−Ag1^{iv}	2.8987(9)				
N1−O3^{v}	2.909(6)	N1−O1^{ix}	2.8982(17)		
		O2−O4	2.6958(16)		
		O3−O4	2.7877(18)		
		O4−O5	2.8795(19)		
O1^{ii}−Ag1−S1^{i}	92.90(9)	O1^{vii}−Ag1−S1	123.38(3)	O2^{X}−Ag1−N1	171.80(8)
O2^{iii}−Ag1−S1^{i}	69.96(11)	O2^{viii}−Ag1−S1	107.71(3)	O2^{X}−Ag1−O1^{i}	94.42(7)
O1^{ii}−Ag1−O2^{iii}	131.29(14)	O1^{vii}−Ag1−O2^{viii}	100.72(4)	N1−Ag1−O1^{i}	86.95(8)
O2^{iii}−Ag1−S1	135.70(11)	N1^{vi}−Ag1−S1	152.64(4)	O2^{X}−Ag1−S1	108.75(6)
Ag1^{iv}−Ag1−S1	120.29(3)	N1^{vii}−Ag1−O1^{vii}	70.42(4)	N1−Ag1−S1	78.85(6)
Ag1^{iv}−Ag1−O1^{ii}	73.94(9)	N1^{vii}−Ag1−O2^{viii}	90.66(4)		
Ag1^{iv}−Ag1−O2^{iii}	81.47(10)				
Ag1−S1−Ag^{vi}	121.01(5)				

[a]Symmetry operations i = x, 1 + y, z; ii = 0.5 + x, 0.5 + y, z; iii = 0.5 − x, 0.5 + y, 1 − z; iv = 1 − x, y, 1 − z; vi = x, −1 + y, z; vii = 1 − x, 1 − y, 2 − z; viii = x, 0.5 − y, 0.5 + z; ix = 1 − x, 0.5 + y, 1.5 − z; X = −1 + x, 1 + y, z.

powder in 10 mL of water with acetone as the external solvent, which gave water-soluble, colorless, granular crystals after standing at room temperature for a few days (yield 70 mg). Anal. Calcd for $C_4H_8NO_2SAg$ or [Ag(L-mecys)] as a monomer unit: C, 19.85; H, 3.33; N, 5.79. Found: C, 19.80; H, 2.90; N, 5.79. Decomposition began at around 112 °C with an endothermic peak at 144 °C. Prominent IR bands in the 1800−400 cm^{-1} region (KBr disk): 1585 vs, 1398 s, 1357 m cm^{-1}. ^{1}H NMR (D_2O, 23.5 °C): δ 2.46 (CH_3S, s, 3H), 3.08 and 3.23 (CH_2S, two multiplets, 2H), 3.73 (CH, dd 1H) ppm. ^{13}C NMR (D_2O, 25.3 °C): δ 20.86 (SCH_3), 43.14 (CH_2), 56.80 (CH), 180.72 (COO) ppm. ^{109}Ag NMR (D_2O, 25.5 °C, 0.08 M): δ 549 ppm. The color of the powder and aqueous solution changed to brown in a few days.

Preparation of {[Ag(L-Hcys)]}$_n$ (5). To a colorless solution of 0.472 g (1.00 mmol) of silver(I) *R*,*S*-2-pyrrolidone-5-carboxylates ({[Ag$_2$(*R*-Hpyrrld)(*S*-Hpyrrld)]}$_n$, H_2pyrrld = pyrrolidone-5-carboxylic acid)[6d] in 40 mL of water was added a colorless solution containing 0.242 g (2.00 mmol) of L-cysteine (L-H_2cys) in 40 mL of water. The solution was vigorously stirred overnight to form a suspension. The white powder that formed was collected on a membrane filter (JG 0.2 μm), washed with water (50 mL × 2), acetone (50 mL × 2), and diethyl ether (100 mL × 2), and dried in vacuo. The light-stable and thermally-stable white powder (0.421 g, 92.3% yield) was insoluble in water and most organic solvents. Anal. Calcd for $C_3H_6NO_2SAg$ or [Ag(L-Hcys)] as a monomer unit: C, 15.80; H, 2.65; N, 6.14. Found: C, 15.69; H, 2.37; N, 6.00. TG/DTA data: no weight loss was observed before the decomposition temperature. Decomposition began at around 118 °C with an endothermic peak at 215 °C. Prominent IR bands in the 1800−400 cm^{-1} region (KBr disk): 1677 s, 1620 s, 1565 vs, 1485 s, 1390 vs, 1351 m cm^{-1}. Solid ^{13}C CP MAS NMR: δ 37.34 (SCH_2), 59.66 (CH), 171.84 (COO) ppm. The color of the white powder gradually changed to yellow in about 1 week.

RESULTS AND DISCUSSION

Preparation and Properties of {[Ag(L-acmet)]}$_n$ (1), {[Ag$_2$(D-acmet)(L-acmet)]}$_n$ (2), and Other Related Silver(I) Complexes. Water-soluble powder and crystals of silver(I) acetylmethioninates **1** and **2** were obtained from reaction of Ag_2O and acetylmethionines (L-Hacmet or DL-Hacmet) in molar ratios of Ag_2O:Hacmet = 1:2 and 1:4 in water at ambient temperature (Scheme 1). The obtained solids were characterized by FT-IR, TG/DTA, NMR, CHN analysis, and X-ray crystallography, confirming that the isolated materials contain Ag and acmet$^-$ in a 1:1 ratio in the solid state and in both reaction mixtures. Black particles of Ag_2O disappeared more quickly when higher equivalents of acetylmethionine were employed.

Water-soluble powder and crystals of silver(I) DL-methioninate **3** and silver(I) *S*-methyl-L-cysteinate **4** were also prepared

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from reactions of Ag_2O with DL-Hmet and L-Hmecys, respectively. The synthetic conditions used here gave neutral silver(I) methioninate **3** but not the anionic complex reported previously.[13] The light stability and water solubility of silver(I) acetylmethioninates **1** and **2** in the solid state and in aqueous solution are more remarkable than those of silver(I) methioninate (**3**), silver(I) *S*-methyl-L-cysteinate (**4**), and silver(I) L-cysteinate (**5**). Properties such as the solubility in water of **1** and **2** are slightly different depending on whether chiral or achiral ligands were used. Complex **5** is insoluble in most solvents. Judging from elemental analysis, $\{[Ag_2(R\text{-Hpyrrld})(S\text{-Hpyrrld})]\}_n$ as a silver(I) source for preparation of **5** was superior to $AgNO_3$, because the former formed pure polymeric silver(I) cysteinate.[14] In the FT-IR spectrum of **5**, disappearance of the 2552 cm^{-1} band of ν_{SH} in L-H_2cys and an absorption shift of the $\nu_{C=O}$ band from 1608 to 1677 cm^{-1} were observed. The signal shift of the methine carbon in the ^{13}C CP MAS spectrum also suggests that the metal ion of **5** is coordinated by sulfur and nitrogen atoms, so Ag−S (thiolate) bridging coordination may be a cause for the low solubility. These results support our hypothesis of ligand selection for light-stable and water-soluble silver(I) complexes.

Crystal and Molecular Structures of 1, 3 and 4. Crystal data are summarized in Table 1, and selected bond distances and angles with their estimated standard deviations are listed in Table 2.

Structure of $\{[Ag(L\text{-acmet})]\}_n$ ***(1).*** The molecular structure of **1** with atom-numbering scheme is depicted in Figure 2a. Ag1 is surrounded by two O ($O1^{ii}$ and $O2^{iii}$) and two S atoms (S1 and $S1^{i}$) in a distorted tetrahedral coordination geometry belonging to four separate L-acmet$^-$ ligands. A short distance between Ag1 and $Ag1^{iv}$ (symmetry operation iv = 1 − *x*, *y*, 1 − *z*) (2.8987(9) Å), indicating argentophilic interaction, is also observed in complex **1**.[15] The two close silver(I) atoms are bridged by two carboxylato-*O*,*O*′ groups of acmet$^-$ ligands to create a syn−syn-type Ag_2O_4 moiety. Two thioether S atoms bridge the Ag_2O_4 moieties, and the S1, Ag1, $Ag1^{iv}$, $S1^{iv}$, $Ag1^{v}$, and Ag^{vi} (symmetry operations v = 1 − *x*, −1 + *y*, 1 − *z*; vi = *x*, −1 + *y*, *z*) atoms form a chairlike 6-membered ring. The rings are connected like ladders as if two infinite linear $Ag1^{vi}$−S1−Ag1−$S1^{i}$ are connected by silver(I)−silver(I) separation in the direction of the *b* axis (Figure 2b). No donor atoms of the acetyl group (N1 and O3) coordinate to the silver(I) center. Instead, they form hydrogen bonds between the acmet$^-$ ligands.

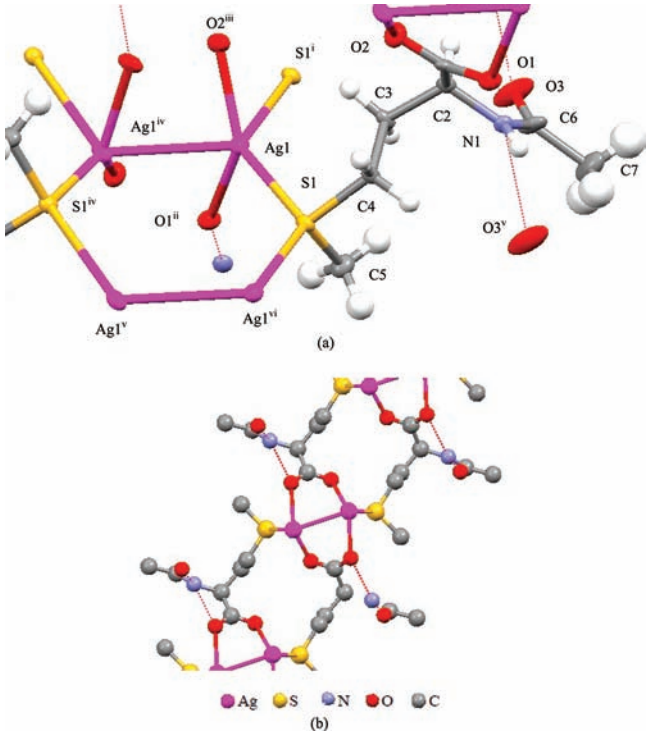

Figure 2. (a) Local structure of $\{[Ag(L\text{-acmet})]\}_n$ (**1**) with 50% probability thermal ellipsoids, and (b) 3D polymeric structure of crystal **1** viewed along the *b* axis in which hydrogen atoms are omitted for clarity. Symmetry operations: i = *x*, 1 + *y*, *z*; ii = 0.5 + *x*, 0.5 + *y*, *z*; iii = 0.5 − *x*, 0.5 + *y*, 1 − *z*; iv = 1 − *x*, *y*, 1 − *z*; v = 1 − *x*, −1 + *y*, 1 − *z*; vi = *x*, −1 + *y*, *z*.

Structure of $\{[Ag_2(D\text{-met})(L\text{-met})]\}_n$ ***(3).*** The molecular structure of **3** with atom-numbering scheme is depicted in Figure 3. Unlike that of **1**, none of Ag−Ag interaction, μ-S coordination and Ag_2O_4 moiety was observed in the crystal structure of complex **3**. Ag1 is surrounded by S1, two O atoms ($O1^{vii}$ and $O2^{viii}$, symmetry operations vii = 1 − *x*, 1 − *y*, 2 − *z*, viii = *x*, 0.5 − *y*, 0.5 + *z*), and one N ($N1^{vii}$) atom in a distorted tetrahedral coordination geometry belonging to three separate met$^-$ ligands. Coordination of the carboxylato-*O*,*O*′ of the met$^-$ ligands is in a syn−anti form. The N and O atoms of the α carbon coordinate to silver(I) in a 5-membered, chelated manner. Each met$^-$ ligand connects three Ag^I atoms, leading to infinite polymeric chains. Intermolecular hydrogen bonds were observed between one water molecule (O4) and one carboxylate (O2), in the three hydrated water molecules (O3, O4, and O5) and met$^-$ ligands (N1···$O1^{ix}$ 2.8982(17) Å, symmetry operations ix = 1 − *x*, 0.5 + *y*, 1.5 − *z*).

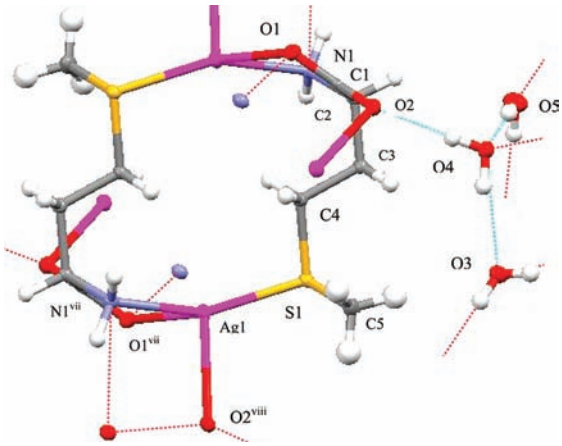

Figure 3. Polymeric structure of crystal $\{[Ag_2(D\text{-met})(L\text{-met})]\}_n$ (**3**) with 50% probability thermal ellipsoids. Symmetry operations: vii = 1 − *x*, 1 − *y*, 2 − *z*; viii = *x*, 0.5 − *y*, 0.5 + *z*.

Structure of $\{[Ag(L\text{-mecys})]\}_n$ ***(4).*** The molecular structure of **4** with atom-numbering scheme is depicted in Figure 4. Ag1 is surrounded by S1, two O atoms ($O1^{i}$ and $O2^{X}$, symmetry operations i = *x*, 1 + *y*, *z*; X = 1 + *x*, 1 + *y*, *z*) ,and a N1 atom in a distorted tetrahedral coordination geometry belonging to three separate mecys$^-$ ligands. Coordination of the carboxylato-*O*,*O*′ group of mecys$^-$ ligands is in a syn−anti form. The N and S atoms coordinate to silver(I) in a 5-membered, chelated manner (Ag1−N1−C2−C3−S1). Each met$^-$ ligand connects three Ag^I atoms, leading to infinite polymeric chains.

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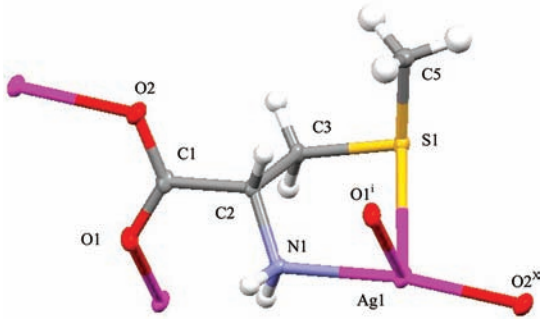

Figure 4. Polymeric structure of crystal $\{[Ag(L\text{-mecys})]\}_n$ (**4**) with 50% probability thermal ellipsoids. Symmetry operations: i = *x*, 1 + *y*, *z*; X = 1 + *x*, 1 + *y*, *z*.

Solution Behavior of Silver(I) Acetylmethioninate Monitored by ^{109}Ag NMR. Because of poor sensitivity, which stems from very low gyromagnetic ratios γ for ^{109}Ag, relatively highly concentrated samples are required for ^{109}Ag NMR experiments.[16] Silver(I) complexes **1**−**4** were soluble enough in water for ^{109}Ag NMR measurements.

Solutions of chiral and achiral silver(I) acetylmethioninates **1** and **2** dissolved in D_2O (0.2 M, pH 5) show the same single peak at around 380 ppm in the ^{109}Ag NMR spectra (Figure 5a and 5b), the value of which is larger than those of Ag−O bonding complexes (<100 ppm) such as $\{[Ag_2(R\text{-Hpyrrld})(S\text{-Hpyrrld})]\}_n$[6d] (48 ppm) but lower than those of water-soluble Ag−S (thiolate) bonding complexes such as $\{Na[Ag(mba)]\}_n$ (H_2mba = 2-mercaptobenzoic acid, 856 ppm),[6f] $\{Na[Ag(mna)]\cdot H_2O\}_n$ (H_2mna = 2-mercaptonicotinic acid, 1029 ppm),[6g] $\{NaH[Ag(tma)]\cdot 0.5H_2O\}_n$ (H_3tma = thiomalic acid, 869 ppm)[6i] in D_2O, and [HQ][Ag(pspa)] (HQ = diisopropylammonium, H_2pspa = 3-phenyl-2-sulfanylpropenoic acid, 841 ppm in DMSO and 809 ppm in MeOD).[17] No significant difference in the chemical shifts was observed for **1** and **2** under the same conditions in the ^{109}Ag NMR spectra regardless of the chirality of acmet$^-$.

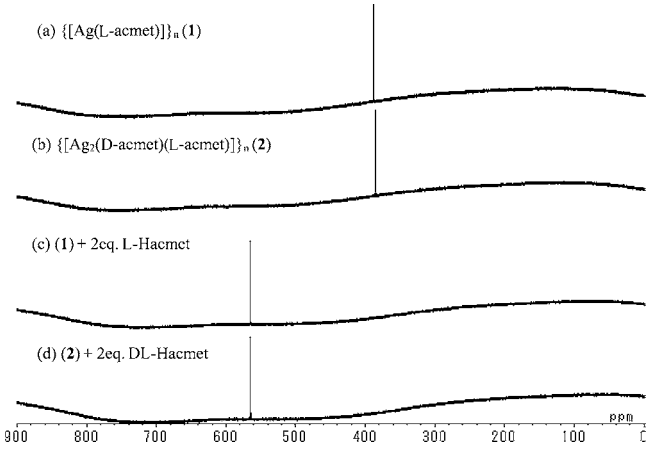

Figure 5. ^{109}Ag NMR spectra of solutions of silver(I) *N*-acetylmethioninate (0.2 M in D_2O at ambient temperature) and a mixture containing 2 equiv of Hacmet.

Addition of free Hacmet to the solutions moved the ^{109}Ag NMR signals to a lower field, although no observable changes occurred; the solution remained colorless, and no precipitation was noted. Following addition of 2 equiv of acidic Hacmet, the signal appeared at 565 ppm ($\{[Ag_2(D\text{-acmet})(L\text{-acmet})]\}_n$ (pH 3) (Figure 5c and 5d), and thus, the chemical shift became closer to those of Ag−S (thiolate) bonding complexes, such as silver(I) 2-mercaptonicotinate (856 ppm).[6f] In water, the S (thioether) and O atoms of acmet$^-$, as well as water oxygen atoms, coordinate to silver(I) because the coordination number of silver(I) is often reported to be more than two.[1d] Fast ligand exchange between the O atoms of acmet$^-$ and/or water molecules takes place in aqueous solutions of **1** and **2**. Addition of Hacmet to the NMR sample solutions of **1** and **2** increases the concentration of thioether S atoms in the solutions. The lower signal shift of the ^{109}Ag NMR spectra shows that ligand exchange between the O atom and the S atom (thioether) around the silver(I) atom easily takes place in water. As the ratio of Hacmet increases, more sulfur coordination occurs, indicating that the neutral thioether S atom can coordinate to the silver(I) atom more strongly than the O atom, but that is not the case for the thiolate S atom. Addition of Hacmet to aqueous solutions of **1** and **2** causes a decrease in the pH of the solutions, which also increases the light stability of the silver(I) complexes in solution (see Experimental Section, complex (**1**)).

When the Hacmet ligand was added to an aqueous solution of $\{[Ag_2(R\text{-Hpyrrld})(S\text{-Hpyrrld})]\}_n$ the signal in the ^{109}Ag NMR spectrum shifted to around 400 ppm. The opposite reaction did not occur, however. No signal shift was observed when H_2pyrrld was added to the solution of $\{[Ag(L\text{-acmet})]\}_n$. By addition of 2-mercaptobenzoic acid to the aqueous solution of $\{[Ag(L\text{-acmet})]\}_n$ the signal of ^{109}Ag moved to 1000 ppm. Again, the opposite reaction did not take place. These signal shifts clearly show that the affinity of acmet$^-$ for the Ag^I atom is between the Ag−O bond (<100 ppm) and the Ag−S (thiolate) bond (>800 ppm). The chemical shifts of ^{109}Ag NMR and the ligand exchangeability of the silver(I) thioether complexes, **3** (494 ppm) and **4** (549 ppm), also show that the Ag−S (thioether) bond is between Ag−O and Ag−S (thiolate).

Antibacterial and Antifungal Activities. The antimicrobial activities of complexes **1**−**5** together with their free ligands and related silver(I) complexes are listed in Table 3, as estimated by the minimum inhibitory concentration (MIC, μg mL^{-1}). Aqueous solutions of **1**−**4** were added to the test media. A suspension of **5** was added to the test media because **5** was insoluble in water.

The antimicrobial activities of the free ligands, i.e., DL-Hacmet, DL-Hmet, L-Hmecys, L-H_2cys, H_2pyrrld, H_2mba, and H_2mna, were estimated as >1000 μg mL^{-1} for selected bacteria, yeast, and mold, indicating no activity. The hydrated Ag^+ ion was reported to show effective activity against Gram-negative bacteria (*E. coli* and *P. aeruginosa*), moderate activity against Gram-positive bacteria (*B. subtilis*), and no activity against yeast and mold.[6f] Complexes **1** and **2** with Ag−O and Ag−S (thioether) bonds showed effective activities against Gram-negative bacteria (*E. coli* and *P. aeruginosa*) and yeasts (*C. albicans* and *S. cerevisiae*), moderate activities against Gram-positive bacteria (*B. subtilis* and *S. aureus*), and modest activities against mold (*A. niger* and *P. citrinum*). A similar wide spectrum of activity was observed for complex **3**. Complex **4** with Ag−O and Ag−S (thioether) bonds, which has a shorter backbone ligand compared with methionine, also exhibited effective activities against Gram-negative bacteria (*E. coli* and *P. aeruginosa*) and a Gram-positive bacterium (*B. subtilis*), moderate activity against a Gram-positive bacterium (*S. aureus*), modest activities against yeasts, and no activities against molds. The ligand exchageability of the silver(I) thioether complexes might be influenced by the backbone length of the ligand.

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Table 3. Antimicrobial Activities of Silver(I) Complexes 1−5[a]

	DL-Hacmet	{[Ag(L-acmet)]}$_n$ (1)	{[Ag$_2$(D-acmet)(L-acmet)]}$_n$ (2)	DL-Hmet	{[Ag$_2$(D-met)(L-met)]}$_n$ (3)
Escherichia coli (ATCC8739)	>1000	15.7	15.7	>1000	15.7
Bacillus subtilis (ATCC6633)	>1000	62.5	62.5	>1000	62.5
Staphylococcus aureus (ATCC6538)	>1000	125	62.5	>1000	62.5
Pseudomonas aeruginosa (ATCC9027)	>1000	31.3	31.3	>1000	15.7
Candida albicans (ATCC9763)	>1000	15.7	15.7	>1000	15.7
Saccharomyces cerevisiae (ATCC10231)	>1000	31.3	31.3	>1000	15.7
Aspergillus niger (ATCC16404)	>1000	125	250	>1000	125
Penicillium citrinum (NBRC6352)	>1000	>1000	1000	>1000	1000

	S-methyl-L-cysteine (L-Hmecys)	{[Ag(L-mecys)]}$_n$ (4)	L-cysteine (L-H$_2$cys)	{[Ag(L-Hcys)]}$_n$ (5)
E. coli	>1000	31.3	>1000	>1000
B. subtilis	>1000	31.3	>1000	>1000
S. aureus	>1000	62.5		>1000
P. aeruginosa	>1000	7.9		>1000
C. albicans	>1000	250		>1000
S. cerevisiae	>1000	500		>1000
A. niger	>1000	>1000		>1000
P. citrinum	>1000	>1000		>1000

	{[Ag$_2$(*R*-Hpyrrld)(*S*-Hpyrrld)]}$_n$[6d]	{Na[Ag(mba)]}$_n$[6f]	{Na[Ag(mna)]}$_n$[6g]	AgNO$_3$[6f]
E. coli	7.9	<2	12.5	6.3
B. subtilis	31.3	<2	>1000	100
S. aureus	15.7	32	>1000	>1600
P. aeruginosa	7.9	16	31.5	6.3
C. albicans	7.9	1000	>1000	>1600
S. cerevisiae	7.9	125	>1000	1600
A. niger	500	>1000	>1000	>1600
P. citrinum	125	>1000	>1000	>1600

[a]"Free" ligand and relating silver(I) complexes evaluated by minimum inhibitory concentration (MIC; μg mL^{-1}). Compound **5** was added as a suspension in water because it was insoluble in water. H$_2$pyrrld = pyrrolidone-5-carboxylic acid, Hmba = 2-mercaptobenzoic acid, H$_2$mna = 2-mercaptonicotinic acid.

As shown in Table 3, water-soluble Ag−S (thiolate) bonding complexes ({Na[Ag(mba)]}$_n$ and {Na[Ag(mna)]}$_n$) exhibited effective activity against Gram-negative bacteria but only modest or no activity against yeast and mold.[6f,g] The pattern of antimicrobial-activity spectra of **1**−**3** with Ag−O and Ag−S (thioether) bonds is similar to that of water-soluble Ag−O bonding complexes rather than Ag−S (thiolate) complexes. The effectiveness of **1**−**3** is a little weaker than Ag−O bonding complexes. ^{109}Ag NMR data and ligand-exchange experiments of **3** and **4** support the fact that the ligand exchangeability of Ag−S (thioether) of silver(I) complexes is between Ag−O and Ag−S (thiolate). The relationship between the ligand-exchange ability of Ag−S (thioether) of **3** and **4** as well as **1** and **2** and antimicrobial activity supports our hypotheses that the antimicrobial activities of silver(I) complexes depend on the nature of the atom that coordinates to the silver(I) center and its bonding properties and the ease of ligand replacement. The antimicrobial activity of **4** was slightly less effective than those of complexes **1**−**3** with a methionine backbone. Although the bond distances and angles of **4** were normal, the molecular structure of **4** may be strained compared to those of **1**−**3**. These results are in agreement with the fact that the ligand exchangeability of Ag−S (thioether) of silver(I) complexes is between Ag−O and Ag−S (thiolate), consistent with ^{109}Ag NMR data. Water-insoluble complex **5** showed no activities against the selected bacteria, yeasts and molds.

CONCLUSION

Water-soluble and remarkably light-stable silver(I) acetylmethioninates {[Ag(acmet)]}$_n$ (**1** and **2**) were prepared as powder or crystals from Ag$_2$O and acetylmethionine in water at ambient temperature. They were fully characterized by CHN elemental analysis, IR, solution ^{1}H, ^{13}C, and ^{109}Ag NMR, and TG/DTA and compared to related complexes such as silver(I) methioninate (**3**), silver(I) *S*-methyl-L-cysteinate (**4**), and silver(I) cysteinate (**5**). X-ray crystallography of **1** shows that the O and S atoms of the thioether ligand coordinate to Ag^I but not N atoms. Hydrogen bonds are formed between the acetyl groups of the ligands. The properties of the neutral silver(I) complexes, **1** and **2**, are much different from those of silver(I) thiolates, attributable to coordination of the O- and S-(thioether) donor atoms to Ag^I. The silver(I) acetylmethioninates showed effective antimicrobial activities against two Gram-negative bacteria and two yeasts. The remarkable light stability and water solubility and a wide spectrum of antimicrobial activities of silver(I) complexes **1** and **2**, compared to those of related silver(I) complexes, indicate that the thioether and a partial $^-$OOC−C−N−C=O moiety, including the acetyl group of acmet$^-$, achieve a good balance between stability and antimicrobial activities in silver(I) complexes. These silver(I) acetylmethioninates are easy to handle and would be excellent starting silver(I) materials for synthesis of more complicated metal complexes.

ASSOCIATED CONTENT

Supporting Information

Crystallographic information files (CIF format) of crystals **1**, **3**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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