

# Synthesis and Structure of a Water-Soluble Hexanuclear Silver(I) Nicotinate Cluster Comprised of a "Cyclohexane-Chair"-Type of Framework, Showing Effective Antibacterial and Antifungal Activities: Use of "Sparse Matrix" Techniques for Growing Crystals of Water-Soluble Inorganic Complexes

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The synthesis of a water-soluble anionic silver 2-mercaptanicotinate complex having effective antibacterial and antifungal properties is described. Its structure has been confirmed to be a hexameric cluster by an X-ray diffraction analysis of a mixed Na<sup>+</sup>/Tris<sup>+</sup> salt (Tris<sup>+</sup> = tris(hydroxymethyl)methylammonium cation). The [Ag(mna)]<sub>6</sub><sup>6-</sup> cluster has a Ag<sub>6</sub>S<sub>6</sub> core and an overall shape of twisted hexagonal cylinder with six sulfur atoms and six silver atoms alternating on a puckered drum-like surface. Each Ag atom is trigonally coordinated by one N and two S ligands. The overall [Ag(mna)]<sub>6</sub><sup>6-</sup>·4Na<sup>+</sup>·2[(HOCH<sub>2</sub>)<sub>3</sub>CNH<sub>3</sub>]<sup>+</sup>·10H<sub>2</sub>O complex has a layered appearance in the crystal packing diagram, with a [Ag(mna)]<sub>6</sub><sup>6-</sup> cluster layer alternating with a solvent layer consisting of sodium atoms, Tris buffer cations, and water molecules. The structure is almost identical to that of a neutral [Ag(Hmna)]<sub>6</sub> complex reported earlier. The neutral and charged complexes are both known to possess antimicrobial activities, and some biological properties of these and related compounds are briefly discussed in this paper.

## Introduction

There is considerable interest in the coordination chemistry of silver(I) and gold(I) complexes with biological and pharmacological activity. Studies of gold(I) complexes have focused mostly on their antiarthritic applications<sup>1,2</sup> and antimicrobial activities,<sup>3,4</sup> while studies of silver(I) complexes have been mainly related to their antimicrobial and antifungal properties.<sup>4,5</sup> However, compared to the number of gold(I) complexes, far fewer Ag(I) complexes have been investigated in this connection. The molecular design of such silver(I)

and gold(I) complexes are an intriguing aspect of the bioinorganic chemistry of metal-based drugs. One of the problems in the study of pharmacologically active silver(I) and gold(I) compounds is the fact that, in some cases, their three-dimensional structures are not well-established. Many metal complexes of thiol and nitrogen-containing heterocyclic ligands (especially those of gold) are hard to crystallize and some are believed to be polymeric.<sup>2,6,7</sup>

In the past decade, the antimicrobial activities of Ag(I) and Au(I) complexes have been actively studied.<sup>3–5,7</sup> The main aims of that research are the synthesis of compounds with Ag(I)–N, Ag(I)–S, Ag(I)–O, and Ag(I)–P bonds and the establishment of structural relationship of such complexes with antimicrobial activities. It was suggested<sup>5,8</sup> that one of the key factors determining the antimicrobial effects of silver complexes is the nature of the atom coordinated to Ag and

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its bonding properties, rather than the solubility, charge, chirality, or degree of polymerization of the complexes. For example, it has been speculated that the weak Ag(I)–N<sup>5</sup> and Ag(I)–O<sup>8</sup> bond strengths might play an important role in exhibiting a wider spectrum of antimicrobial and antifungal activities and that the potential target sites for the inhibition of bacterial and yeast growth by Ag(I)–N complexes might be the sulfur-containing residues of proteins.<sup>4</sup> In general, Ag(I)–S complexes have been shown to have a narrower spectrum of antimicrobial activity than Ag(I)–N complexes, but no antifungal activity.<sup>5b</sup> In contrast, almost all compounds with Ag(I)–P bonds investigated thus far have shown no activity against bacteria, yeast, or molds.<sup>5,7</sup>

Recently, several silver complexes of 2-mercaptionicotinic acid (H<sub>2</sub>mna = 2-HS(C<sub>5</sub>H<sub>3</sub>N)COOH) have been prepared and investigated for their antimicrobial properties.<sup>4</sup> Under acidic conditions, the neutral species [Ag(Hmna)]<sub>6</sub> could be synthesized, and its hexameric nature was confirmed by X-ray analysis. In contrast, under alkaline conditions a water-soluble charged species, {Na[Ag(mna)]}<sub>n</sub>, was formed and this compound was also believed to be hexameric, but a full structural analysis could not be completed because of crystallographic difficulties.<sup>4,13</sup>

Our group had been successful earlier in using systematic crystallization procedures<sup>9</sup> that have been used widely for the crystallization of macromolecules to obtain crystals of various water-soluble compounds that had never been crystallized before.<sup>2,10,11</sup> The idea behind these procedures is to change various crystallization parameters (concentration of sample, concentration of precipitants, nature of solvents, ionic strength, pH, etc.) in a systematic way until optimum conditions for the formation of high-quality crystals are obtained.<sup>9b</sup> In this paper, we describe the application of this approach to the water-soluble anionic Ag/mna complex and have confirmed the hexameric nature of this cluster, [Ag(mna)]<sub>6</sub><sup>6-</sup>, by X-ray structural analysis.

## Experimental Section

**Synthesis. (1) Sodium Salt of Silver 2-Mercaptionicotinate, {Na[Ag(mna)]}<sub>6</sub>·nH<sub>2</sub>O.** This compound was obtained according to the previously reported method<sup>4</sup> in 90.0% yield (0.90-g scale) by a reaction in an aqueous solution of Ag<sub>2</sub>O:H<sub>2</sub>mna:NaOH = 1:2:4 molar ratio, followed by crystallization by vapor diffusion of a water/acetone system and identified with CHNS analysis and TG/DTA, FTIR, and <sup>1</sup>H, <sup>13</sup>C, and <sup>109</sup>Ag NMR spectroscopy.

**(2) Potassium and Cesium Salts of Silver 2-Mercaptionicotinate, {K[Ag(mna)]}<sub>6</sub>·nH<sub>2</sub>O, and {Cs[Ag(mna)]}<sub>6</sub>·nH<sub>2</sub>O.** These compounds were obtained in a fashion analogous to the sodium salt, with slightly different yields: 98.4% for the potassium salt and 76.8% yield for the cesium salt.

## Initial Structural Analysis of the Na<sup>+</sup> Salt of [Ag<sub>6</sub>(mna)]<sub>6</sub><sup>6-</sup>.

The sample of [Ag<sub>6</sub>(mna)]<sub>6</sub>Na<sub>6</sub> used was prepared as described above. Commercially available crystallization kits (Crystal screens I and II, from Hampton Research) were used to determine the preliminary crystallization conditions for a 0.2 M solution of [Ag<sub>6</sub>(mna)]<sub>6</sub>Na<sub>6</sub> with the vapor diffusion hanging drop technique.<sup>9</sup> After numerous trials, it was found that this compound could be successfully crystallized using the following precipitation conditions: 1.5 M ammonium sulfate, 0.1 M Tris buffer (pH 8.5), and 12% glycerol. We also found that crystal size and appearance could be significantly improved by carrying out the crystallization in a gel,<sup>12</sup> which has the effect of slowing down the crystal growth process.<sup>9</sup>

The sodium salt of silver mercaptionicotinate crystallizes<sup>13</sup> as a hexameric complex in the triclinic space group *P* $\bar{1}$  with the unit cell dimensions *a* = 12.590(6) Å, *b* = 12.908(5) Å, and *c* = 13.892(5) Å with  $\alpha$  = 62.75(1)°,  $\beta$  = 65.12(2)°,  $\gamma$  = 61.48(3)°, and *V* = 1303.5(19) Å<sup>3</sup>. Data were collected on a Siemens P4 X-ray diffractometer at –100 °C. The structure was solved by direct methods and refined to an agreement factor of *R* = 0.080. A centrosymmetric [Ag<sub>6</sub>(mna)]<sub>6</sub><sup>n-</sup> cluster was found together with two Na<sup>+</sup> ions and numerous water molecules, and the basic structure of the [Ag<sub>6</sub>(mna)]<sub>6</sub><sup>n-</sup> cluster is similar to the neutral Ag<sub>6</sub>(Hmna)<sub>6</sub> molecule reported earlier.<sup>4</sup> However, the final stoichiometry of the anionic complex could not be definitively established because the presence of the other four expected Na<sup>+</sup> cations could not be determined unambiguously from the X-ray data (in other words, it was difficult to distinguish potential Na<sup>+</sup> ions from the oxygen atoms of water molecules in the electron density maps). The application of silica hydrogel did slow the crystallization process and improve the crystal quality, but even so the results did not lead to an unambiguous structure for the sodium salt of [Ag<sub>6</sub>(mna)]<sub>6</sub><sup>6-</sup>.

## Structural Analyses of the K<sup>+</sup> and Cs<sup>+</sup> Salts of [Ag<sub>6</sub>(mna)]<sub>6</sub><sup>6-</sup>.

In an attempt to resolve the ambiguity of the number of cations in the structure of the alkali salts of [Ag<sub>6</sub>(mna)]<sub>6</sub><sup>6-</sup>, the structures of the K<sup>+</sup> and Cs<sup>+</sup> salts of this cluster were also studied.<sup>14</sup> The hope was that the larger sizes of the K<sup>+</sup> and Cs<sup>+</sup> ions would make them more easily distinguishable from the O atoms of the water molecules and that this would lead to an unambiguous count of the number of alkali metal cations.

Clear chunky crystals of the potassium salt of [Ag<sub>6</sub>(mna)]<sub>6</sub><sup>n-</sup> could be grown from a precipitating solution consisting of 35% v/v MPD (2-methyl-pentane-2,4-diol), 0.1 M K-HEPES pH 7.5 (*N*-2-hydroxyethylpiperazine-*N*-2-ethanesulfonate buffer), and 0.4 M ammonium sulfate. It crystallizes as a hexameric complex in the triclinic space group *P* $\bar{1}$ . Data were collected at 183(2) K and the unit cell dimensions are *a* = 12.837(4) Å, *b* = 12.595(5) Å, *c* = 13.725(4) Å,  $\alpha$  = 64.67(2)°,  $\beta$  = 63.26(2)°,  $\gamma$  = 61.55(2)°, *V* = 1676.8(10) Å<sup>3</sup>, and *Z* = 2; structure refined down to *R* = 7.6% for 5583 reflections. In the case of the Cs<sup>+</sup> salt, crystals were grown from very similar conditions (35% MPD, 0.1 M HEPES–Cs pH 7.5, and 0.4 M ammonium sulfate), and the unit cell also had very similar dimensions: space group *P* $\bar{1}$ , *a* = 12.665(3) Å, *b* = 12.898(4) Å, *c* = 14.014(3) Å,  $\alpha$  = 62.72(1)°,  $\beta$  = 65.449(9)°,  $\gamma$  = 61.15(1)°, *V* = 1725.8(12) Å<sup>3</sup>, and *Z* = 2; structure refined to *R* = 4.3% for 5876 reflections.

Unfortunately, even in those cases the “solvent regions” were still disordered and could not be resolved completely, despite the fact that the structures appeared to have been refined satisfactorily in both cases. Thus, the use of heavier cations could not resolve

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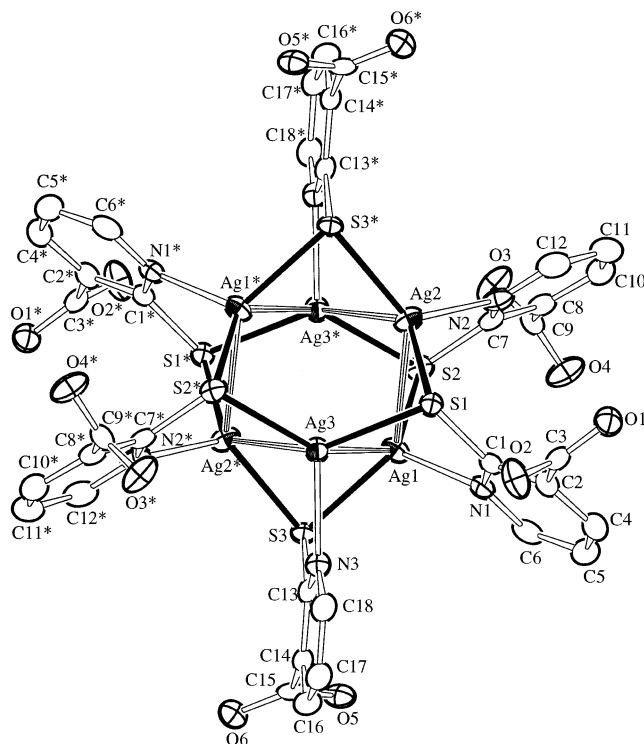
the ambiguity of the charge of the central  $[\text{Ag}_6(\text{mna})_6]^{n-}$  cluster: the solvent regions were still intractably disordered, and cations could not be distinguished from  $\text{H}_2\text{O}$  molecules.

**Structural Analysis of the Mixed  $\text{Na}^+/\text{Tris}^+$  Salt of  $[\text{Ag}_6(\text{mna})_6]^{6-}$ .** At this stage, we noticed that a crystallization tray that we had set up earlier with the original  $\text{Na}^+$  salt of  $[\text{Ag}_6(\text{mna})_6]^{n-}$  had produced excellent crystals. In this tray we had used the water-soluble polymer PEG (poly(ethylene glycol)) as the main precipitant instead of ammonium sulfate, and the conditions were as follows: 30% PEG 4000 (mol. wt. 4000), 0.1 M Tris HCl buffer  $[(\text{HOCH}_2)_3\text{C}-\text{NH}_3^+\text{Cl}^-]$ , pH 8.5, and 0.2 M sodium acetate. This crystallization tray had been neglected for a long period of time because initially (after the first 2–3 weeks) the only thing visible in that drop was a small amount of precipitation. However, over a period of a few months, the microcrystalline precipitate had gradually transformed itself into a crop of excellent diffraction-quality crystals, subsequently found to be that of a mixed  $\text{Na}^+/\text{Tris}^+$  salt (vide infra). Poly(ethylene glycol) is a high-viscosity precipitant, and crystallization trials using PEG 4000 as a dehydrating agent usually proceed slowly.

Diffraction data for the mixed  $\text{Na}^+/\text{Tris}^+$  salt of  $[\text{Ag}_6(\text{mna})_6]^{n-}$  were collected at low temperature [ $T = 85(2)$  K] on a Bruker SMART/APEX CCD diffractometer with graphite monochromated Mo  $K\alpha$  radiation ( $\lambda = 0.71073$  Å). The cell parameters were initially obtained from the least-squares refinement of the spots from three sets of 20 frames, collected at different regions of reciprocal space, and later improved using spots from the full set of collected data. A hemisphere of data was collected up to a resolution of 0.75 Å, and the intensity data were processed using the SAINT-PLUS program [ $R(\text{int}) = 0.015$ ]. All calculations for the subsequent structure determination were carried out using the SHELXTL package (version 5.1),<sup>15</sup> and absorption corrections were applied using SADABS.<sup>16</sup> The initial atomic positions of the Ag atoms were located by direct methods, and the structure was expanded using standard heavy-atom techniques. The structure was refined by least-squares methods using data within the  $\theta$  range from 1.8° to 28.2° (completeness of the highest shell = 88%). Calculated hydrogen positions were input and refined in a riding manner along with the attached carbons. All non-hydrogen atoms were refined anisotropically to yield a final  $R$  factor of 3.26% for 6936 independent reflections. A summary of the refinement details and the resulting factors are given in Table 1.

## Results and Discussion

**Molecular Structure of  $[\text{Ag}(\text{mna})_6]^{6-} \cdot 4\text{Na}^+ \cdot 2[\text{C}_4\text{O}_3\text{H}_{12}\text{N}]^+ \cdot 10\text{H}_2\text{O}$ .** The mixed Tris/sodium salt of silver(I) mercaptocotinate crystallizes as a hexameric complex in the triclinic space group  $P\bar{1}$ . There are three independent  $[\text{Ag}(\text{mna})]^-$  units in the asymmetric unit, forming the centrosymmetric  $\text{Ag}_6\text{S}_6$  cluster through crystallographic inversion center (Figure 1). In addition, two sodium atoms and one protonated Tris cation,  $(\text{HOCH}_2)_3\text{C}-\text{NH}_3^+$ , were found in the asymmetric unit, which corresponds to an overall stoichiometry of  $[\text{Ag}(\text{mna})_6]^{6-} \cdot 4\text{Na}^+ \cdot 2[\text{C}_4\text{O}_3\text{H}_{12}\text{N}]^+$  and confirms that the  $\text{Ag}_6\text{S}_6$  cluster has a charge of  $-6$  under the conditions of crystallization (pH 8.5). The  $\text{Ag}_6\text{S}_6$  core has an overall shape of a twisted hexagonal cylinder consisting of two connected  $\text{Ag}_3\text{S}_3$  units, with six sulfur



**Figure 1.** A view of the  $[\text{Ag}_6(\text{mna})_6]^{6-}$  cluster, with an overall shape of a twisted hexagonal cylinder. The cylinder consists of two  $\text{Ag}_3\text{S}_3$  connected units, with six sulfur atoms and six silver atoms alternating on the pucker drumlike surface.

**Table 1.** Crystal and Refinement Data for  $[\text{Ag}(\text{mna})_6]^{6-} \cdot 4\text{Na}^+ \cdot 2[\text{C}_4\text{O}_3\text{H}_{12}\text{N}]^+ \cdot 10\text{H}_2\text{O}$

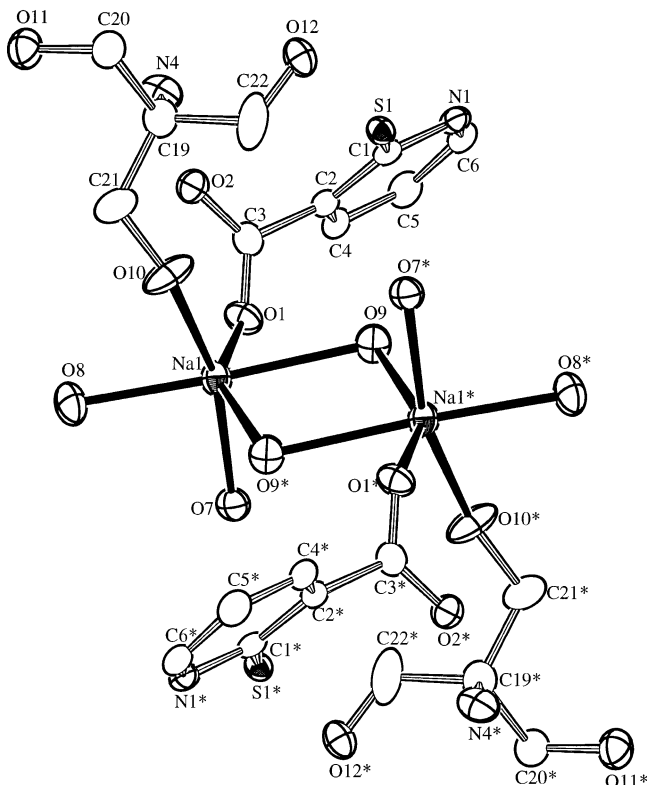
empirical formula	$\text{C}_{44}\text{H}_{42}\text{Ag}_6\text{N}_8\text{Na}_4\text{O}_{28}\text{S}_6$
fw	2060.3
temp	85(2) K
wavelength	0.71073 Å
cryst syst	triclinic
space group	$P\bar{1}$ (#2)
unit cell dimensions	$a = 12.1119(15)$ Å; $\alpha = 62.874(2)^\circ$ $b = 12.5555(15)$ Å; $\beta = 70.151(2)^\circ$ $c = 12.6565(15)$ Å; $\gamma = 84.075(2)^\circ$
vol	$1608.2(3)$ Å <sup>3</sup>
Z	1
$\theta$ range for data collection	1.79–28.19°
independent reflns	6936 [ $R(\text{int}) = 0.0153$ ]
completeness to $\theta = 28.19^\circ$	87.9%
final R indices [ $I > 2\sigma(I)$ ]	$R1 = 0.0326$ , $wR2 = 0.0763$
R indices (all data)	$R1 = 0.0347$ , $wR2 = 0.0775$
transm factors	min/max ratio: 0.869

atoms and six silver atoms alternating on a pucker drumlike surface (Figure 1). The  $\text{Ag}_3\text{S}_3$  units are distinctly crown-shaped, having chairlike conformations, and are staggered with respect to each other. They are attached to each other by two sets of  $\text{Ag}\cdots\text{Ag}\cdots\text{Ag}$  triangular interactions, also shown in Figure 1. The  $\text{Ag}-\text{Ag}$  distances in the present complex are slightly elongated compared to those in the neutral  $[\text{Ag}(\text{Hmna})_6]$  compound previously analyzed<sup>4</sup> (Table 2) and those in  $\text{Ag}_6[\text{SC}_6\text{H}_3\text{SiH}_2\text{C}_4\text{H}_9]_6$ .<sup>17</sup> The  $\text{Ag}\cdots\text{Ag}$  separations, which are slightly longer than those in metallic silver (2.88 Å)<sup>18</sup> and less than the expected van der Waals radius for silver atoms (3.44 Å),<sup>19</sup> indicate the existence of weak metal–metal interactions.<sup>4,20</sup>

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**Figure 2.** The region around one of the  $\text{Na}^+$  ions, showing the distorted octahedral coordination. Each  $\text{Na}^+$  ion is coordinated to one of the oxygen atoms of the  $\text{Tris}^+$  cation,  $[(\text{HOCH}_2)_3\text{CNH}_3]^+$ , an oxygen atom from one of the  $(\text{mna})^{2-}$  ligands of the cluster, and four water molecules. A crystallographic center of symmetry is situated at the center of this plot.

**Table 2.** Comparison of Selected Bond Distances (Å) and Angles (deg) between the Anionic  $[\text{Ag}(\text{mna})]_6^{6-}$  and Neutral  $[\text{Ag}(\text{Hmna})_6]$  Clusters (Ref 4)

$[\text{Ag}(\text{mna})]_6^{6-}$ cluster (this work)		neutral $[\text{Ag}(\text{Hmna})_6]$ cluster <sup>4</sup>	
Ag1–Ag2'	2.9373(4)	Ag1...Ag2	2.911(1)
Ag1–Ag3'	2.9884(5)	Ag1...Ag3'	2.924(1)
Ag2–Ag3	3.3485(5)	Ag2...Ag3'	3.1129(8)
Ag1'–Ag3–Ag2	54.874(9)	Ag1–Ag3'–Ag2	57.54(2)
Ag1'–Ag2–Ag3	56.316(10)	Ag1–Ag2–Ag3'	57.97(3)
Ag3'–Ag1–Ag2'	68.810(12)	Ag2–Ag1–Ag3'	64.48(3)
Ag3–N3	2.292(3)	Ag1–N1a	2.273(5)
Ag1–N1'	2.293(3)	Ag2–N1	2.317(5)
Ag2–N2	2.298(3)	Ag3–N1b	2.294(5)
Ag1–S2	2.4682(9)	Ag1–S1	2.490(2)
Ag1–S3	2.4773(9)	Ag1–S3'	2.491(2)
Ag2–S3	2.4742(9)	Ag2–S2	2.465(2)
Ag2–S1	2.5175(9)	Ag2–S3	2.497(2)
Ag3–S2	2.4795(9)	Ag3–S1	2.505(2)
Ag3–S1	2.5180(9)	Ag3–S2'	2.459(2)
C3–O1	1.246(4)		
C3–O2	1.266(4)		
C9–O3	1.239(4)		
C9–O4	1.266(4)		
C15–O5	1.255(4)		
C15–O6	1.255(4)		

The coordination environments around each silver atom in the salt and neutral  $\text{Ag}_6\text{S}_6$  clusters are identical: two weak silver(I)–silver(I) interactions, two sulfur atoms, and one monodentate nitrogen atom from each  $\text{mna}^{2-}$  ligand.<sup>4</sup> The

observed Ag–N bond distances, which connect the six carboxyl–pyridine rings to the  $\text{Ag}_6\text{S}_6$  cluster, are almost identical [2.292(3), 2.298(3), and 2.292(3) Å] and are very similar to the Ag–N distances found in the other hexanuclear complexes of silver(I) with derivatives of pyridine-2-thione [2.273(5)–2.345(2) Å].<sup>4,17,21</sup> All observed Ag–S bond distances are within the range of 2.4682(9)–2.5180(9) Å and in agreement with the Ag–S bond distances found in similar complexes.<sup>4,17,21</sup>

**Cation and Solvent Region.** There are, unambiguously, three cations present in the asymmetric unit and five water molecules. The cations consist of two  $\text{Na}^+$  and one  $[\text{C}_4\text{H}_{12}\text{O}_3\text{N}]^+$  cation (a protonated Tris buffer molecule), which confirms that the total complex is neutral (one  $[\text{Ag}(\text{mna})]_6^{6-}$ , four  $\text{Na}^+$ , and two  $\text{Tris}^+$  ions). Both  $\text{Na}^+$  ions have a distorted octahedral coordination, and one of them is shown in Figure 2 coordinated to an oxygen atom from a  $\text{Tris}^+$  cation. The packing structure of the full complex is quite interesting. It packs as layers in the crystal, with the  $[\text{Ag}(\text{mna})]_6^{6-}$  clusters forming a layer which is followed by a layer of solvent, then another layer of  $[\text{Ag}(\text{mna})]_6^{6-}$  ions, and so on. It appears that the interstitial space between the layers cannot be efficiently filled just by a combination of alkali metal ions and water molecules. This leads to a disordered solvent region in the previous structure analyses of the  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$  salts of  $[\text{Ag}(\text{mna})]_6^{6-}$  (vide supra) and prevented the determination of the exact number of alkali metal cations in those cases. In the present structural analysis, the key feature is that two  $\text{Tris}^+$  buffer cations help to efficiently fill the available space in the solvent region, leading to a very smooth refinement of the overall structure,  $[\text{Ag}(\text{mna})]_6^{6-} \cdot 4\text{Na}^+ \cdot 2[\text{C}_4\text{O}_3\text{H}_{12}\text{N}]^+ \cdot 10\text{H}_2\text{O}$ , to a final  $R$  factor of 3.3%.

**Antimicrobial Activities of the Neutral and Anionic  $\text{Ag}_6(\text{mna})_6$  Complexes.** Silver(I) and gold(I) complexes have shown a variety of noteworthy antimicrobial activities, although mode of action and mechanism of their antimicrobial activities have not been clarified. Generally speaking, the antimicrobial activities by metal complexes strongly depend on the metal centers. Moreover, it has been found that most silver(I) complexes having the same or similar core structures consisting of the same coordinating donor atoms have shown a very similar spectrum of the antimicrobial activities (Supporting Information).

For example, silver(I) complexes with the dimeric  $\text{Ag}_2\text{O}_4$ -core molecular structure, such as  $\{[\text{Ag}(\text{S-Hpyrrld})]_2\}_n^{5a}$  ( $\text{H}_2\text{pyrrld} = 2\text{-pyrrolidone-5-carboxylic acid}$ ),  $\{[\text{Ag}(\text{R-Hpyrrld})]_2\}_n^{22}$ ,  $\{[\text{Ag}_2(\text{R-Hpyrrld})(\text{S-Hpyrrld})]_2\}_n^{22}$ ,  $\{[\text{Ag}(\text{S-othf})]_2\}_n^{23}$  ( $\text{Hothf} = 5\text{-oxo-2-tetrahydrofuran-2-carboxylic acid}$ ),  $\{[\text{Ag}(\text{R-othf})]_2\}_n^{23}$ ,  $\{[\text{Ag}_2(\text{R-othf})(\text{S-othf})]_2\}_n^{23}$ ,  $\{[\text{Ag}_2(\text{D-Hasp})(\text{L-Hasp})]_2\}_n^{24}$  ( $\text{H}_2\text{asp} = \text{aspartic acid}$ ), and  $[\text{Ag}(\text{hino})]_2^{24}$  ( $\text{Hhino} = \text{hinokitiol or 4-isopropyltropolone}$ ), have shown a very

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similar and wide spectrum of antimicrobial activities against selected bacteria, yeasts, and molds. On the other hand, phosphine gold(I) complexes with a linear two-coordinate AuNP-core structure, such as  $[\text{Au}(\text{im})(\text{PPh}_3)]^{25}$  (Him = imidazole),  $[\text{Au}(\text{py})(\text{PPh}_3)]^{25}$  (Hpy = pyrazole),  $[\text{Au}(1,2,3\text{-triz})(\text{PPh}_3)]^{25}$  (Htriz = triazole),  $[\text{Au}(1,2,4\text{-triz})(\text{PPh}_3)]^{25}$  and  $[\text{Au}(\text{tetz})(\text{PPh}_3)]^{3c,25}$  (Htetz = tetrazole), have shown a very similar spectrum of selective activities against Gram-positive bacteria. Such a spectrum of antimicrobial activities has also been found in phosphine gold(I) complexes with a linear two-coordinate AuSP-core structure, such as  $[\text{Au}(2\text{-Hmpa})(\text{PPh}_3)]$  ( $\text{H}_2\text{mpa}$  = mercaptopropionic acid) and  $[\text{Au}(\text{D-Hpen})(\text{PPh}_3)]$  ( $\text{H}_2\text{pen}$  = penicillamine).<sup>26</sup> These silver(I) and gold(I) complexes show that their antimicrobial activities are related to their molecular structures. For metal complexes with the same or similar core structures, we have proposed that the magnitudes of their antimicrobial properties are related to the ease with which they participate in ligand-exchange reactions.<sup>24,26</sup>

In this work, we have found that the anionic complex  $[\text{Ag}(\text{mna})]_6^{6-}$  with  $\text{mna}^{2-}$  ligand has almost the same hexanuclear core structure as that of the previously reported, neutral complex  $[\text{Ag}(\text{Hmna})]_6$ . Surprisingly, these two silver(I) complexes have shown a different spectrum of antimicrobial activities: the neutral complex has shown activity against both Gram-negative and -positive bacteria, while the anionic complex has shown activity against only Gram-negative bacteria.<sup>4</sup> The most remarkable difference is found with the Gram-positive bacteria *B. subtilis* and *S. aureus*; the neutral complex is active, while the salt complex is not.<sup>4</sup>

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Because both complexes are active against the Gram-negative bacteria *E. coli* and *P. aeruginosa*, the permeability<sup>27</sup> of the outer membrane of the Gram-negative bacteria cannot be a factor. The results would suggest a mechanism for the antimicrobial function, which is determined not only by the structure of the anion and its conjugate acid but also by solubility and transport phenomena and by ligand exchange equilibria.

In relation to the present work, we know in fact that the neutral complex can be changed by reaction with  $\text{PPh}_3$  in solution, to the monomeric three-coordinate Ag–(S, P)-bonding complex,  $[\text{Ag}(\text{mna})(\text{PPh}_3)_2]$ .<sup>28</sup> It is conceivable that ligand replacement from the Ag–(N, S)-core cluster to a new Ag–S(biological ligand) complex could occur in the presence of sulfur-containing biological molecules. Thus, we suggest that, rather than the geometries of the silver(I) clusters, other factors may account for observed differences in antimicrobial activity: factors such as the hydrophobicity or hydrophilicity of the clusters or the ease of ligand exchange between Ag–(N, S) cores and Ag–S (biological ligand) bonds.

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**Supporting Information Available:** Summary of the antimicrobial activities of selected silver(I) and gold(I) complexes studied in the Nomiya laboratory; details of crystallographic analysis of  $[\text{Ag}(\text{mna})]_6^{6-} \cdot 4\text{Na}^+ \cdot 2[\text{C}_4\text{O}_3\text{H}_2\text{N}]^+ \cdot 10\text{H}_2\text{O}$ . This material is available free of charge via the Internet at <http://pubs.acs.org>.

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