doi:10.2533/chimia.2013.851 Chimia 67 (2013) 851–854 

# Bioinorganic Chemistry of Silver: Its Interactions with Amino Acids and Peptides

Katharina M. Fromm*

*Abstract:* Silver and its compounds have been used for centuries for *e.g.* water storage, burn wounds or as eye ointment. Almost forgotten after the discovery of antibiotics, silver chemistry has had a revival over the past years as a means to combat multi-resistant bacteria. Although the details of its mechanism of action are still unknown, silver seems to be efficient as it interacts with many biomolecular targets in a cell. In our group, we contribute to the elucidation of this mechanism of action by investigating the interactions of silver ions with amino acids and peptides as well as the formation of nanoparticles related to the mechanism of biomineralization of silver.

**Keywords:** Amino acids · Bioinorganic chemistry · Nanoparticles · Peptides · Silver

## Introduction

The antimicrobial effect of silver is by now well documented and recognized.[1,2] While the effect is directly observable with microbiological tests[3] and microscopy[4] for example, its mechanism of action at the molecular level remains mostly obscure. This has to do with the history of the use of silver in this context. Indeed, in the 1940s after the discovery of antibiotics, the use of silver was almost completely abandoned in favor of these new drugs. Researchers have investigated the mechanism of action of these antibiotics in much detail and understand the molecular interplays that are responsible for the antimicrobial effect. For example, the tricyclic glycosylated peptide antibiotic vancomycin[5] is known to bind to terminal D-alanyl-D-alanine groups of the N-acetylmuramic acid and N-acetylglucosamine, preventing their crosslinking to form a stable cell wall in Gram-positive bacteria. This interaction is based on multiple hydrogen bonding interactions, which are disturbed if bacteria mutate one of the D-alanine groups to D-lactate, rendering the antibiotic inefficient. This resistance build-up among bacteria is an important problem in society, in particular in hospitals where multi-resistant strains can be difficult to treat.[6] In the case of vancomycin, re-engineering the peptide can be a solution,[7] at least until the bacteria find a new mutation at the cell wall building blocks – which is only a matter of time.

Hence, silver has come back into the center of interest of many researchers in the field of antimicrobial compounds. As a coordination chemist may predict, silver is expected to interact with many different biomolecules, starting at the cell membrane,[8] with enzymes in the cell[9] and finally even with DNA, for which it is expected to inhibit replication by replacing the H-atoms in the base pairings.[10] In particular, O-, N- and S-donor groups are prone to be strong binders for silver ions.

## Silver–Amino Acid Complexes

Our group has been interested in the synthesis of silver-ion containing coordination compounds, in particular coordination polymers.[11–25] We investigate the structure, light stability and antimicrobial as well as biocompatibility properties of these compounds in the context of using them in the medical or hygienic application sectors.[26–34]

The phenomenological aspects are quite straightforward: Silver and its ions are good antimicrobial compounds and biocompatible up to certain concentrations.[2] On the other hand, the mechanism of action involved in the antimicrobial properties is still far from being understood. This has to do with the fact that there is not one single target for silver, but many interactions are possible – which is of course also one of the strengths of the system, as resistance build-up is therefore more difficult. Two defense mechanisms are known in principle: i) storage of the silver, *e.g.* as silver nanoparticles (AgNPs), or ii) an efflux pump able to export the silver ions out of the cell. Indeed, some microorganisms are capable of generating AgNPs, which is also used for the biochemical synthesis of the latter.[35–37] Efflux systems were shown to possess the silver binding SilE protein, which consists of 143 amino acids.[38] Surprisingly, it does not, like other metal-binding proteins, contain any sulfur-containing amino acids like cysteine, but it has 10 histidine moieties, which are predicted to be able to bind five silver ions.[39]

We were therefore interested in a first step to analyze the silver coordination compounds with amino acids before launching our study on the complexation of silver with peptides. Surprisingly few results are known describing the structural details of such complexes of silver with amino acids, but a theoretical study lists the binding energies between a silver ion and the individual amino acids arginine, lysine and histidine as the strongest binders, followed by glutamine and methionine, whereas for cysteine only a medium strong binding is observed.[40] Therefore, we were striving to obtain structural data of amino acid coordination of silver and tested several complexation conditions for these reactions, varying the pH and solvents as well as the silver counter ions of the starting material.[41] In acidic pH, we obtained with protonated L-histidine ('L-Hhis$^+$') the compound

*Correspondence: Prof. Dr. K. M. Fromm
Department of Chemistry
University of Fribourg
Chemin du Musée 9
CH-1700 Fribourg
E-mail: Katharina.fromm@unifr.ch

$[\{Ag(L\text{-}Hhis)(NO_3)_2\}_2H_2O]_n$ as a coordination polymer with two silver ions, two protonated histidinium ligands ($Hhis^+$), and two nitrate anions as repetition units (Fig. 1), as well as two uncoordinated nitrate anions and a water molecule per monomer.

The two silver ions Ag1 and Ag2 are bridged by two oxygen atoms (O1 and O2) of one of the two $Hhis^+$ ligands and additionally by O3 of the second $Hhis^+$ ligand with bond lengths ranging from 2.216(4) Å to 2.716(5) Å. O4 of this second $Hhis^+$ molecule coordinates to a neighbor equivalent silver ion Ag2' with 2.299(4) Å, leading to a Ag1–Ag2' distance, which is <3Å and can thus be considered as a metal–metal interaction. While Ag1 is further coordinated by $O1_N$ of a first nitrate anion, the Ag2 and Ag2' ions are pairwise bridged by $O4_N$ and $O6_N$ of the second nitrate anion with distances between 2.392(7) Å and 2.510(7) Å. Ag1 reaches thus a coordination number of three with respect to the oxygen donor atoms arranged in a distorted trigonal planar coordination sphere, plus the Ag–Ag contact, while Ag2 has a coordination of five oxygen atoms arranged in a distorted square pyramid and an Ag–Ag contact. A one-dimensional coordination polymer results from this arrangement (Fig. 1, right).

Using a racemic mixture of D- and L-histidine in acidic pH to coordinate to silver nitrate, we obtained the compound $[Ag_2(D\text{-}Hhis)(L\text{-}Hhis)(NO_3)_4]_n$. While the asymmetric unit consists of one histidinium cation, one silver cation and two nitrate anions, a center of inversion as symmetry element produces the mirror image of this unit and hence of the initial amino acid ligand (Fig. 2, left). A 'dimer' formation as indicated in the formula above is obtained by pairwise coordination of two $Hhis^+$ cations of opposite chirality to two silver ions *via* both of their oxygen atoms O1 and O2 and their symmetry equivalents. O1 binds to Ag1 with 2.300(1) Å, while O2 connects to Ag1' of the same dimer with a distance of 2.250(1) Å. The amino acid bridged silver ions are connected by a very short distance of 2.814(1) Å, indicating attractive interactions between them. O1 acts also as bridging atom to Ag1" of the next dimer with a distance of 2.456(1) Å. Such a pseudo-dimer is also bridged into a coordination polymer by the oxygen atoms of one of the nitrate anions, leading to a one-dimensional chain structure. The silver-bridging nitrate anion is involved in hydrogen bonding using two of its oxygen atoms to connect to the ammonium groups of two different $Hhis^+$ cations of a parallel neighbor chain. The second nitrate anion is not connected to the silver cations, but is involved in hydrogen bonding between three $Hhis^+$ cations, two of which belong to the same coordination polymer chain and which interact *via* the ammonium group around N1 with an oxygen atom of the nitrate anion ($O4_N$ for one and $O5_N$ for the other), while the third connects to the third oxygen atom *via* one of the two N–H groups of the protonated imidazolium moiety, forming the shortest hydrogen bond of the three with N3–$O6_N$ of 2.791(3) Å (Fig. 2, right).

In contrast to the previous two structures, at neutral pH, the reaction of L-histidine with silver nitrate leads to the formation of a discrete complex of the composition $[Ag(L\text{-}his)_2(NO_3)]_2(H_2O)$. In this case, two histidine ligands coordinate to the silver cation *via* the N-atoms of the now deprotonated imidazole moieties (Fig. 3), indicating a stronger donor capacity of these N-atoms versus the carboxylate O-atoms of the amino acid. We discussed this as probably due to the protonated ammine function in close proximity, which is not compensated by other negative charges than the carboxylate group.[41] Both L-his ligands are hence overall neutral and in their zwitterionic form. The counter ion, nitrate, is also coordinating to the silver cation *via* $O2_N$ with a long distance of 2.871(2) Å, while the N-atoms coordinate with *ca.* 2.10 Å. The strong coordination by the N-atoms is also indicated by the quasi-linear N2–Ag1–N5 angle of 176.2(1)°.

In the literature, the reaction of $Ag_2O$ with histidine under unspecified pH conditions is described to yield a coordination polymer, forming a left-handed helix for L-His[42] and its right-handed mirror image for D-His.[43] In both cases, the histidine ligands connect the silver ions by coordi-

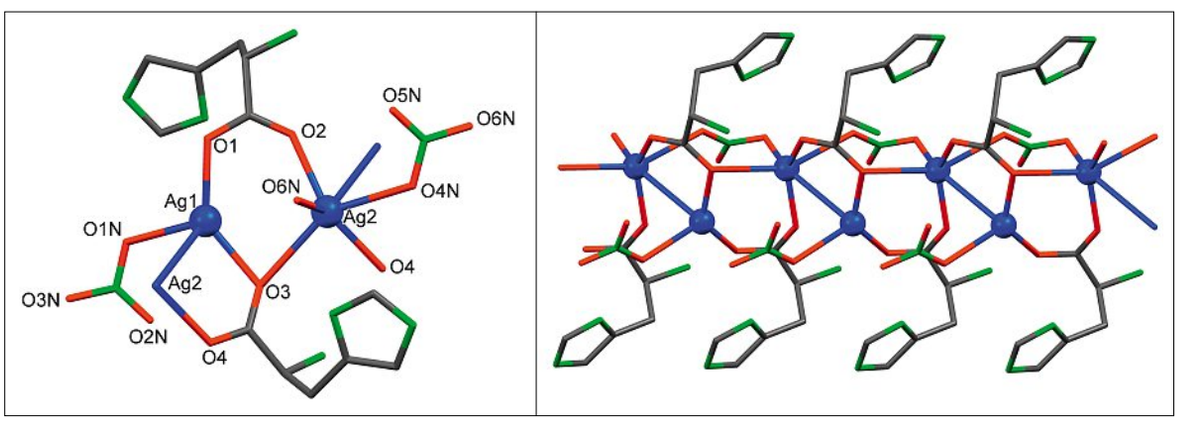


Fig. 1. The labeling of compound $[\{Ag(L\text{-}Hhis)(NO_3)_2\}_2H_2O]_n$ (left) and the coordination polymer obtained (right; blue = Ag; green = N; red = O; grey = C) (H-atoms omitted).

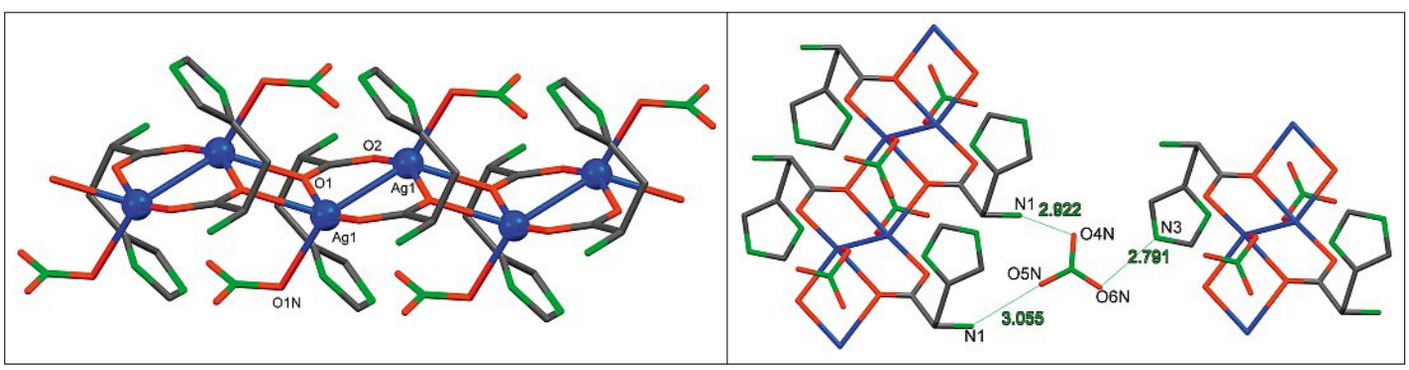


Fig. 2. Coordination polymer and its labeling of compound $[Ag_2(D\text{-}Hhis)(L\text{-}Hhis)(NO_3)_4]_n$ (left) and hydrogen-bonds formed by the second nitrate anion (right).

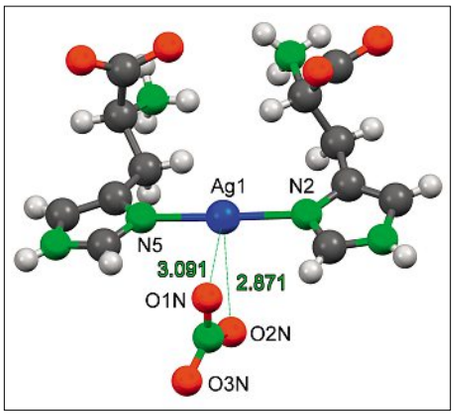


Fig. 3. Labeling of compound $[Ag(L\text{-his})_2(NO_3)]_2(H_2O)$ (water molecule omitted).

nating *via* two N-atoms, one of the imidazole moiety, and one of the $NH_2$ group. While the positions of the H-atoms are not clear from the X-ray data, the coordination mode of histidine indicates their zwitterionic form.

We have also obtained single crystals from a reaction of L-glutamic acid with silver nitrate at neutral pH,[44] at which both acid functions of the amino acid are deprotonated, while the amine is protonated, hence, the acid side group is deprotonated, and the α-amino acid part forms the zwitterion. The compound, which we obtained, has an asymmetric unit of $[Ag_4(L\text{-glu})_2(NO_3)_2]$ and forms again a one-dimensional coordination polymer (Fig. 4). It crystallizes in the non-centrosymmetric, monoclinic space group $P2_1$ (Flack parameter = 0.06). Two silver ions, Ag1 and Ag2 are coordinated by O1 and O2 of one glu-ligand (called glu1), and by O5 and O6 of a second amino acid ligand (glu2).

O1 and O2 are from the side group of the amino acid of glu1, while O5 and O6 belong to the amino acid function of glu2. The other oxygen atoms of glu1 and glu2, namely O3 and O4, as well as O7 and O8, respectively, bind to two more silver ions, Ag3 and Ag4. In this way, Ag1, Ag2, Ag3 and Ag4 form a rectangle with short Ag–Ag distances of 2.82 Å on average between Ag1 and Ag2, as well as Ag3 and Ag4, while the distances between Ag1 and Ag3, as well as Ag2 and Ag4 are on average 3.57 Å in length. The two glu-ligands bridge this rectangle above and below the mean plane through the four silver ions with Ag–O distances between 2.141(3) Å and 2.376(4) Å. O1 and O4 of such an entity coordinate furthermore to Ag3' of the next Ag4-rectangle (on Fig. 4 on the left) with an average distance of 2.63 Å, and, on the opposite side, O5 and O7 connect to Ag2" of a neighbor entity on the right of Fig. 4 with 2.56 Å on average. The silver ions Ag1 and Ag4 are further coordinated by O10 and O12 respectively, each oxygen atom belonging to a different nitrate anion. O9 of the first nitrate anion connects loosely to Ag1", and O13 of the second anion coordinates weakly to Ag4' with on average 2.95 Å. The so-formed one-dimensional ribbons are connected to each other *via* hydrogen bonds between the O-atoms of the nitrate anions and the ammonium groups of the amino acid ligands, yielding an overall three-dimensional connected network.

## Interaction of Silver with Model Peptides

The above results give an indication of how silver can be coordinated by the side groups of the amino acids within a peptide. It is obvious for histidine for example, that the N-coordination is by far preferred over the O-coordination at neutral pH, but finally not surprising if one thinks of the coordination of ammonia to silver ions, dissolving even AgCl. Similarly, peptides and proteins typically possess N-donor atoms in many of the amino acid side groups, and hence the targets of silver are manifold. A peptide can in principle react in two ways with a silver ion: i) by coordinating to one or more silver ions, which might also have an impact on the secondary structure of a peptide; and ii) by coordinating AND reducing the silver ion(s) and getting oxidized itself. With the aim to learn which amino acids in peptides are prone to coordinate to silver ions, and which are able to reduce them, we investigated in collaboration with the Wennemers group the behavior of a peptide library (Fig. 5) with 343 different peptides towards silver ion uptake and subsequent reduction with light or with ascorbate.[45] From these 343 peptides, two classes of peptides were identified. Three peptides were identified as able to reduce silver ions to silver nanoparticles (AgNPs) upon irradiation with light as well as with ascorbate, while all peptides containing His and His, His and Asp, His and Tyr, His and Ser, Asp and Asp or Ser and Asp in the first and last position connected by any of the linkers, are able to bind silver, but reduce it only with the help of sodium ascorbate. The common feature in the three peptides that are able to reduce silver ions with light is the presence of tyrosine. The role of tyrosine in the light-reduction process is currently under investigation in the Fromm group[46] in order to better understand *e.g.* the processes of biomineralization of silver by bacteria or fungi.[35–37]

Our group is also investigating if a combination of silver ions and antibiotics, such as vancomycin can be used as a synergetic active compound for combating multi-resistant bacteria. To this end, vancomycin is functionalized at the C-terminus in order to either graft it to a substrate surface or to coordinate to silver ions or both (Fig. 6).[26] Ongoing investigations hint at that this combination of silver and vancomycin derivatives is indeed a more powerful antimicrobial agent than the two ingredients alone.[47]

## Conclusions

Surprisingly little is known about the structural aspects and details of silver ions binding to amino acids, peptides and proteins. Our group will thus continue to elucidate the mechanism of action of silver

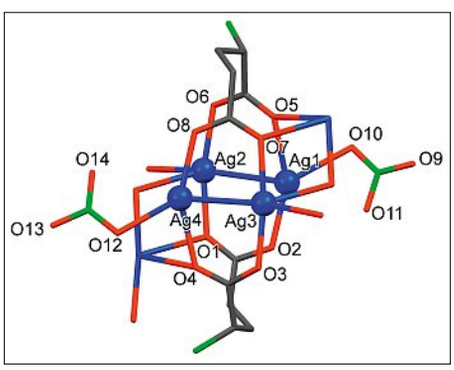


Fig. 4. Labeling of the glutamate derivative $[Ag_4(L\text{-glu})_2(NO_3)_2]$ (H-atoms omitted).

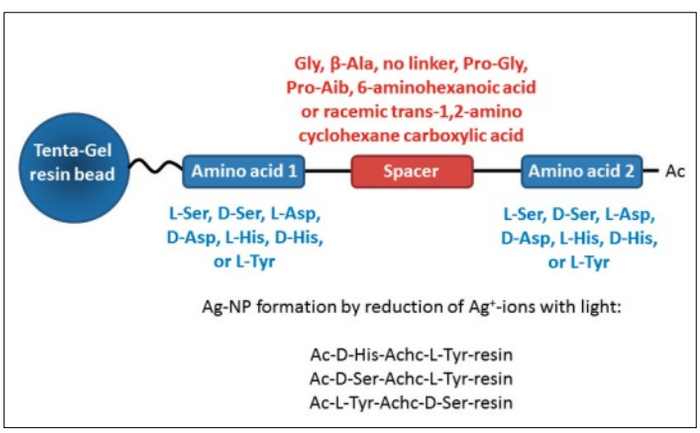


Fig. 5. Peptide library used for selectivity in silver binding and reduction tests (adapted from ref. [45]).

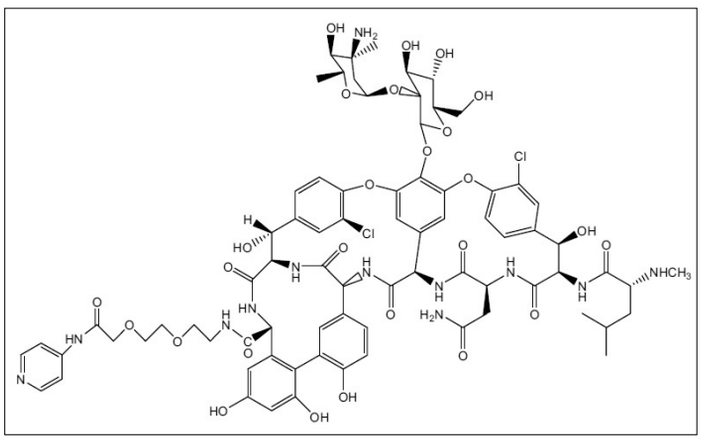

Fig. 6. One of the chemical modifications of vancomycin in order to attach it to substrate surfaces and/or for silver ion binding.[26]

ions and NPs when exposed to bacteria as well as eukaryotic cells to gain better insight and control over the design of silver-containing drugs.

Received: August 26, 2013


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[44] Synthesis and crystal structure of $[Ag_4(L\text{-}glu)_2(NO_3)_2]$: The title compound is typically obtained by reacting a 2:1 mixture of silver nitrate and L-glutamic acid at pH = 7 in 10 ml water and in an autoclave at 60 °C under autogenous pressure for 2h, and cooling down to room temperature. Single crystals of the title compound were obtained in 34% yield. All single crystals were mounted on loops and all geometric and intensity data were taken from one single crystal. Data collection, using Mo-$K\alpha$ radiation ($\lambda$ = 0.71073 Å) was performed at 293 K on a STOE IPDS-II diffractometer equipped with an Oxford Cryosystems open flow cryostat.[45] Absorption correction was partially integrated in the data reduction procedure.[49] The structure was solved by SIR 2004[50] or SHELX-99 and refined using full-matrix least-squares on $F^2$ with the SHELX-99 package.[51] All heavy atoms could be refined anisotropically. Hydrogen atoms were introduced as fixed contributors when a residual electronic density was observed near their expected positions. Single crystal data for 2: $Ag_4C_{10}H_{16}N_4O_{14}$, M = 847.75 g.mol$^{-1}$, monoclinic, space group $P2_1$ (No. 4), $a$ = 5.2496(3), $b$ = 11.3191(5), $c$ = 15.6805(7) Å, $\beta$ = 98.912(4), $V$ = 920.50(8) Å$^3$, Z = 2, $T$ = 293(2) K, $\rho$ = 3.059 Mg/m$^3$, $\mu$(MoK$\alpha$) = 4.280 mm$^{-1}$, 5610 reflections of which 3585 observed, 285 parameters refined, *GooF* = 0.938, $R1$ = 0.0796, $wR2$ = 0.1839 for $I > 2\sigma$ and $R1$ = 0.1209, $wR2$ = 0.2045 for all data, Flack parameter = 0.06(11). Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-954019. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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