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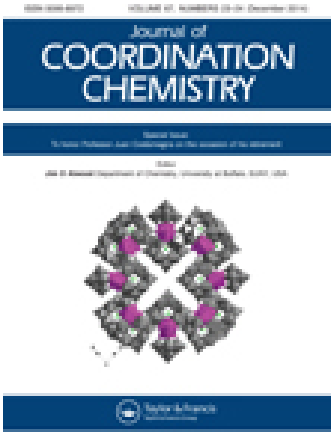

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Review: Antibacterial behavior of carboxylate silver(I) complexes

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Review: Antibacterial behavior of carboxylate silver(I) complexes

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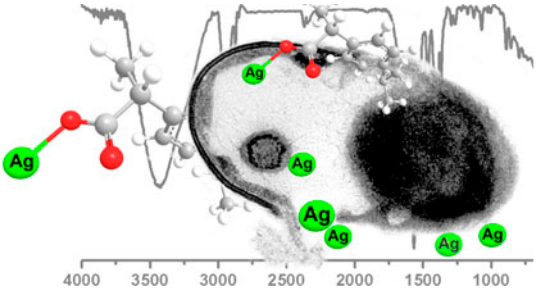

Since ancient times, silver ions have been known to be effective against a broad range of micro-organisms but in the last decade, this metal has been greatly studied because of their antimicrobial capability against a wide range of bacteria, viruses, and fungi. For the same reason, it is the most extensively studied metal with antibacterial applications in medicine. Besides applications, the antimicrobial activity is associated with high effectiveness, low toxicity, and virtually no resistance of micro-organisms to the presence of this metal. The appearance of new bacterial strains resistant to antibiotics is a serious health problem; so, there is a strong incentive to develop new bactericides. This makes current research in bactericidal silver complexes particularly important. This review summarizes the most important aspect related to coordination chemistry of Ag(I) carboxylate complexes and their influence as antibacterial agents.

Keywords: Silver(I); Antibacterial; Carboxylic bonds; FT-IR

1. History

The biocidal properties of silver have been known since the times of the Egyptians, Greeks, Romans, and Phoenicians. These cultures used silver vessels to store water, but they were unaware that the focus of disease was due to the presence of bacteria, viruses, and fungi, and knew nothing of the effect that this metal had on these unknown micro-organisms [1].

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Persian Kings drank boiled water from silver flagons to prevent sickness, and they knew that it could be stored in them for years. This property was useful to keep fresh drinking water during military conflicts [2].

Aristotle suggested to Alexander the Great (335 BC) the transport of fresh water in silver containers during many campaigns, and the Macedonians used silver plates to prevent infections in wounds [3].

Hippocrates (460–370 BC), the father of medicine, prescribed the use of silver preparations for the treatment of ulcers and to promote wound healing, but the Romans reported the first silver salt $AgNO_3$ for therapeutic uses in 69 B.C. [1].

Several centuries later, Carl S. F. Crede, a German obstetrician, introduced in 1884 the application of $AgNO_3$ solution diluted to 1% in the eyes of newborn children to prevent gonorrheal infection [4].

In the twentieth century, William S. Halstead introduced the use of silver foil wound dressings, a use that continued until just after World War II, when antibiotics (e.g. the discovery and use of penicillin in the 1940s and other antibiotics) largely replaced silver in bacterial infection treatment [5]. However, with intensive use of antibiotics, many bacteria develop resistance to them. This led to resurgence in the use of silver as antibacterial agents because all pathogenic organisms failed to develop immunity to this metal. Thus, Ag began to be used as a wide spectrum antiseptic in several applications [6]. In the 1960s, as a diluted $AgNO_3$ solution and later, Ag(I) ions were combined with sulfadiazine in 1968 to produce silver sulfadiazine (SSD), the first silver complex, a cream with a broader bactericidal spectrum, that even today continues to be prescribed for the management of burns [7].

SSD is a water insoluble complex and obtained from direct reaction between $AgNO_3$ and sulfadiazine. The structure was determined for the first time by crystallography in 1975 [8(a)], where a silver ion is coordinated to three sulphadiazine molecules with a distorted tetrahedral configuration of three nitrogen atoms (Ag–N: 2.24, 2.24, and 2.44 Å) and one oxygen atom (Ag–O 2.52 Å). The molecules are also linked by sheets of NH···OS hydrogen bonds as in related sulfonamide structures (see figure 1). Additionally, a second report [8(b)] showed for the same molecule a trigonal bipyramidal distorted structure around the silver. In this case, each silver is coordinated to one oxygen atom (2.571 Å) of a sulfonyl

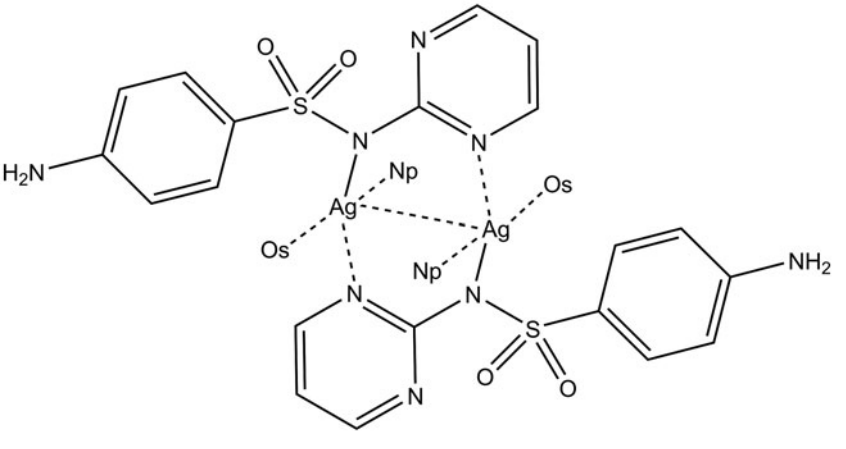

Figure 1. Scheme of silver [(4-aminophenyl)sulfonyl](pyrimidin-2-yl)azanide or SSD. OS: Oxygen from sulfonyl group. Np: Nitrogen from pyrimidine ring.

group of the sulfadiazine molecule in the chain. The nitrogen atoms of the pyrimidine ring coordinate (2.459 and 2.205 Å) to two different silver atoms to form polymeric chains. Each silver ion in this chain is also coordinated to one oxygen atom (2.571 Å) of a sulfonyl group of the sulfadiazine molecule. A second identical chain is joined by coordination of the silver from each chain to the imido nitrogen (2.277 Å) from the sulfadiazine molecule. In addition, in the fifth coordinate position about Ag, a close Ag–Ag bond with a distance of 2.916 Å was reported in both of the structures.

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2. Silver complexes as antimicrobial agents

During recent decades, silver complexes have been extensively studied for their excellent antibacterial properties, which have proven to be even more effective than silver salts. This metal is active at low concentrations and has a low toxicity [9]. Additionally, silver(I) compounds have displayed anticarcinogenic and antiviral activity [10].

In the last decade, there is a revival of silver in medicine, principally in the addition of silver to medical instruments and in wound dressings (especially burns and chronic wounds) to avoid infections and also for the increase of antibiotic-resistant bacteria [11]. Further, a greater variety of silver-based dressings are commercially available (Acticoat, Actisorb, etc.), which offer wider therapeutic options and infection management. These include the stimulation of healing in wounds, prophylactic use for patients at risk of contracting a wound infection, and the management of critically colonized wounds [5, 12].

The exact mechanism (antibacterial properties and cytotoxic effects) by which silver ions perform such functions is not known (and scarcely described), but is accepted that there are several possibilities of mechanism for silver ions [9, 13–19]:

(i) Generation of reactive oxidative species.
(ii) Binding of the silver with cell's DNA, preventing DNA from unwinding, which is an essential step for cellular replication.
(iii) Reaction with bacterial cell membranes by the attachment of silver ions to surface radicals.
(iv) Interaction with the thiol group in vital enzymes (this may disturb many biological processes due to the affinity of the silver cation with sulfur, nitrogen, and oxygen) to inactivate them.

Despite numerous investigations related to the topic, the underlying mechanisms and biological activities are not well understood [7–19]. Nonetheless, it is known that the type of atom coordinated to Ag(I) and the properties of the resulting bond are both crucial factors for the effectiveness of silver complexes [11, 18].

3. Antibacterial experiments

Minimum inhibitory concentration (MICs) experiments have shown broader antimicrobial activity spectra for silver complexes with Ag–O and Ag–N bonds than for Ag–P and Ag–S bonds [15, 18]. These investigations on silver complexes to date have attributed their

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enhanced antimicrobial properties to distinctive weak Ag–O and Ag–N bonds in their structure. Moreover, several authors have suggested that the antibacterial properties of silver complexes are more associated with the Ag–ligand bond than with solubility, chirality, or the degree of polymerization of these complexes [15, 16, 20–24].

Generally, Ag–S complexes have been shown to have a narrower spectrum of antibacterial activity than Ag–N complexes but no antifungal activity [25]. On the other hand, silver compounds with Ag–P bonds have shown no antimicrobial activity against bacteria, yeast, or molds [15, 26].

It has been speculated that weak Ag–O [13(b)] and Ag–N [15] bond strengths might play an important role in exhibiting wider spectrum of antimicrobial and antifungal activities, and that the potential target sites for inhibition of bacterial and yeast growth by silver complexes might be the sulfur containing residues of enzymes and proteins [27]. The antimicrobial action of the silver(I)–oxygen compounds could be related with the binding properties of weak Ag–O bonds. The Ag–O bonding complexes can readily undergo ligand replacement with O-, N-, or S-(thiols) donors of biological ligands.

The antimicrobial activities are due to the silver(I) ion itself, i.e. due to a direct interaction between the silver(I) and biological ligands such as DNA, proteins, enzymes, and membranes. The ligands used in the silver(I) complexes play the role of carrier for the silver(I) ion to the biological system [25] and the magnitude of antimicrobial properties of silver complexes could be related to the ease with which they participate in ligand exchange reactions [16, 20].

Although there is consensus that the structure–activity relationship is important in the display of antimicrobial properties, investigations thus far have not been able to provide a general conclusion since the antibacterial activity of the complexes studied depends on the type of bacteria tested [1, 19, 20, 22–24]. Abu-Youssef *et al*. showed this behavior by testing seven different compounds in the presence of a wide variety of pathogenic bacteria (see figure 2) [24, 28]. However MIC values for *Escherichia coli* bacteria show a correlation to the silver ion concentration in several studies which have established a great sensitivity of the bacteria (see figure 3), but in most cases the antibacterial activity depends on the bacteria–compound pair (see figure 2). In addition, the effectiveness of the silver complexes is the same toward Gram-positive and Gram-negative bacteria; therefore, the antimicrobial effect exerted could not only involve cell wall disruption as a mechanism of action [9(g) and (k), 10, 15, 22, 25, 28].

For a best understanding, figure 3 shows the antibacterial activity of 20 different structures of silver(I) complexes in the presence of 4 kinds of bacteria: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacilus subtilis*, and *E. coli*. It is evident that *E. coli* has the lowest value of MIC (μg/mL) in all the cases, demonstrating the sensitivity of this Gram-negative strain to the presence of silver compounds [9(d) and (g), 10, 14(a), 15, 22, 25, 28, 29].

4. Bonding effect

Spectroscopic studies on the carboxylic group structure have allowed further understanding on the metal–oxygen association and their flexibility on the coordination modes. Carboxylate coordination to Ag(I) from a weak ligand field of this d^{10} ion and from the mismatch in acid–base properties between the soft Lewis acid (Ag^{+}) and the hard Lewis base (oxygen atoms) illustrates the flexibility of the coordination [30].

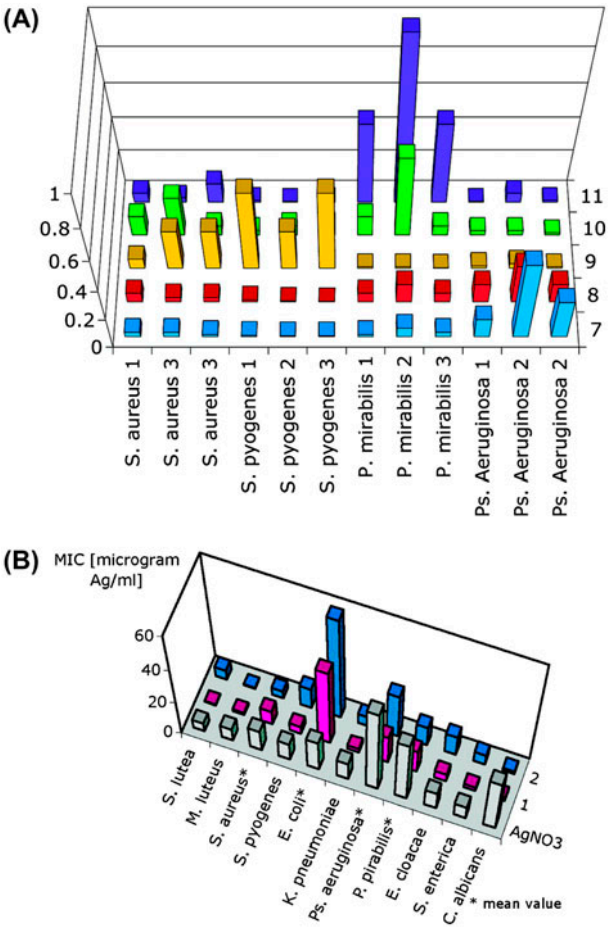

Figure 2. From M.A.M. Abu-Youssef *et al.* Col [24, 28]. Reprinted(adapted) with permission from (**A**) M.A.M. Abu-Youssef, R. Dey, Y. Gohar, A.A. Massoud, L. Öhrström, V. Lange. *Inorg. Chem.*, **46**, 5893 (2007) and (**B**) M.A.M. Abu-Youssef, S.M. Soliman, V. Langer, Y.M. Gohar, A.A. Hasanen, M.A. Makhyoun, A.H. Zaky, L.R. Ohrstrom. *Inorg. Chem.*, **49**, 9788 (2010). Copyright (2007, 2010) American Chemical Society.

Analysis of the differences between the wavenumber of asymmetric and symmetric stretches and the wavenumber of symmetric in-plane deformations of COO– anions have been shown to reflect the metal–oxygen character of the bond [30–33]. Consequently, this technique has been proposed as a tool for the determination of biological properties in these compounds [34–36].

In a first approximation and using infrared data of carboxylates, Sawyer and McKinnie [37] reported in several studies that complexes formed between metallic ions and EDTA reveal different types of bonding. They proposed that IR data on the frequency differences for COO– absorptions supported the conclusion that bonding could be primarily ionic for some complexes and primarily covalent for others. This fact is very useful in discriminating between the ligands and the metal complexes [37–40], because symmetric and asymmetric vibrations change the intensity and the position.

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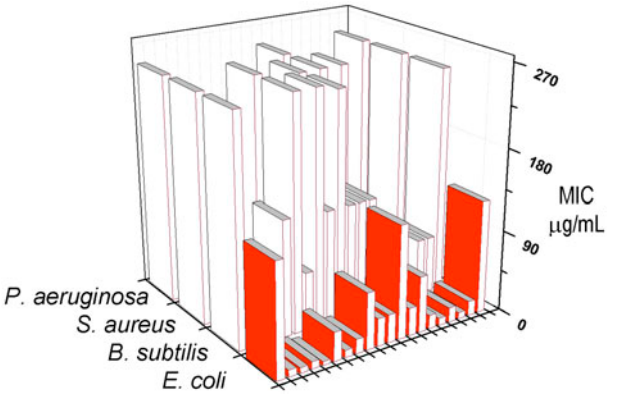

Figure 3. Antibacterial activity of 20 different silver(I) complexes against *P. aeruginosa*, *S. aureus*, *B. subtilis*, and *E. coli*.

Deacon and Phillips [30] have examined FTIR spectra of many metal–carboxylate complexes with known X-ray crystal structures and drawn useful conclusions for the correlations between carboxylate stretching frequencies and their geometries.

The carboxylate ion usually coordinates to metal ions in three main ways [30, 41] as illustrated by figure 4. The values of $\Delta\nu = \nu\text{asym(COO)}–\nu\text{sym(COO)}$ with a high probability in monodentate [42] complexes (figure 5) are expected to be much larger than 200 cm^{-1} or much greater than the ionic complexes [30]. In most cases, complexes with $\Delta\nu < 200$ have chelating and/or bridging (see figures 6 and 7) carboxylate groups [30, 43]. This cannot form the basis of a correlation direct, since there are a number of exceptions that break this rule; therefore, it is necessary to have rigorous crystallographic analysis [31, 43]. Using infrared spectra of carboxylic groups, it is possible to determine monodentate or chelating and/or bridging bonds in metal complexes and also the nature of the Ag–ligand bond (from ionic to primarily covalent) [37].

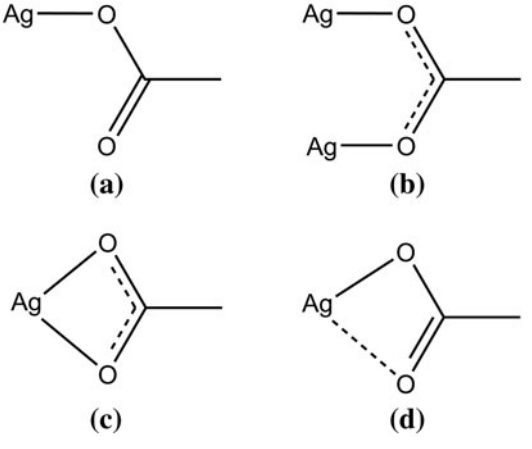

Figure 4. A carboxylate ion, RCO_2^-, can coordinate as a monodentate ligand (a), bridging bidentate ligand (b), bidentate symmetric: isobidentate (c), or as a bidentate unsymmetric: anisobidentate (d).

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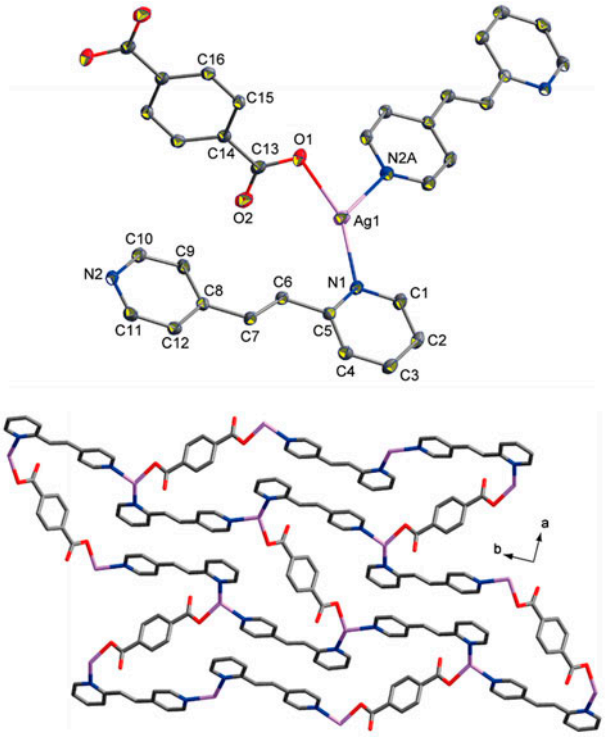

Figure 5. Structure with monodentate carboxylate: $[Ag(tp)_{1/2}(bpe)]_n$. From Cheng-Peng Li *et al.* [42]. Reprinted (adapted) with permission from C.-P. Li, J. Chen, Q. Yu, M. Du. *Cryst. Growth Des.*, **10**, 1623 (2010). Copyright (2010) American Chemical Society.

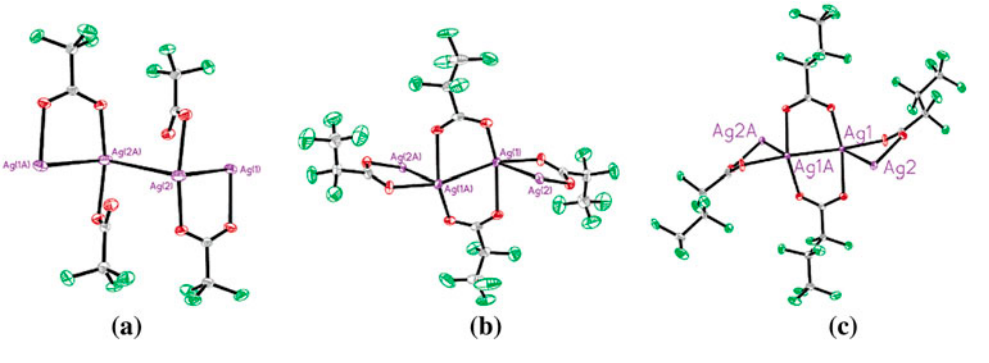

Figure 6. Carboxylate-bridging bidentate ligands. (a) $[Ag_2L^4{}_{0.5}(CF_3CO_2)_2]\infty$, (b) $[Ag_2L^4(CF_3CF_2CO_2)_2]\infty$, (c) $[Ag_2L^4(CF_3CF_2CF_2CO_2)_2]\infty$. From Mohamed Osman Awaleh *et al.* (Ref. [43]). Reprinted (adapted) with permission from M.O. Awaleh, A. Badia, F. Brisse. *Inorg. Chem.*, **45**, 1560 (2006). Copyright (2006) American Chemical Society.

These frequency differences have been used in previous studies [37, 38] as a criterion for the degree of covalent character. In an arbitrary designation, primary covalent bonds were determined according to whether the differences were higher or lower than 225 cm^{-1}. For a

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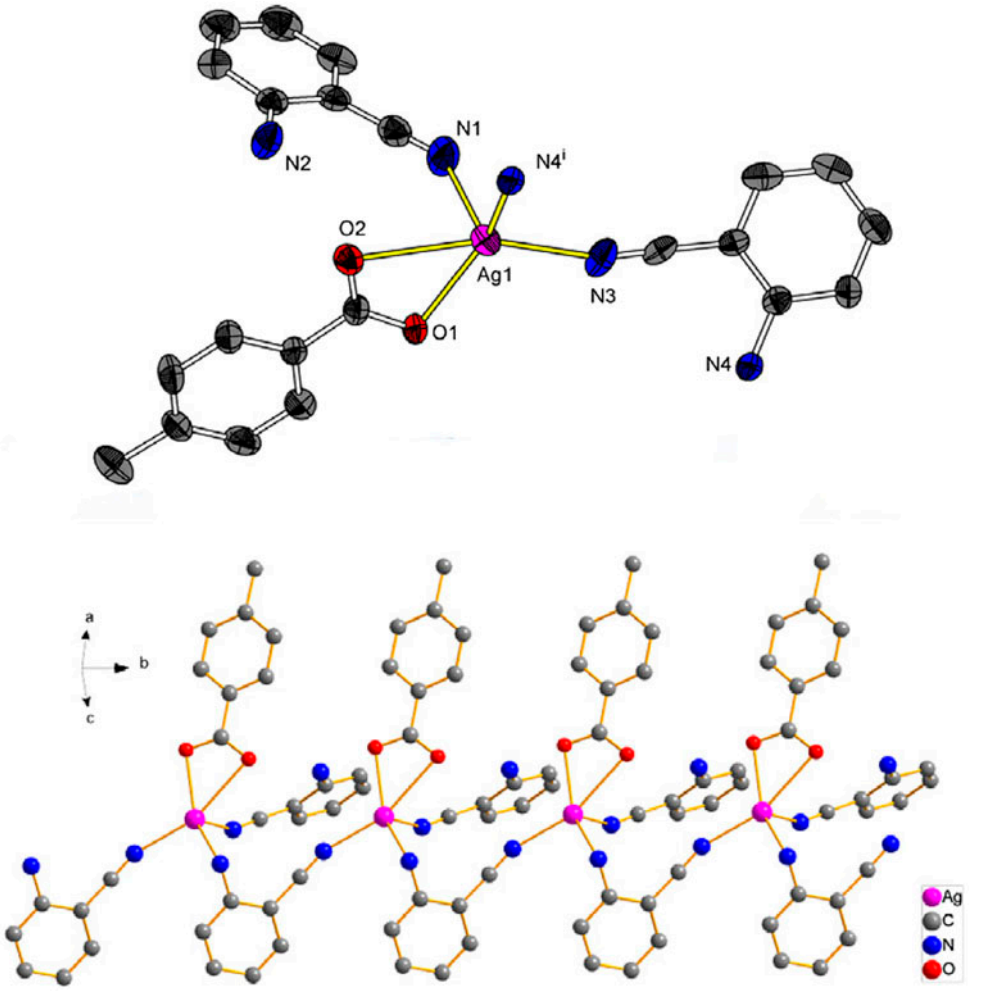

Figure 7. Carboxylate-bridging bidentate ligands: $[Ag(abn)_2(4\text{-mba})]_n$. From Di Sun *et al.* (Ref. [44]). Reprinted (adapted) with permission from D. Sun, F.-J. Liu, H.-J. Hao, Y.-H. Li, R.-B. Huang, L.-S. Zheng. *Inorg. Chim. Acta*, **387**, 271 (2012). Copyright (2012) Elsevier.

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difference of less than 225 cm^{-1}, the bond is primarily ionic. In the same way, some early reports related to silver sulfanilamides and analogous molecules suggested that the nature of the counter ion of silver is decisive for the development of biological activity. The "pKa" of the sulfanilamides and the "Log K" values of silver sulfanilamides were determined, and the antibacterial effectiveness and the risk of sensitization reactions were made on the basis of the conditional stability constants at pH 7.4. When both characteristics are combined, it can be expected that higher values have a reduced antibacterial effect and induce more sensitization reactions [7(c)]. Thus, the ligand and the nature of their interaction with silver ions could play an important role in metal release in the biological environment.

Koczón *et al.* also suggested a relationship between pyridine carboxylate structures and their antimicrobial activities. Their investigations demonstrated that although the ionic

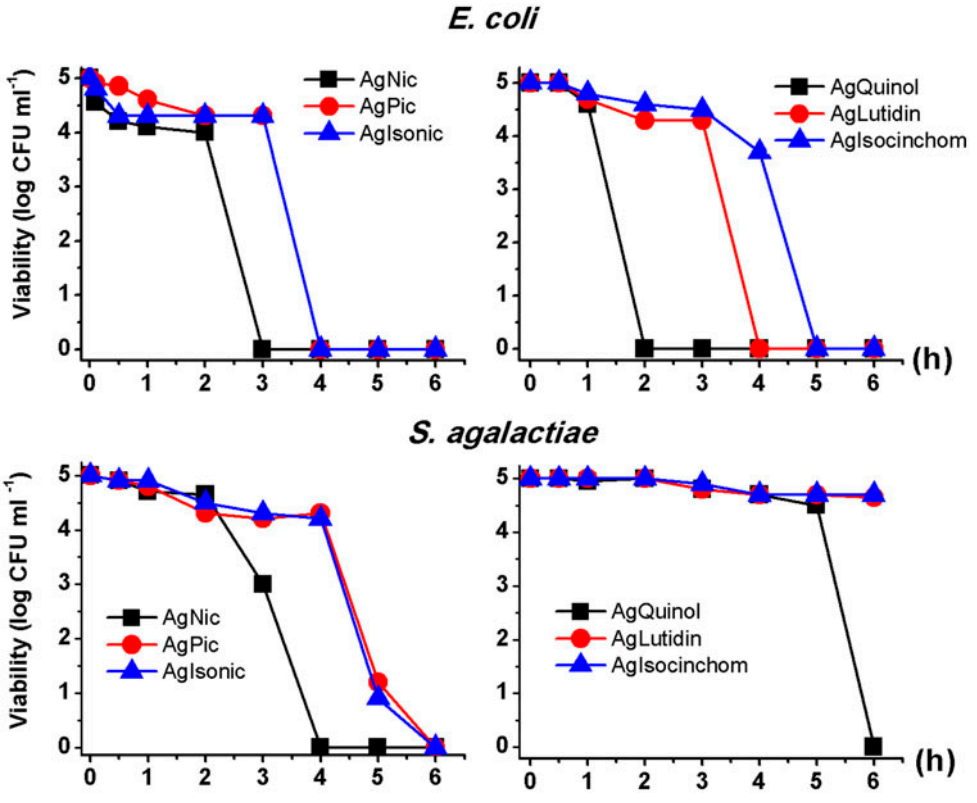

Figure 8. Bactericidal activity (cell viability curves): AgNic: silver(I) nicotinate, AgPic: silver(I) picolinate, AgIsonic: silver(I) isonicotinate, AgQuinol: pyridine-2,3-dicarboxylatosilver(I), AgLutidin: pyridine-2,4-dicarboxylatosilver(I), Ag-Isocinchom: pyridine-2,5-dicarboxylatosilver(I). From Abarca *et al.* [34]. Reprinted (adapted) with permission from R. Abarca, G. Gomez, C. Velasquez, M.A. Paez, M. Gulppi, A. Arrieta, M.I. Azocar. *Chin. J. Chem.*, **30**, 1631 (2012). Copyright (2012) Wiley.

character of the interaction is necessary for the display of antimicrobial activity, the degree of interaction is more important since this determines the effectiveness of the complexes [38].

Abarca *et al.* reported no correlation between the structure of a series of Ag(I) complexes and their antibacterial activity in MICs experiments; however, the efficiency in time of the compounds (see figure 8) showed a tendency directly related to the nature of Ag–O bond [34]. The most ionic silver complexes, AgNic and AgQuinol, show a remarkably rapid response to reach 0% viability in the presence of *E. coli* as a model of Gram-negative strains and *S. agalactiae* as a Gram-positive strain model.

Following the criteria of Murtha *et al.* and using infrared techniques, AgNic and AgQuinol have a more ionic bond than AgPic, AgIsonic, AgLutidin, and Ag-Isocinchom which have a more covalent bond [45]. These results are in concordance with X-ray characterizations of AgQuinol and AgNic; Ag–O bond has been reported to display in a range of distances, 2.705–2.83 Å, which are significantly larger than those found in other chelates, 2.62–2.36 Å [46, 47]. These distances could also be the key to understand the antibacterial efficiency of the silver complexes because this trend in cell viability curves could be directly related to the early work of Fox and Modak. They suggested that the efficiency of

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SSD *in vivo* is the result of the sustained and slow release of silver ions into the wound environs [7].

Figure 9 shows a compilation of 290 bond distances of Ag–OOC and Ag–N in order to understand the versatility of the Ag–OOC in these types of compounds [23, 48–58].

Ag–N shows a low dispersion with a mean of 2.25 Å and a considerable number of bonds with values between 2.20 and 2.35 Å. On the other hand, Ag–OOC bonds show a wider range of length, from 2.10 Å in several cases to 2.83 Å, with a mean of 2.35 Å. These data could indicate variable Ag–O interaction in comparison to the Ag–N bond; consequently, it is reasonable to assume that exchange between the Ag–O and Ag–X states, where X represents a biological ligand (such as nucleic acids, proteins, and cell membranes) are associated with the ease of displacement, considering the weak Ag–O bond nature, or in other words, the stronger ionic character of the interaction.

On the contrary, a narrowed spectrum of antimicrobial activity of the complexes could suggest that they are highly stable, due to which the ligands could not be displaced easily by biological ligands. Thus, an important factor determining the antimicrobial activity may be the nature of atom coordinated to the silver(I) atom and its bonding properties, (i.e. the ease of ligand replacement), rather than the solid state structure, solubility, charge, and degree of polymerization of the complexes, etc. [16, 18].

In the same way, one of the last studies related to the cytotoxic effects of silver carboxylate compounds showed for the first time a structure–activity relationship and was attributed to the geometry of the compounds [59]; however, this result could be related to the nature of the metal–ligand bond [7]. Unfortunately, this fact was not analyzed in detail.

5. Stability of silver complexes

The light insensitivity (and resistance toward intense UV radiation) and also their thermal stability properties of silver(I) complexes are very important for potential applications in medical devices, such as additives to curable photopolymers in dental implants [60, 61].

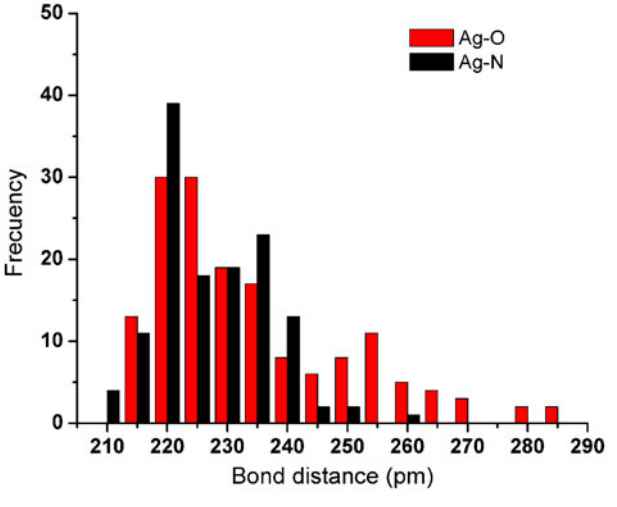

Figure 9. Statistical analysis of bond distances Ag–OOC and Ag–N.

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Figure 10. Reduction of synthesized silver(I) compounds in presence of high-energy UV radiation at 258 nm and 30 watts. Five water soluble silver(I) complex with Ibuprofen (AgIbu), Naproxen (AgNap), Mefenamic acid (AgMef), acetyl salicylic acid (AgAsp), and salicylic acid (AgSal). From Azocar *et al.* [61].

The stability of a set of Ag(I) compounds to short wavelength UV radiation is shown in figure 10. AgMef and AgAsp show great stability for a prolonged period of time in comparison with the control, AgCl, which is completely darkened after 10 min. AgIbu, AgSal, and AgNap show a gradual color change from white/pale-yellow to orange/brown in less than 1 h. As reported recently by Gerasimchuk, the product of the photodegradation of silver complexes generates metallic silver as a colloid of nanosized particles [61(b)].

In summary, the differences and the origin of the resistance toward visible and UV light, and their stability when exposed to light, air, and temperature (in solution or solid state) could be related to the significant covalent character of Ag–O and Ag–N bond energies [30, 31, 34, 60, 61] of the ligand and polymeric structure in every compound [61, 62].

6. Conclusion

From SSD to date, silver complexes have demonstrated high antibacterial activity in presence of Ag–N and Ag–O bonds. The activity is apparently influenced by the weak silver–O/N bond which easily replaced with biological ligands, and even the light stability could relate to the nature of these Ag–O/Ag–N bond energies. The bibliographic analysis of the last decades suggests that one of the key factors determining the antimicrobial effects of

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silver complexes is the nature of the atom coordinated to Ag(I) and its bonding properties rather than the solubility, charge, chirality, or degree of polymerization of the silver(I) complexes.

Finally, a combination of five properties including (1) thermal stability, (2) air-light insensitivity, (3) water solubility (4) antimicrobial activity, and (5) low cytotoxicity is important for their potential applications in medical devices, prevention of biofilm formation, and as broad-spectrum antibiotic ointment. All these properties could be directly related to the Ag–ligand bond and their differences directly associated with the structure of each compound, and therefore could be modulated in the future.

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