Synthesis, X-ray structure and antimycobacterial activity of silver complexes with α-hydroxycarboxylic acids

ARTICLE *in* JOURNAL OF INORGANIC BIOCHEMISTRY · MARCH 2007

Impact Factor: 3.44 · DOI: 10.1016/j.jinorgbio.2006.10.001 · Source: PubMed

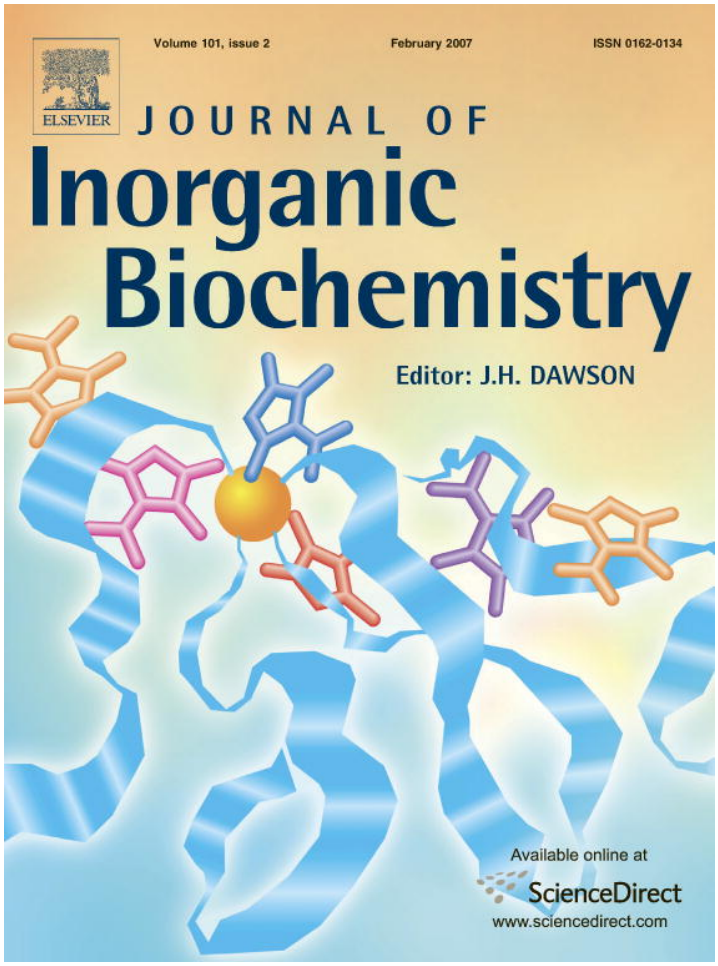
8 AUTHORS, INCLUDING:

Alexandre Cuin
Federal University of Juiz de Fora
28 PUBLICATIONS **173** CITATIONS
SEE PROFILE

Daisy Nakamura Sato
57 PUBLICATIONS **841** CITATIONS
SEE PROFILE

Ademir Neves
Federal University of Santa Catarina
198 PUBLICATIONS **3,574** CITATIONS
SEE PROFILE

Bruno Szpoganicz
Federal University of Santa Catarina
94 PUBLICATIONS **2,051** CITATIONS
SEE PROFILE



Available online at www.sciencedirect.com
ScienceDirect
Journal of Inorganic Biochemistry 101 (2007) 291–296
Journal of Inorganic Biochemistry
www.elsevier.com/locate/jinorgbio

Synthesis, X-ray structure and antimycobacterial activity of silver complexes with α-hydroxycarboxylic acids

Alexandre Cuin [d,*], Antonio C. Massabni [a], Clarice Q.F. Leite [b], Daisy N. Sato [c], Ademir Neves [d], Bruno Szpoganicz [d], Marlon S. Silva [d], Adaílton J. Bortoluzzi [d]

[a] *Departamento de Química Geral e Inorgânica, Instituto de Química, UNESP, CEP 14801-970 Araraquara, SP, Brazil*
[b] *Departamento Ciências Biológicas, Faculdade de Ciências Farmacêuticas, UNESP, CEP 14800-900 Araraquara, SP, Brazil*
[c] *Instituto Adolfo Lutz, Laboratório de Ribeirão Preto, CEP 14085-410 Ribeirão Preto, SP, Brazil*
[d] *Laboratório de Bioinorgânica e Cristalografia, Departamento de Química, UFSC, CEP 88040-900 Florianópolis, SC, Brazil*

Received 8 June 2006; received in revised form 3 October 2006; accepted 6 October 2006
Available online 20 October 2006

Abstract

In this paper, synthesis, characterization and antimycobacterial properties of a new water-soluble complex identified as silver-mandelate are described. Elemental and thermal analyses are consistent with the formula $[Ag(C_6H_5C(OH)COO)]_n$. The polymeric structure was determined by single X-ray diffraction and the two-dimensional structure is based on the bis(carboxylate-*O*,*O*′) dimer [Ag–O, 2.237(3), 2.222(3) Å]. The structure is extended along both the *b* and *c* axes through two oxygen atoms of a bidentate α-hydroxyl-carboxylate residue [Ag–OH(hydroxyl), 2.477(3) Å; Ag–O(carboxylate), 2.502(3) Å; O–Ag–O, 63.94(9)°]. A strong d^{10}–d^{10} interaction was observed between two silver atoms. The Ag···Ag distance is 2.8307(15) Å. The NMR ^{13}C spectrum in D_2O shows that coordination of the ligand to Ag(I) occurs through the carboxylate group in solution. Potentiometric titration shows that only species with a molar metal:ligand ratio of 2:2 are formed in aqueous solution. The mandelate complex and the silver-glycolate, silver-malate and silver-hydrogen-tartarate complexes were tested against three types of *mycobacteria*, *Mycobacterium avium*, *Mycobacterium tuberculosis* and *Mycobacterium kansasii*, and their minimal inhibitory concentration (MIC) values were determined. The results show that the four complexes are potential candidates for antiseptic or disinfectant drugs for discharged secretions of patients affected with tuberculosis.

Keywords: Silver; Mycobacteria; α-Hydroxycarboxylic acids; O-donor ligands

1. Introduction

Tuberculosis (TB) remains as a public health issue at the beginning of the 21st century. TB causes nearly 3 million deaths annually worldwide. The estimated 8.8 million of new cases every year corresponds to 52,000 deaths per week or more than 7000 deaths each day. In developing countries TB is a leading cause of morbidity and mortality [1]. Co-infection with human immunodeficiency virus (HIV) has been responsible for changes in the TB epidemiologic situation and also for the emergence of multidrug-resistant strains [2]. Because of this critical situation, an intense effort has been directed to develop new drugs for TB therapy. Metal complexes have been used for treatment of several diseases [3]. Silver complexes, for example, are antibacterial agents and have been used for a long time as therapeutic compounds [4,5]. Many silver complexes are sparingly soluble in common solvents, especially water, which limits their uses in ointments and creams, as is the case of the most used topical antibacterial agent silver-sulfadiazine (SSD) [6]. The mechanisms of antibacterial action of the silver complexes have been scarcely described, although there are three possibilities: (i) interference with electron transport; (ii) inhibition of bacterial deoxyribonucleic acid (DNA) replication caused by the silver ion

* Corresponding author. Tel.: +55 16 3301 6630; fax: +55 16 3322 7932.
E-mail address: alexandre_cuin@yahoo.com (A. Cuin).

0162-0134/$ - see front matter © 2006 Published by Elsevier Inc.
doi:10.1016/j.jinorgbio.2006.10.001

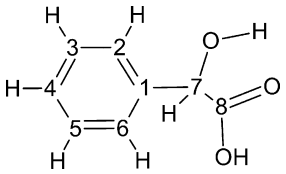


Fig. 1. Representation of mandelic acid. The carbon atoms were replaced by numbers from 1 to 8.

moiety, and (iii) modification of the bacterial cell membrane [7,8].

The silver complexes with similar ligands have been described as more effective as therapeutic agents than the silver salts [9] and silver complexes of N- and/or O-donor ligands have a special biological interest [10,11]. Few water-soluble silver complexes were obtained with amino-acids, a class of N- and O-donor ligands, which show a wide spectrum of effective antimicrobial activities against bacteria, yeasts and molds [8]. O-donor ligands, like the α-hydroxycarboxylic acids (mandelic, glycolic, malic, and tartaric) also form complexes with Ag(I). The crystalline structures of the glycolate, malate and tartarate silver-complexes have been described in the literature [12–14]. The silver-mandelate (AgMand) complex is new.

Mandelic acid ($C_8H_8O_3$, Fig. 1) – an O-donor ligand – can be found in almonds and inhibits bacterial growth in the urinary tract [15]. It has been reported that this hydroxycarboxylic acid has been used as an antitumoral compound [16].

The complex AgMand and other three complexes, silver-glycolate – AgGlyc [12], silver-malate – Ag_2Mal [13], and silver-hydrogen-tartarate – AgHTart [14], are water-soluble and showed to be effective against *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium kansasii*.

2. Experimental

2.1. Materials and methods

DL-Mandelic and glycolic acids (both 99.5%, purity) were purchased from Riedel-deHaën and Merck, respectively, while tartaric and malic acids (both 99% purity) were purchased from Synth. Silver nitrate and sodium hydroxide of analytical purity were purchased from Acros Organics and Vetec Laboratories, respectively. Isoniazid, a standard antitubercular drug, was purchased from Sigma. Elemental analyses for CHNS-O were performed using an EA1110 analyzer (CE Instruments). IR spectra were recorded on a FT-IR Spectrophotometer Spectrum 2000 (Perkin–Elmer) with samples as KBr pellets. NMR ^{13}C spectra were recorded on a Varian 500 MHz equipment; samples were analyzed in D_2O solutions. NMR ^{13}C spectra of the solid samples were recorded on a Varian 300 MHz equipment using the CP-MAS (cross-polarization magic angle spinning) techniques. Simultaneous thermal analysis (STA) was performed on a STA-409 equipment (Netzsch) under the following conditions: synthetic air, and heating rate of 10 °C/min, from 40 to 500 °C. Potentiometric measurements were carried out with a Corning pH/ion analyzer, model 350, fitted with blue-glass and Ag/AgCl reference electrodes were calibrated to read $-\log[H^+]$ or pH, directly. Bidistilled water and $KMnO_4$ were used to prepare the aqueous solutions. The electrode was calibrated using the data obtained from a potentiometric titration of a known volume of a standard 0.0100 M HCl aqueous solution with a standard 0.100 M KOH aqueous solution. Measurements were carried out using a thermostated cell containing the complex in aqueous solution (1.0 M in water and 1.00 mL of HNO_3, 0.100 M). An aqueous solution of KNO_3 of concentration 0.100 M was used as the ionic strength buffer at 25.00 ± 0.05 °C. The experiments were performed under an argon flow to eliminate CO_2. The samples were titrated by addition of a fixed volume (0.100 mL) of a standard CO_2-free KOH aqueous solution (0.100 M). Calculations of the stability constants were carried out by employment of the BEST7 least squares computer program and the SPECIATION (L.D.Pettit, Academic Software) program was used to build a species distribution curve [17].

2.2. Synthesis of the silver complexes

AgMand, AgGlyc and AgHTart: the sodium salt aqueous solution of the α-hydroxycarboxylic acid was prepared by adding 30.0 mmol of sodium hydroxide to an aqueous solution containing 30.0 mmol of mandelic, glycolic or tartaric acid (molar ratio of 1:1). The complex was obtained by adding slowly 30.0 mmol of a freshly prepared aqueous solution of $AgNO_3$ to the sodium α-hydroxycarboxylate aqueous solution. This reaction was carried out at room temperature with strong stirring. The complexes precipitated as white solids, after 10 min of stirring. The white powders were filtered, washed with cold ethanol, and dried in a desiccator under silica. The AgMand solution was left at room temperature and after one week crystals suitable for X-ray analysis were formed. Anal. Calc. for AgMand – $[Ag(C_8H_7O_3)]$ (%): C, 37.1, H, 2.73 and Ag, 41.7. Found: C, 37.1, H, 2.67 and Ag, 41.8 (thermogravimetric analysis). Anal. Calc. for AgGlyc – $[Ag(C_2H_2O_3)\cdot\frac{1}{2}H_2O]$ (%): C, 13.1 and H, 1.65. Found: C, 12.8 and H, 1.51. Anal. Calc. for AgHTart – $[Ag(HC_4H_4O_6)]$ (%): C, 18.7 and H, 1.96. Found: C, 18.7 and H, 1.91.

The same procedure was followed to obtain Ag_2Mal, although a molar ratio of 2:1:2 was used instead of 1:1:1 (hydroxide:acid:silver). Anal. Calc. for Ag_2Mal – $[Ag_2(C_4H_4O_5)]$ (%): C, 13.8 and H, 1.16. Found: C, 13.8 and H, 1.14. Yields were about 90%.

2.3. X-ray measurements

The crystal data were obtained on an Enraf-Nonius CAD4 diffractometer, using a graphite monochromated

Mo Kα radiation ($\lambda = 0.71069$ Å), at room temperature. A colorless crystal with dimensions $0.50 \times 0.36 \times 0.07$ mm was selected for the crystallographic analysis. Unit-cell parameters were determined from 25 carefully centered reflections in the θ range 8.67–17.34° and refined by the least-squares method. Intensities were collected using the ω–2θ scan technique. All diffracted intensities were corrected for Lorentz and polarization effects [18]; ψ-scan absorption correction was applied to 1623 collected reflections [19]. The structure was solved by direct methods and was refined by the full-matrix least-squares method using SHELXS97 [20] and SHELXL97 [21] computer programs. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atom of the alcohol moiety was found from a Fourier map and it was treated with a riding model. Other hydrogen atoms were added at their calculated positions and included in the structure factor calculations, with C–H distances and U_{eq} taken from the default of the refinement program. Hydrogen atoms were placed in idealized positions using standard geometric criteria. The ORTEP3 [22] program was used to generate a picture of the molecular structure.

3. Results and discussion for silver-mandelate

3.1. Single X-rays

The crystallographic parameters for the AgMand complex are summarized in Table 1, while selected bond distances and bond angles are given in Table 2. The AgMand complex formulated as $[Ag(C_8H_7O_3)]_n$ is closely related to the AgGlyc complex [12]. The unsymmetrical unity of AgMand is shown in Fig. 2 and its two-dimensional structure can be described as a centrosymmetric dimer with an inversion center between two Ag(I) atoms (see Fig. 3). The polymeric structure of AgMand is type III, based on the classical bis(carboxylate-*O*,*O*′) dimer

Table 1
Crystal data and structure refinement for AgMand

Empirical formula	$C_8H_7AgO_3$
Formula weight	259.01
Temperature (K)	293(2)
Wavelength (Å)	0.71069
Crystal system	Monoclinic
Space group	*P*21/*c*
a (Å)	16.3040(10)
b (Å)	4.750(6)
c (Å)	10.393(6)
β (°)	95.27(2)
Volume (Å^3)	801.5(11)
Z	4
D_{calc} (Mg/m^3)	2.146
Absorption coefficient (mm^{-1})	2.472
F(000)	504
Crystal size (mm)	$0.50 \times 0.36 \times 0.07$
θ Range for collected (°)	8.67–17.34
Reflections collected	1623
Independent reflections [R_{int}]	1569 [0.0123]
Completeness to theta = 25.96° (%)	100.0
Refinement method	Full matrix least-squares on F^2
Data/restraints/parameters	1569/0/110
Goodness-of-fit on F^2	1.176
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0287$, $wR_2 = 0.0800$
R indices (all data)	$R_1 = 0.0344$, $wR_2 = 0.0825$
Largest difference peak and hole (e Å^{-3})	0.749 and 0.950

Table 2
Selected bond lengths (Å) and angles (°) for AgMand

Bond lengths (Å)		Angles (°)	
Ag–O2^{i}	2.222(3)	O2^{i}–Ag–O1	161.79(10)
Ag–O1	2.237(3)	O2^{i}–Ag–O3^{ii}	100.18(12)
Ag–O3^{ii}	2.477(3)	O1–Ag–O3^{ii}	97.11(11)
Ag–O1^{ii}	2.502(3)	O2^{i}–Ag–O1^{ii}	87.83(10)
Ag···Ag^{i}	2.8307(15)	O1–Ag–O1^{ii}	105.00(7)
		O3^{ii}–Ag–O1^{ii}	63.94(9)

Symmetry transformations used to generate equivalent atoms: $^{i}-x+1, -y, -z+1$; $^{ii}-x+1, y+1/2, -z+1/2$.

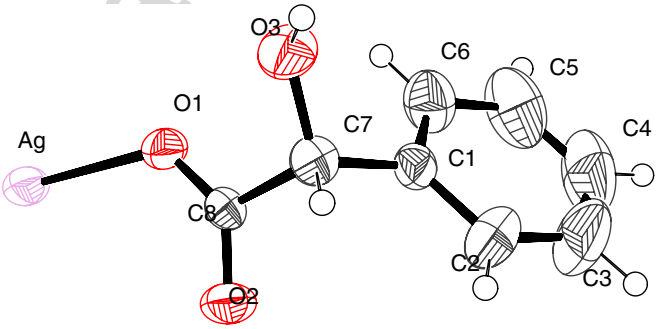


Fig. 2. Asymmetric unit contents determined for AgMand with labeling scheme and ellipsoids at 40% probability level.

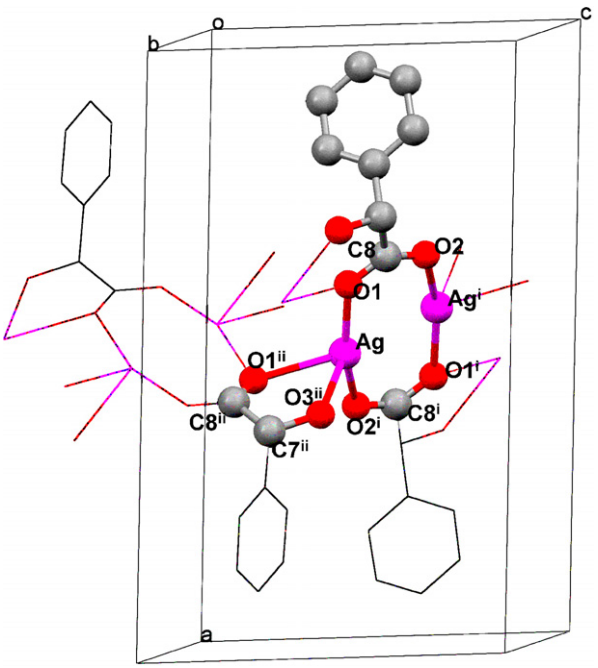


Fig. 3. View of *b* and *c* axes of the bidimensional polymeric structure for AgMand. The hydrogen atoms have been omitted for clearness.

[23]. Oxygen atoms of the carboxylate groups from different mandelate ligands are bonded to two Ag(I) atoms in a *syn–syn* mode [24] with the distances 2.222(3) and 2.2237(3Å) for Ag–O2^{i} and Ag–O1, respectively, arranged as an eight-membered ring or as Ag-bis(*O*,*O*′-carboxylate)-Ag^{i}. Coordination around Ag(I) atoms is completed by axial bonds to two oxygen atoms from the carboxylate and hydroxyl groups of the mandelate resulting in a five-membered ring with a twisted conformation geometry. The bond distances for Ag–O1^{ii} and Ag–O3^{ii} in the five-membered ring are 2.502(3) Å and 2.477(3) Å, respectively. As expected, a two-dimensional polymeric structure along the *010* and *001* vectors is formed through two oxygen atoms of the α-hydroxyl and carboxylate groups. Weak hydrogen bonding interactions were also observed.

The Ag···Ag^{i} distance is 2.8307(15) Å (see Table 2). This distance is shorter than that found for metallic silver (2.89 Å) [25]. This short distance shows a strong d^{10}–d^{10} interaction [26].

3.2. Thermal analysis

Simultaneous thermoanalytical techniques (STA) that combine both thermogravimetric (TGA) and differential thermal analyses (DTA) show the mass loss occurs in one exothermic step that started at 150 °C; at 500 °C the final residue was identified by X-ray powder diffraction as metallic silver [27]. Mass loss required is 58.3% (found 58.2%).

3.3. IR spectroscopy

The IR spectrum of the complex was compared to the respective spectra of the sodium salt and free mandelic acid. As expected, the strong band at ~1700 cm^{-1} assigned to the carbonyl group was not observed in the spectra of the salt or of the complex, since the group involved in coordination to the metal is COO^{-} (carboxylate). The frequencies $\nu_{asym}(COO^{-})$ and $\nu_{sym}(COO^{-})$ changed after complexation and the difference $\Delta\nu$ between $\nu_{asym}(COO^{-})$ and $\nu_{sym}(COO^{-})$ for the complex was 186 cm^{-1} (1583 and 1397 cm^{-1}, respectively). A similar difference was found for sodium mandelate [$\Delta\nu = 196$ cm^{-1}, 1608 and 1412 cm^{-1} for $\nu_{asym}(COO^{-})$ and $\nu_{sym}(COO^{-})$, respectively]. The $\Delta\nu$ values are very close each other since the carboxylate group is coordinated to the Ag(I) ion as a bridge [28,29]. The band assigned to $^{\alpha}$C–OH was found at 1083 cm^{-1} for mandelic acid, 1065 cm^{-1} for sodium mandelate and 1051 cm^{-1} for AgMand. A shift to low frequencies of this band in the spectrum of the complex also confirms that the $^{\alpha}$C–OH group (OH protonated) is coordinated to Ag(I). These results are in agreement with the X-ray data (see Fig. 3).

3.4. Potentiometric measurements

The species distribution curve of pH from 2 to 12 is shown in Fig. 4. The dimer is formed by a common eight-membered ring Ag-bis(carboxylate,*O*,*O*′)-Ag^{i} (see Fig. 4c). The protonation constant ($\log K_n^{H}$) for mandelic acid and the formation constant of the dimer-complex ($\log\beta$) were calculated using the BEST7 least-squares program. The constants were calculated by Eq. (1), where L = mandelate (−1).

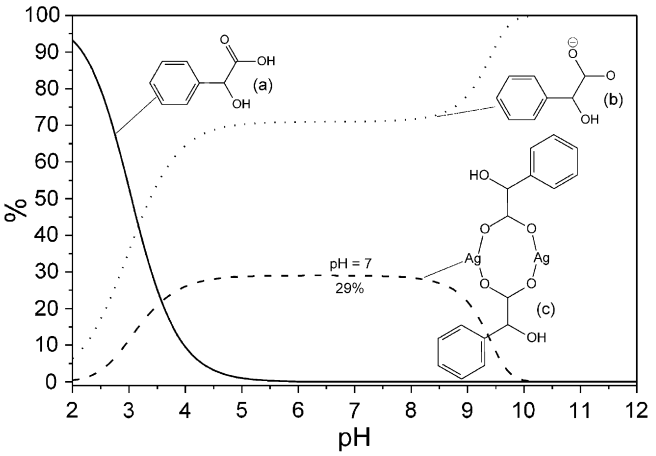


Fig. 4. Species distribution curve of AgMand in aqueous medium in the range of pH from 2 to 12: (a) mandelic acid (dash-dot); (b) sodium mandelate (dash); (c) AgMand (solid), and (d) metal (dot).

$$L^{-1} + H^{+} \leftrightharpoons HL \qquad \log K^{H} = [HL]/[L^{-1}][H^{+}] \tag{1}$$

Values found: $\log K^{H} = 3.17(3)$ and $\log K^{H} = 3.20$ for mandelic acid ([HL]/[L][H]) and $\log\beta = 9.36(5)$ for the dimer-complex AgMand ($[Ag_2L_2]/[L]^2[Ag]^2$) [30].

At pH 2 only about 10% of the Ag(I) ions are in the AgMand dimer form. However, in the range of pH from 4.5 to 8.0, the percentage of the dimer species increases to about 30% (about 60% of Ag(I) ions are present as the complex form). For pH > 8.0 concentration of the dimer species decreases and at pH 10.5 its concentration is lower than 0.5%.

3.5. NMR ^{13}C spectroscopy (solid state and D_2O solution)

NMR ^{13}C spectra of AgMand and mandelic acid were recorded in D_2O solutions and in the solid state. The peaks observed in the NMR ^{13}C spectra of mandelic acid and AgMand are shown in Table 3. The peak of $C_8(COO^{-})$ for AgMand in the solid state was observed, as expected, downfield of the same group of the ligand, at 193 ppm since this group forms three bonds with silver atoms – C8O1–Ag, C8O2–Ag^{i}, and C8^{ii}O1^{ii}–Ag (see Fig. 3). The peak of $C_8(COO^{-})$ for AgMand in solution (D_2O) is located at 181 ppm which is shifted downfield compared to the signal of the same group for free mandelic acid (D_2O) at 176.5 ppm. This result indicates that the carboxylate group is involved in coordination to the Ag(I) ions in aqueous solution. However, this value is lower than that of the same carbon in the solid state, and it is probable that the O1^{ii}–Ag

Table 3
Peaks observed in the NMR ^{13}C spectra of AgMand and mandelic acid

	Complex		Ligand	
	Solid state (ppm)	D_2O solution (ppm)	Solid state (ppm)	D_2O solution (ppm)
C_8	193	181	177	176.5
C_1	140	143	136	138.2
$C_{2,3,4,5}$ and C_6	126 (broad band)	129–31	130–128	129–7
C_7	76	76	73	73

bond is broken when the AgMand complex is dissolved in aqueous solution. The $C7^{ii}$–$O3^{ii}$(–Ag) bond was observed in the X-ray diagram (Table 2) and the peak assigned to C_7(COH) is observed at 76 ppm for AgMand in the solid state while the chemical shift for the same carbon for mandelic acid is observed at 73 ppm. In D_2O solution, $\Delta\delta$ (δcomplex–δmandelic acid) for C_7(COH) is also of 3 ppm (see Table 3). Based on the potentiometric data one can conclude that the α-hydroxyl group is not involved in the coordination around the Ag(I) ions in aqueous solution. The upshift observed is an indication of the interaction between the α-alcohol group with water. Therefore, in solution it is probable that the $O3^{ii}$–Ag bond is also broken.

4. Antimycobacterial activities of the silver complexes

The MIC values of the four silver compounds against *M. avium* (ATCC 27294), *M. tuberculosis* (ATCC 27294) and *M. kansasii* (ATCC 12478) are shown in Table 4. The MIC values were determined using microdilution plates and Alamar Blue as a vital dye, according to the methodology of Franzblau et al. [31]. The bacterial suspension used was prepared by adjusting its turbidity by the McFarland No. 1 scale, and further dilution (1:25 v/v) in the culture medium 7H9. Twofold serial dilutions of the complexes were used to titrate the plates. Concentrations of the silver complexes and isoniazid ranged from 1.00 to 100 μg/mL and 0.50 to 0.015 μg/mL, respectively. Isoniazid is a standard antitubercular drug and it was used to confirm that all strains of mycobacteria were active or not. A control was run without bacterial *inoculum* in the medium to confirm that there is no reaction of the complexes themselves with the Alamar Blue. The maintenance of a blue color in the wells was considered to reflect a lack of bacterial growth and the development of a pink color was interpreted as the contrary. Thus, MIC is considered as the minimum concentration able to inhibit the change of color from blue to pink.

Table 4
MIC values of the silver complexes

Compound	MW	Ag (%)	Mycobacteria species		
			M. avium	*M. tuberculosis*	*M. kansasii*
AgGlyc	181.9	59.3	(5.0) [27]	(10) [55]	(5.0) [27]
Ag_2Mal	347.8	62.0	(5.0) [14]	(10) [29]	(10) [29]
AgHTart	256.9	41.2	(2.0) [8.0]	(8.0) [31]	(4.0) [16]
AgMand	259.0	41.6	(4.0) [15]	(16) [62]	(8.0) [31]
$AgNO_3$	169.9	63.5	(3.1) [18]	(12) [71]	(6.2) [36]

The MIC values in parenthesis are in μg/mL and in square brackets are in μM.

The commercial compound silver(I)-sulfadiazine (SSD) was also tested against *M. tuberculosis* and showed a MIC value of 7.8 μg/mL. AgHTart showed a MIC value of 8.0 μg/mL. The MIC values are similar each other and show that AgHTart is so efficient against *M. tuberculosis* as SSD. The four silver complexes and SSD are less effective against *M. tuberculosis* than isoniazid which showed a MIC value of 0.030 μg/mL and is much more effective than pirazinamide (MIC value of 25 μg/mL) [32]. The four free ligands, two salts and silver nitrate solutions were also tested against *M. avium*, *M. tuberculosis* and *M. kansasii*. As expected, the ligands and their salts (potassium mandalate and sodium malate) do not show activity while the silver nitrate solution showed MIC values of 12 μg/mL, 3.1 μg/mL and 6.2 μg/mL against *M. tuberculosis*, *M. avium* and *M. kansasii*, respectively [33]. The silver complexes were also tested against *M. avium*; AgGlyc and Ag_2Mal showed a MIC value of 5.0 μg/mL while AgMand and AgHTart showed MIC values of 4.0 and 2.0 μg/mL, respectively (see Table 4). MIC values for *M. avium* demonstrate that the silver complexes are more effective than isoniazid (MIC value of 32 μg/mL) [31]. The four silver complexes show MIC values from 62 to 29 μM and from 16 to 31 μM for *M. tuberculosis* and *M. kansasii*, respectively, while silver nitrate shows MIC values of 71 and 36 μM for the two mycobacteria (see Table 4). These MIC values demonstrate that the silver complexes are so effective as silver nitrate for *M. tuberculosis* and *M. kansasii*. Silver nitrate shows MIC value of 18 μM for *M. avium* and it is more effective than AgGlyc for the same bacteria (MIC value of 27 μM). Ag_2Mal, AgHTart and AgMand have MIC values of 14, 8.0 and 15 μM for *M. avium*, respectively. These values demonstrate that these complexes are more effective than silver nitrate against *M. avium*. So, the four silver complexes described here showed a good activity against environmental mycobacteria normally resistant to isoniazid [34]. This drug and pirazinamide have been used extensively for tuberculosis treatment nowadays [35].

5. Conclusions

Silver-complexes of four α-hydroxycarboxylic acids (mandelic, glycolic, tartaric and malic) or of their respective anions were obtained. The polymeric structure of AgMand was determined and it can be described as a dimer with a classical eight-membered ring Ag-bis(carboxylate,*O*,*O*′)-Ag^i, which is extended along *010* and *001* vectors through two oxygen atoms from adjacent hydroxyl and carboxylate groups. The NMR ^{13}C (D_2O) spectra and potentiometric titration data clearly indicate that the solid-state polymeric structure is not maintained in

solution. Only neutral dimer species were found in aqueous solution. The AgHTart complex showed a MIC value of 2.0 μg/mL against *M. avium*. Besides the antimicrobial activity, the silver complexes described here can be easily prepared in high yields, they are water-soluble and the ligands involved are of low cost. So, these complexes could be used as antiseptic or disinfectant agents for places and materials contaminated with environmental mycobacteria or for disinfection of discharged secretions of patients affected with tuberculosis.

6. Abbreviations

AgGlyc	silver-glycolate
AgHTart	silver-hydrogen-tartarate
Ag_2Mal	silver-malate
AgMand	silver-mandelate
SSD	silver-sulfadiazine
TB	tubercolosis
MIC	minimal inhibitory concentration
STA	simultaneous thermal analysis
TGA	thermogravimetric analysis
DTA	differential thermal analysis

Acknowledgments

The authors are grateful to CNPq (Proc. 151528/2004-7), FAPESP (Proc. 01/09797-1) and FINEP for financial support.

Appendix A. Supplementary data

Supplementary crystallographic data are available through Cambridge Crystallographic Data Center, CCDC 606650. Copies of this information may be obtained free of charge from the director, CCDC 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jinorgbio.2006.10.001.

References

[1] World Health Organization Bulletin 70 (1992) 17–21.
[2] A. Rattan, A. Kalia, N. Ahmad, Emerg. Infect. Dis. 4 (1998) 195–209.
[3] C. Orvig, M.J. Abrams, Chem. Rev. 99 (1999) 2201–2203.
[4] H.J. Klasen, Burns 26 (2000) 117–130.
[5] H.J. Klasen, Burns 26 (2000) 131–138.
[6] C.L. Fox, Surg. Gynecol. Obstet. 157 (1983) 82–88.
[7] A.J.L. Gear, T.B. Hellewell, H.R. Wright, P.M. Mazzarese, P.B. Arnold, G.T. Rodeheaver, R.F. Edlich, Burns 23 (1997) 387–391.
[8] K. Nomiya, H. Yokoyama, J. Chem. Soc., Dalton Trans. 12 (2002) 2483–2490.
[9] K.I. Batarseh, J. Antimicrob. Chemother. 54 (2004) 546–548.
[10] K. Nomiya, K. Tsuda, T. Sudoh, M. Oda, J. Inorg. Biochem. 68 (1997) 39–44.
[11] K. Nomiya, K. Tsuda, Y. Tanabe, H. Nagano, J. Inorg. Biochem. 69 (1998) 9–14.
[12] G. Smith, A.N. Reddy, K.A. Byriel, C.H.L. Kennard, Aust. J. Chem. 47 (1994) 1179–1183.
[13] S.M. Cortez, R.G. Raptis, Coord. Chem. Rev. 169 (1998) 363–426.
[14] R.C. Bott, G. Smith, D.S. Sagatys, D.E. Lynch, A.N. Reddy, H.L. Kennard, Z. Kristallogr. 209 (1994) 803–807.
[15] J.B. King, C. Winters, D.J. Sticker, Medec. Maladies Infect. 22 (1992) 614–620.
[16] H. Brunner, F. Maiterth, B. Treittinger, Inorg. Chim. Acta 200 (1992) 79–84.
[17] A.E. Martell, R.J. Motikaitis, Determination and use of Stability Constants, second ed., VHC Publishers, Weinheim, Germany, 1992.
[18] A.L. Spek, HELENA. Program for Reduction of CAD-4 Data, University of Utrecht, The Netherlands, 1996.
[19] A.C.T. North, D.C. Phillips, F.S. Mathews, Acta Cryst. A 24 (1968) 351.
[20] G.M. Sheldrick, SHELXS97. Program for Crystal Structure Resolution, University of Göttingen, Göttingen, Germany, 1997.
[21] G.M. Sheldrick, SHELXL97. Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen, Germany, 1997.
[22] L.J. Farrugia, J. Appl. Crystallogr. 30 (1997) 565.
[23] B.T. Usubaliev, E.M. Movsumov, I.R. Amiraslanov, A.I. Akhmedov, A.A. Musaev, K.S. Mamedov, J. Struct. Chem. 22 (1981) 73–77.
[24] R.L. Rardin, W.B. Tolman, S.J. Lippard, New J. Chem. 15 (1991) 417–430.
[25] M. Jansen, Angew. Chem. Int. Ed. 26 (1987) 1098–1110.
[26] H.C. Kandpal, R. Seshadri, Solid State Sci. 4 (2002) 1045–1052.
[27] International Centre for Diffraction Data, Powder diffraction file release 1–49 (1999) 70–86 Pennsylvania, File 04-0783.
[28] K. Nakamoto, Infrared Spectra of Inorganic and Coordination Compounds, fourth ed., Wiley, New York, 1986, p. 232.
[29] K. Nakamoto, Y. Morimoto, A.E. Martell, J. Am. Chem. Soc. 83 (1961) 4528–4532.
[30] L. Babcock, R. Pizer, Inorg. Chem. 19 (1980) 56–61.
[31] S.G. Franzblau, R.S. Witzig, J.C. McLaughlin, P. Torres, G. Madico, A. Hernandez, M.T. Degnan, M.B. Cook, V.K. Quenzer, R.M. Ferguson, R.H. Gilman, J. Clin. Microbiol. 36 (1998) 362–366.
[32] P.T. Kent, C. Kubica, Public Health Mycobacteriology: A Guide for the Level-III Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, 1985.
[33] S. Ahmad, A.A. Isab, S. Ali, A.R. Al-Arfaj, Polyhedron 25 (2006) 1633–1645.
[34] M.J.M. Vaerewijck, G. Huys, J.C. Palomino, J. Swings, F. Portaels, FEMS Microbiol. Rev. 29 (2005) 911–934.
[35] F.A. Castelo, A.L. Kritiski, A.W. Barreto, J. Bras. Pneumol. 30 (2004) S24–S37.