

Research Article

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Synthesis and characterization of silver(I) complexes with ligands having anti-inflammatory properties

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Abstract: Five water soluble silver(I) complex with Ibuprofen (AgIbu), Naproxen (AgNap), Mefenamic acid (AgMef), acetyl salicylic acid (AgAsp) and salicylic acid (AgSal) were synthesized and characterized by elemental analysis, FT-IR, ¹H and ¹³C NMR. Data suggest coordination of the ligand to Ag(I) through the oxygen atom of the carboxylic group. AgAsp was obtained as a mixture of AgAsp and Ag(I)-2-hydroxybenzoate (AgSal) due to decomposition by thermal and hydrolysis of acetylsalicylic acid into salicylic acid. AgSal structure was confirmed by FT-IR, NMR and X-ray diffraction. Synthesized compounds were tested toward UV-radiation (258 nm, 30 W) and compared with AgCl in order to characterize their light sensibility.

Supporting information: FT-IR, ¹H-NMR, ¹³C-NMR, HSQC, X-Ray.

Keywords: Silver complexes, antibacterial, anti-inflammatory, FT-IR, HSQC. Light sensibility.

1. INTRODUCTION

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 [1]. Antibacterial experiments have shown broader antimicrobial activity spectra for silver complexes with Ag-O and Ag-N bonds than with Ag-P and Ag-S bonds [1, 2]. Investigations on silver complexes to date have attributed their enhanced antimicrobial properties to distinctive weak Ag-O and Ag-N bonds in their structure [3,4]. Herein, we describe the preparation and characterization of five silver (I) complexes: AgIbu, AgNap, AgMef, AgAsp and AgSal, where Ibu= iso-butyl-propanoic-phenolate, Nap=(+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoate, Mef=2-(2,3-dimethylphenyl)aminobenzoate, Asp=2-acetoxybenzoate and Sal= 2-hydroxybenzoate(See figure 1) as a potential antibacterial agents.

2. EXPERIMENTAL

All chemicals were analytical grade of Merck and Aldrich and used without purification. The methods used for preparing all the new Ag(I) complexes was quite similar to previously repor-

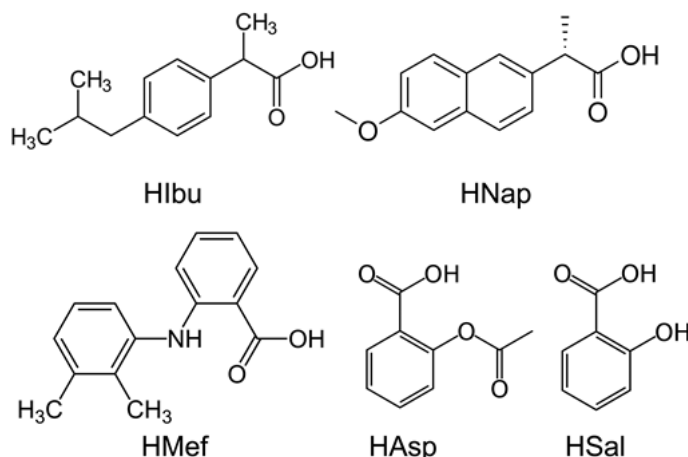


Figure 1: Ligands used in the synthesis of silver compounds.

ted procedures [5,6,7]. C, H, and N were analyzed with a CE elemental analyzer (EA 1108 model). IR spectra (KBr discs) were recorded on a FT-IR spectrometer BRUKER (Vector 22 model). NMR Spectra were recorder in a Bruker 400 Mhz spectrometer in DMSO-d₆. The crystal structure of AgSal was determined by X-ray diffraction, using a low temperature data set collected with a BRUKER SMART CCD diffractometer, with SMART as a driving software and SAINT for data reduction. The structure was solved by direct methods using SHELXS-97 and refined on F2 by full-matrix least-squares with SHELXL-97 [8]. The molecular representations shown in the figure 2 were generated using XP in the SHELXTL package, VESTA and Mercury. Light sensibility of Ag(I) compounds was studied at 293K using a low-pressure Hg lamp: 258 nm, 30 Watts. The radiation source was positioned 10 cm from the sample. Fresh AgCl was used as a control substance. Digital pictures of irradiated samples were taken every 30 minutes using a digital camera (Canon 60D, 18 Mpx) and images were cropped to square shapes without editing.

3. RESULTS AND DISCUSSION

Synthetic procedures for all the complexes involved the straightforward mixing of a previously treatment of the ligands with NaOH at pH=8.0 in aqueous solution with AgNO₃ in Ag⁺: ligand = 1:1 molar ratio. The syntheses were carried out with stirring and at room temperature for 15 minutes. The insoluble

products were then filtered off, washed with cold water and ethanol, and dried *in vacuo* over calcium chloride at room temperature.

AgNap: White powder, 56% Yield, m.p.: 190°C, Anal. Calculated for $C_{14}H_{13}AgO_3$: C, 49.88; H, 3.89. Anal. Found: C, 49.91; H, 3.86, FT-IR: 3401(w, COOH), 2935(w, CH), 1606(w, ring mode), 1564(s, (COO⁻), 1394(m, COO⁻), 1357(m, CH₃), 1218 (m, CH₃), 1029(m, COC), cm^{-1} . ¹H-NMR: 1.43(d, CH₃), 3.72(m, CH), 3.85(s, OCH₃), 7.11(dd, Ar-H), 7.24(d, Ar-H), 7.44(dd, Ar-H), 7.71(m, Ar-H), ppm. ¹³C-NMR: 20.3(CH₃), 47.8(CH), 55.4 (OCH₃), 106.3(Ar-C), 118.6(Ar-C), 125.5(Ar-C), 126.8(Ar-C), 127.4(Ar-C), 128.7(Ar-C), 129.2(Ar-C), 157.0(Ar-CO), 178.0 (COOH) ppm.

AgIbu: White powder, 58% Yield, m.p.: 206°C, Anal. Calculated for $C_{13}H_{15}AgO_2$: C, 49.86; H, 5.47. Anal. Found: C, 48.80; H, 5.44. FT-IR: 3392 (w, COOH), 2954(w, CH), 1567(s, COO⁻), 1463(w, CH₃), 1393(m, COO⁻), 1360(w, CH₃), cm^{-1} . ¹H-NMR: 0.86(d, CH₃), 1.33(d, CH₃), 1.79(m, CH), 2.38(d, CH₂), 3.55(q, CH), 7.03-7.19(d, Ar-H). ¹³C-NMR: 19.4(CH₃), 21.7(CH₃), 29.3 (CH), 44.2(CH), 46.9(CH₂), 128.0(Ar-C), 126(Ar-C), 138(Ar-C), 177.9 (COOH), ppm.

AgMef: Pale yellow powder, 30-32% Yield, m.p.: 170°C, Anal. Calculated for $C_{15}H_{14}AgNO_2$: C, 51.75; H, 4.05; N, 4.02. Anal. Found: C, 50.70; H, 3.96; N, 3.96. FT-IR: 3250 (w, -NH), 1605 (s, COO⁻), 1375 (s, COO⁻), cm^{-1} . ¹H-NMR: 2.13(CH₃), 2.30 (CH₃), 6.83 (t, Ar-H), 6.63(dd, Ar-H), 6.87, 7.04(t, Ar-H), 7.12 (t, Ar-H), 7.13, 7.98(d, Ar-H), 10.53(s, NH). ¹³C-NMR: 14.0 (CH₃), 20.7(CH₃), 113.3(Ar-C), 116.4(Ar-C), 119.4(Ar-C), 124.7(Ar-C), 126.0(Ar-C), 129.5(Ar-C), 131.4(Ar-C), 132.87, 137, 7, 140.5, 147.1, 172.4 (COOH), ppm.

AgAsp: White powder, 76-80% Yield, m.p.: 180°C, Anal. Calculated for $C_9H_7AgO_4$: C, 37.66; H, 2.46. Anal. Found: C, 37.29; H, 2.3. FT-IR: 1736.5(s, CO, arylester), 1608(sh, ring), 1594(s, COO), 1560(s, ring), 1378(s, COO), 1224.6(s, COC, arylester), 1185.5(m, COC, arylester), cm^{-1} . ¹H-NMR: 2.24 (s, CH₃), 7.04(d, Ar-H), 7.42(td, Ar-H), 7.90 (dd, Ar-H). ¹³C-NMR: 21.6(CH₃), 119.8(Ar-C), 123.4(Ar-C), 125.6(Ar-C) 131.0 (Ar-C), 131.9(Ar-C), 150.1(Ar-C), 168.8(arylester), 169.7(COOH), ppm.

AgSal: Colorless crystals suitable for X-ray diffraction, 25-37% Yield. FT-IR: 2745 (w, COOH), 1553(s, COO), 1457 (s), 1379 (s, COO), 1333(s), 1260(s, Ar-OH), cm^{-1} . ¹H-NMR: 6.72-6.77 (m, Ar-H), 7.26(m, Ar-H), 7.80(t, Ar-H), 13.93(s, OH). ¹³C-NMR: 116.0(Ar-C), 117.4(Ar-C), 118.5(Ar-C), 130.7(Ar-C), 132.5(Ar-C), 161.1(Ar-C), 172.2(COOH) ppm.

Silver(I) carboxylates are commonly obtained as poorly soluble and light-sensitive white-yellow powders. In solid state, Ag(I) carboxylates mostly form bridged dimers (Ag₂L₂) and also polymeric networks[5].

IR bands of the carboxylate groups are very useful in discriminating between the ligands and the metal complexes[9-13]. Symmetric and asymmetric COO⁻ vibrations change the intensity and the position and it is possible to determinate monodentate or bidentate bonds in the metal compound[14]. Additionally, O-H stretching (2500-3000 cm^{-1}) in the carboxylic group disappear as an evidence of the coordination between -COO⁻ group and the Ag(I). Free ligands shows C=O stretching mode observed as a band at 1780-1710 cm^{-1} and this signals shift to

Table 1: Infrared data (cm^{-1}) for silver(I) complexes in KBr.

Compound	Carboxylate group			Binding
	$\nu_a COO^-$	$\nu_s COO^-$	Δ_{as}	
AgNap	1564	1394	170	Bidentate
AgIbu	1567	1393	174	Bidentate
AgMef	1605	1375	230	Anisobidentate
AgAsp	1594	1378	216	Anisobidentate
AgSal	1553	1379	174	Bidentate

lower frequency and suggest that the carboxylic group is part in the coordination with the silver ion (see Table I in this Supporting Information). The carboxylate ion usually coordinates to metal ions in three main ways[14]. The values of $\Delta\nu = \nu_{asym}(COO) - \nu_{sym}(COO)$ in monodentate complexes are expected to be much larger than 350 cm^{-1} . When $200 < \Delta\nu < 350$ cm^{-1} contain the carboxylate groups is present as an intermediate state between monodentate and bidentate, which is called anisobidentate and when $\Delta\nu < 200$ cm^{-1} , the carboxylate groups of the complexes can be considered bidentate [14].

Table 1 resume FT-IR carboxylic bands of the silver complexes in KBr discs. In the case of AgMef the absence of large systematic shifts of the NH and bands in the spectra of the complexes compared with those of the ligand indicates that there is no interaction between the NH group and the metal ions.

NMR spectra for ¹H and ¹³C were assigned in concordance with HSQC (¹H-¹³C correlations) experiments and compared with the ligand reported in DMSO[11-13]. 2D correlations were determined for an unequivocal assignation and differentiation between the ligand and the complexes. In every case proton shifts shows a $\Delta\delta$ (ligand-compound) of 0.01-1.20 ppm and ¹³C of the COO⁻ group a shift of 0.20 and 3.0 ppm by effect of metal ion bond to carbonyl group. The hydrogen atom of the -COOH group is absent in the silver complexes ¹H-NMR spectra (range of 10-13 ppm). This data indicates that, upon coordination, the carboxyl group is not protonated.

AgAsp was obtained as a mixture of AgSal crystals and the respective compound, detected by ¹H-NMR, ¹³C-NMR and confirmed by X-Ray diffraction. The crystal structure of the AgSal was obtained as a dimer structure: Ag₂(Sal)₂, but has been previously reported by reacting of salicylic acid with silver nitrate in aqueous ammonia[15]. We obtained the same compound with very similar bonds lengths and angles by thermal hydrolysis of acetylsalicylic in basic solution as shown in the figure 2 [16].

The stability of Ag(I) compounds toward reduction to silver(0) by short wavelength UV-radiation are shown in the figure 3. AgMef and AgAsp shows great stability for a prolonged period of time in comparison with the control, AgCl, which is completely darkened after 10 minutes. AgIbu, AgSal and AgNap show a gradual color change from white/pale-yellow to orange/brown in less than 1 hour. These differences could be related to the different Ag-O bonds energies in every compound as shown in IR spectra (See table 1). The more light-insensitive com-

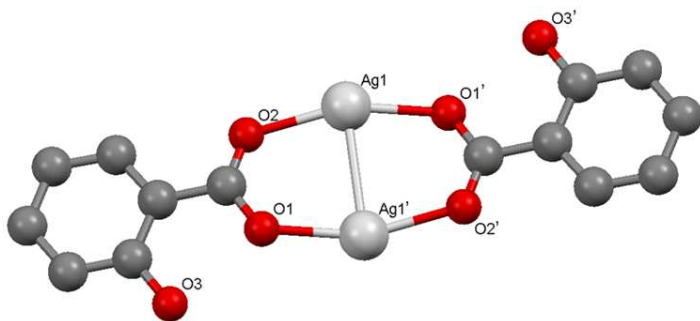


Figure 2: Molecular structure of $\text{Ag}_2(\text{Sal})_2$ (hydrogen atoms are omitted). Selected bond lengths (Å) and angles [°]: O1-Ag1': 2.1887(15), Ag1-O2: 2.2043(15), Ag1-O1': 2.1887(15), Ag1'-O2': 2.2043(15), Ag1-Ag1': 2.8544(4). O(1)-Ag(1)-O(2): 159.35(6), C(7)-O(1)-Ag(1)': 124.42(14), C(7)-O(2)-Ag(1): 123.59(14).

pounds shows anisobidentate binding ($\Delta\nu$ s: 230 and 216 cm^{-1}) because when the differences in frequency increase, the bonding between the metal and the carboxylate groups becomes more covalent[4, 9,10]. The light-insensitive characteristics of silver (I) compounds is important for their potential applications in medical devices where the thermal stability, antibacterial activity, poor solubility and the resistance toward intense UV-radiation could be a good alternative as additives to curable photopolymers in dental implants[17].



Figure 3: Reduction of synthesized silver(I) compounds in presence of high-energy UV radiation at 258 nm and 30 watts.

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