Au(III) complexes of tris-dithiocarbamate derivatives of α-amino acids: spectroscopic studies, thermal behaviour and antibacterial activity

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Abstract

The synthesis and characterization of new coordination compounds of Au(III), with dithiocarbamates derived from α-amino acids (DL-alanine, DL-valine, L-valine and DL-leucine) is reported. As single crystals were not synthesized, a large number of experimental techniques was used to accomplish a definitive characterization and determination of the structures of these compounds. The compounds are hexacoordinated, but diamagnetic, the structure thus corresponding to a distorted trigonal prism. Only one XPS S(2p) signal is recorded, indicating a symmetric dithiocarbamate moiety surrounding the metallic cation; two Au(4f) signals are recorded in all cases, due to Au(III) and Au(I), through reduction of the former in the spectrometer chamber. Results obtained by applying other techniques (FT-IR, Vis–UV, NMR, MS) support the above conclusions. Antibacterial activity against nine Gram+ and Gram− species has been studied for the gold salt, the ligands, the complexes and control antimicrobial agents. Only the gold complexes exhibit a larger activity than the reference compounds, against *Streptococcus pneumoniae*.

Introduction

Among the many and so different families of organic–inorganic chemicals being currently investigated for their applications in medicine, dithiocarbamates (dtc) are one of the most outstanding groups. These compounds find application in vulcanization, high pressure lubricating agents, fungicides and pesticides, but it has been recognized that the residual toxicity of dtc used as fungicides in agriculture is still a matter of controversy [1–4].

The search for new chemicals with antimicrobial activity is an important field of research nowadays. Among the many reasons for this interest, one of them (and not the less important) is the increasing resistance developed by microorganisms to conventional antimicrobials, probably due to their continuous and undirected use. Several authors have recently reported [5, 6] the antimicrobial and antifungal activity of dithiocarbamates, most of them derivatives with two methyl or ethyl radicals. Also, dithiocarbamates derived from 2-aminobenzothiazol [7, 8] have shown a good response as antimicrobial agents.

We have previously reported [9] several studies describing the preparation and characterization of novel complexes of metallic cations with dtc derived from amino acids. Here, we report a study of complexes formed with Au(III), that exhibit new features, not shown by the complexes described in our previous works.

In addition, in the present paper a study is reported of the antimicrobial activity of the complexes prepared, as well as of the free ligands and of the starting Au(III) salt used to obtain the complexes.

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Experimental

Materials and methods

DL-Alanine, DL-valine, L-valine, DL-leucine and $KAuCl_4$ were purchased from Fluka A.G. All other reactives were of high purity and were used as purchased, without any further purification.

Chemical analysis for C, H and N was performed on a elemental analyzer 2400 from Perkin-Elmer, while sulfur was analyzed in the CSIC laboratories (Barcelona, Spain). Gold was determined by atomic absorption after aqua regia digestion (Perkin-Elmer, model 2380).

Molecular weight of the complexes was determined following the Signer's method.

Electrical conductivity in solution was measured using a Radiometer CDM2e conductimeter, using a CDC104 immersion cell. Temperature was monitored with a Unitherm bath (precision ± 0.01 °C).

Magnetic susceptibility of the solids was determined following the Faraday method, using a DSM-9 magnetometer/susceptometer MANICS, equipped with a computer, for measurements produced by a permanent, induced magnetic field, with variable temperature accessories.

Electronic spectra were recorded in a Shimadzu UV-2400 double beam spectrophotometer, using fresh methanol solutions of the samples.

IR spectra were recorded in the 4000–200 cm^{-1} range in a Perkin-Elmer FT-1730 instrument coupled to a Perkin-Elmer 3600 Data Station; KBr pellets were used to record spectra above 400 cm^{-1} and Nujol and polyethylene discs below 400 cm^{-1}.

X-ray photoelectron spectra were recorded using a Leybold-Heraeus LHS-10 apparatus, using Mg Kα radiation, under a pressure of 10^{-9} torr and using the C(1s) peak at 284.6 as reference.

^{13}C NMR were recorded on a Brucker WP 200SY spectrometer in D_2O and CD_3OD solutions using TMS as internal standard.

Thermogravimetric TG (DTG) and differential scanning calorimeter DSC curves were recorded on a Mettler TA-3000 system with a Mettler TG-50 thermobalance and a Mettler DSC-20. TG diagrams were recorded in a dynamic atmosphere of pure air (100 ml min^{-1}). DSC curves were obtained in a static atmosphere of air at the heating rate as for the TG curves.

The mass spectra were recorded in a HP-4988A apparatus, working a heating ramp of 25–300 °C at a heating rate of 40 °C min^{-1}.

Bacterial strains: *Serratia marcescens* CECT 46, *Klebsiella sp.* CECT 367, *Proteus vulgaris* CECT 484, *Pseudomonas aeruginosa* CECT 110, *Yersinia enterocolitica* CECT IP 383, *Staphylococcus aureus* CECT 86, *Bacillus subtilis* CECT 39, *Micrococcus luteus* CECT 51 and *Streptococcus pneumoniae* CECT 993 were obtained from the Colección Española de Cultivos Tipo, Valencia (Spain). The bacteria were grown on tryptic soy broth and tryptic soy agar (TSB, TSA) (Difco Laboratories) enriched with 0.3% yeast extract. Antimicrobial agents used as control were: Ampicillin, Norfloxacin, Colistin and Cefotaxime.

Preparation of the ligands and of the complexes

The ligands were prepared as described elsewhere [9], as barium salts. An aqueous solution of $KAuCl_4$ was dropwise added to an aqueous solution of the ligand (3Ba:1Au). The gold solution, originally yellow, immediately changes to reddish brown, the reaction probably being

$$AuCl_4^- + 3Ba(S_2CNH\text{-}CH(R)\text{-}CO_2)\cdot 3H_2O \xrightarrow[(2)\ HCl]{(1)\ Et_2O}$$

$$\longrightarrow Au(S_2C\text{–}NH\text{–}CH(R)\text{–}CO_2H)_3\cdot 3H_2O + 3BaCl_2(aq)$$

R = DL-Me (**1**), DL-Pr^i (**2**), L-Pr^i (**3**), DL-Bu^i (**4**)

In order to remove barium, the solution is placed in a separation funnel and diethyl ether is added, followed by the stoichiometric amount of 0.1 M HCl to yield $BaCl_2$; barium remains in the aqueous solution, while the complexes move to the organic phase. The solvent is slowly removed by evaporation. The solid thus obtained, of a bright red–brown colour, seemed to be crystalline, but no definitive X-ray diffraction pattern could be obtained. Final yield was 75%. The solid was finally dried in a dessicator with P_4O_{10}. Results from the chemical analysis for the compounds are summarized in Table 1.

Preparation of the microorganisms for the inoculum

For the determination of antimicrobial activity, the plate diffusion technique was used [10]. The microorganisms for the inoculum were prepared in flasks containing 100 ml of culture medium (TSB), enriched with 0.3% yeast extract, and incubated over 24 h at 37 °C with shaking at 240 rpm.

To carry out this study Petri dishes were prepared containing a constant amount of culture medium (TSA, 0.3% yeast extract). After the medium has solidified, 0.1 ml was plated from the inoculum in liquid medium; after 2 h, the excess liquid present in the dish was removed, making 0.9 cm diameter wells. Following this, the substance to be studied was placed in each well at the desired concentrations and thereafter incubated over 24 h at 25 or 37 °C, according to the microorganisms

TABLE 1. Analytical data, molecular weight and conductivity

Complexes	*Anal.* Found (calc.) (%)					Molecular[a] weight	Λ_M[b]
	C	H	N	S	Au		
$Au(dtc\text{-}DL\text{-}Ala)_3 \cdot 3H_2O$ (**1**)	p19.14 (19.38)	p3.11 (3.24)	5.82 (5.64)	26.02 (25.87)	26.71 (26.48)	(743.25)	
$Au(dtc\text{-}DL\text{-}Val)_3 \cdot 3H_2O$ (**2**)	26.34 (26.05)	4.33 (4.37)	5.10 (5.06)	23.20 (23.18)	23.65 (23.65)	835 (827.8)	no elec
$Au(dtc\text{-}L\text{-}Val)_3 \cdot 3H_2O$ (**3**)	26.41 (26.05)	4.31 (4.37)	5.17 (5.06)	23.26 (23.18)	23.60 (23.65)	838 (827.8)	no elec
$Au(dtc\text{-}DL\text{-}Leu)_3 \cdot 3H_2O$ (**4**)	28.53 (28.99)	4.70 (4.86)	4.64 (4.82)	22.04 (22.11)	22.58 (22.64)	874 (869.8)	no elec

[a]Signer method. [b]In methanol (Ω^{-1} cm^2 mol^{-1}) at 25 °C; no elec = no electrolyte.

under study. Then, using a calibrator, the diameter of the inhibition halo was measured.

Results and discussion

From the analysis obtained by elemental chemical analysis and from determination of molecular weight, see Table 1, it can be concluded that the stoichiometry of the complexes is 1Au:3L.

All compounds were diamagnetic. The electric conductivity in ether and methanol has been measured, concluding that no dissociation exists and so these are non-electrolyte substances. With this, the expected geometry for the compounds would be a distorted trigonal prism, D_{3d}–D_{3h}, as reported by McCleverty *et al.* [11] for dithiocarbamate complexes of Cd(II) with a D_3 structure. With heterocyclic dithiocarbamates, hexacoordinated, diamagnetic complexes of Au(III) have been also prepared [12].

Electronic spectroscopy

The bands recorded in the UV region are essentially the same in all cases, and their positions are: λ_{max} (Et_2O) 412 nm (log $\epsilon = 3.4$ dm^3 mol^{-1} cm^{-1}), band I; 286 (4.12), band II; 260 (5.68), band III; 214 (4.31), band IV.

The weakest band I has been ascribed [13] to a metal–ligand charge transfer process, $^1A_g \rightarrow {}^1A_u$, $^1A_{2g} \rightarrow {}^1E_g$, but it can be also ascribed [12, 14] to transitions between metallic d orbitals and the delocalized π^* system of the ligands. Band II corresponds to an intraligand transition $n \rightarrow \pi^*$, most probably between predominantly sulfur energy levels [16]. Band III also corresponds to an intraligand transition, $n \rightarrow \pi$, usually ascribed to the NCS group. It is usually recorded split [12, 15, 16], and shifts depending on the nature of the R moiety bonded to the nitrogen atom. Finally, band IV corresponds to a $\pi \rightarrow \pi^*$ intraligand transition, due to the CS_2 group. Although it is usually affected by the metallic cation, it is almost independent of the nature of the R group bonded to the nitrogen atom [12, 17].

FT-IR spectroscopy

The most significant bands recorded in the IR spectra of the ligands and the complexes have been collected in Table 2.

A wide overlapping band due to ν(OH) and ν(NH) modes is recorded at 3420–3300 (ligands) or 3450–2950 (complexes) cm^{-1}.

For the CN groups, two bands are recorded, one at 1530–1470 cm^{-1} due to the NCS_2^- group (which position has been used to determine the degree of double bond character in dithiocarbamates [16, 18, 19], and the other at 1100–1050 cm^{-1}, due to the $NCCO_2^-$ group. Crystallographic data [20] for one of the barium salts indicate that the former N–C bond corresponds to a double bond, while the second N–C bond is single.

For the carboxylic group, the ligands show two bands, 1570–1560 cm^{-1} (asymmetric νCO_2^-) and 1420–1400 cm^{-1} (symmetric νCO_2^-), and the complexes show only one band at 1730–1710 cm^{-1}, due to the free carboxylic group. This difference undoubtedly indicates that these ligands do not coordinate to the metallic ion through the carboxylic group.

The bands due to the CS_2 are usually coupled to other vibrations and are very sensitive to the environment of this moiety [15], but they are useful to distinguish between monodentate and bidentate coordination. While some authors ascribe these bands to stretching C=S and C–S modes [21–23], others [15, 24–26] ascribe them to the symmetric and antisymmetric modes of a charge-delocalized CS_2 group. Taking into account the crystallographic data above mentioned for the barium salt of these ligands, as well as the fact that only a XPS signal due to 2p orbitals of the sulfur atoms is

TABLE 2. Main IR bands of the ligands and the complexes

Compounds	ν(N–H)	ν(C_1–N)	ν(C_2–N)	ν(CO_2^-)		ν(CO_2H)	ν(C–S)		ν(Au–S)
				asym.	sym.		asym.	sym.	
Ba(dtc-DL-Ala)·3H_2O	3318	1529	1164	1557	1417		964	637	
Ba(dtc-DL-Val)·3H_2O	3382	1489	1153	1562	1412		968	670	
Ba(dtc-L-Val)·3H_2O	3387	1490	1159	1568	1409		972	669	
Ba(dtc-DL-Leu)·3H_2O	3415	1471	1163	1571	1406		968	670	
Au(dtc-DL-Ala)$_3$·3H_2O	2963	1520	1099			1718	1034	602	418 376
Au(dtc-DL-Val)$_3$·3H_2O	2966	1466	1079			1714	1040	608	420 399
Au(dtc-L-Val)$_3$·3H_2O	2967	1470	1068			1728	1047	619	425 398
Au(dtc-DL-Leu)$_3$·3H_2O	3166	1558	1059			1729	1028	646	416 388

recorded (see below), it can be concluded that both sulfur atoms are equivalent.

Finally, only two weak bands are recorded at 430–330 cm^{-1} ascribed to ν(Au–S), a wavenumber range fairly close to that previously reported by other authors for compounds similar to those here studied [12, 27].

X-ray photoelectron spectra

The chemical analysis data for the samples, as obtained by this technique, are in very good agreement with those obtained by conventional chemical analysis methods, the atomic ratio being Au:O = 0.11/0.14 (experimental, calculated), Au:N = 0.33/0.30, Au:S = 0.20/0.24, and Au:C = 0.04/0.04.

Data for the atomic orbitals energies for the ligands and for the complexes have been summarized in Table 3 together with the full-width at half-maximum (FWHM).

The energy of the S(2p) levels is 0.9 eV larger for the complexes than for the ligands, thus indicating the formation of additional bonds. This fact has been previously used by other authors to characterize a moiety where a carbon atom is bonded to two different sulfur atoms, through a single and a double bond, respectively [28, 29]. In our case, the fact that only a signal is recorded, confirms the equivalency between both sulfur atoms.

These results are of paramount importance, as they undoubtedly support the hexacoordinated geometry, against a square planar geometry reported in the literature for some other Au(III) complexes with a 3:1 L:Au stoichiometry [12]. For square-planar, L:Au = 3:1 complexes, one of the ligands would act as bidentate and the other two as monodentate, coordinating through one sulfur atom. In such a case, three different signals due to S(2p) orbitals would be expected, i.e., that due to sulfur atoms implied in bidentate coordination, that due to coordinating sulfur atoms belonging to monodentate ligands, and that due to the free sulfur atom from the monodentate ligand. A simple Lewis structure analysis would indicate formal charges of −0.5, −1 and 0, respectively, for these three types of sulfur atoms. However, only one single S(2p) signal is recorded in our case. A poor resolution of the instrument or small

TABLE 3. Binding energies (FWHM)[a]

Ba(dtc-DL-Leu)·3H_2O	Ba		S	N	C			O
			2p	1s	1s			
	$3d_{3/2}$	$3d_{3/2}$						
					Refer	CS_2^-	CO_2^-	
Binding (eV)	795.5	780.1	161.9	399.2	284.6	286.2	288.0	531.2
	(1.2)		(2.6)	(2.7)		(2.4)		(2.7)
Au(dtc-DL-Leu)$_3$·3H_2O	Au		S	N	C			O
	$4f_{7/2}$		2p	1s	1s			
					Refer	CS_2^-	CO_2H	
Binding (eV)	88.0–84.3		162.8	400.5	284.6	286.1	288.5	531.7
	(1.6)		(2.7)	(2.7)		(2.1)		(2.8)

[a]FWHM = full width at half maximum.

separation between the positions of these signals would be also responsible for this result, but this does not seem to be the case, as the FWHM of the signals is the same, whichever ligands (where crystallographic data have shown the equivalency of both sulfur atoms) or complexes are considered. In addition, it should be noted that the FWHM values coincide with those reported in the literature [30], with values ranging from 2.4 to 2.9 eV; only a value of 3.3–3.4 eV is reported for complexes of dithiomorpholinedithiocarbamate, where a neutral sulfur atom exists, together with those of the dithiocarbamate moiety.

Ascription of signals due to the gold cations to one or another Au(I) or Au(III) is quite difficult, as these signals are very close; however, van Attekum *et al.* [31] have reported that dithiocarbamate complexes of Au(III) may undergo a partial reduction under the extreme experimental conditions used to record the XP spectra. So, the signal close to 88.0 eV should be ascribed to Au(III) species, while the signal at 84.3 eV should be originated by Au(I) species, formed upon reduction of the former in the spectrometer chamber. Very recently [32, 33], Au(4f) signals close to those here found have been reported, these authors claiming as well a partial reduction of the sample, as the position of the signal slightly shifts during recording of the spectrum.

^{13}C NMR

For the ^{13}C NMR study (Table 4) nearly no difference exists between the derivatives of DL- and L-alanine both in the ligands and in the complexes. The signal due to the carboxylic/carboxylate carbon atom shifts from 181 ($-COO^-$) to 171 (–COOH) ppm, as in the latter the electron density on the carbon atom should be lower than in the former. A similar behaviour is observed for the carbon atom of the dithiocarbamate group, whose signal is recorded at 214 ppm for the ligands (where it exists as $-CS_2^-$), but at 200 ppm for the complexes. This result indicates that in solution a rapid exchange between hexacoordinated square planar geometries could exist, as in this last case, coordination through a single sulfur atom would decrease the electron density on the carbon atom.

Thermal analysis

The decomposition processes of the compounds obtained have been studied, in order to establish the different steps and to confirm the proposed stoichiometry and it also confirms the conclusions reached upon application of the spectroscopic techniques.

The results of such analyses have been summarized in Table 5 for compounds **2** and **4**. A good correlation exists between the calculated and found values for compound **2**. The first TG step corresponds to dehydration and decarboxylation, as confirmed by DSC, that shows an endothermic effect overlapped to an exothermic one. A very intense effect is recorded at higher temperatures, that corresponds to removal of the remaining ligand atoms, thus leading to metallic gold formation as the residue. Photometric analysis of this residue confirms its nature.

Mass spectrometry

Interpretation of the mass spectra has been a very difficult task. Fragmentation schemes for the ligands have been reported recently by us [34]. For the gold complexes, series of four analyses have been performed for every complex, both using the electron-impact and chemical ionization techniques. In no case, was the signal corresponding to the molecular ion recorded. The largest m/z value recorded was $m/z = 793$ for com-

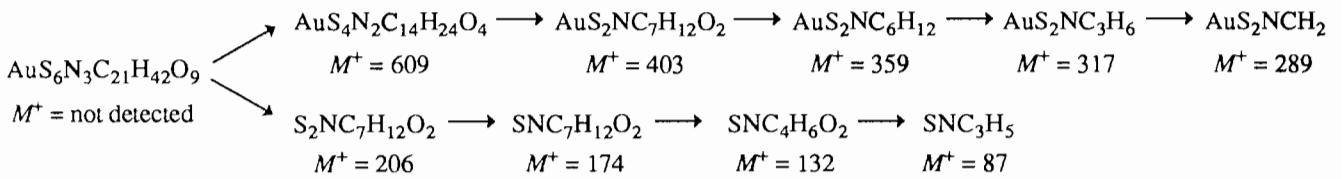
TABLE 4. ^{13}C NMR data (δ, ppm)

Compounds[a]	S_2C	CO_2^-/H	C_1	C_2	C_3	C_4
Ba(dtc-DL-Val)·$3H_2O$	213.70	181.03	71.37	33.47	20.29 21.39	
Au(dtc-DL-Val)$_3$·$3H_2O$	200.76	171.02	71.23	31.31	17.83 18.16	
Ba(dtc-L-Val)·$3H_2O$	213.72	181.03	71.37	33.44	20.28 21.37	
Au(dtc-L-Val)$_3$·$3H_2O$	200.75	171.00	71.22	31.30	17.79 18.20	
Ba(dtc-DL-Leu)·$3H_2O$	213.32	182.75	64.79	43.53	27.58	23.95 25.09
Au(dtc-DL-Leu)$_3$·$3H_2O$	200.83	175.04	61.57	43.05	25.61	22.37 23.44

[a]Atom numbering: ^-S_2C–NH–C(1)(CO$_2^-$/H)–C(2)–C(3)–C(4)

TABLE 5. Thermal data for complexes **2** and **4**

Complexes	TG(DTG)		Weigth loss (%)		DSC	
	T (°C)	Process	Exp.	Theor.	*T* (°C)	Process
Au(dtc-DL-Val)$_3$·3H$_2$O	47–162	dehyd.+decarb.	22.62	22.46	50–425	endo+exo
	162–411	pyrolysis	52.60	53.75		
	411–719	pyrolysis	23.84	23.79(Au)	⩾425	exo
Au(dtc-DL-Leu)$_3$·3H$_2$O	47–178	dehyd.+decarb.	21.58	21.40	50–450	endo+exo
	178–453	pyrolysis		55.96		
	453–723	pyrolysis	22.77	22.64(Au)	⩾450	exo



Scheme 1.

pound **4**, very close to the expected molecular ion. Another feature is the lack of repetition in both series of spectra, and so Scheme 1 includes a selection of the most common ions. One branch of Scheme 1 represents a series of fragments, all them including a gold atom, corresponding to successive loss of ligands, similarly to the data reported in the literature [35, 36], the last ion recorded having $m/z=289$, that can tentatively correspond to $[AuS_2CNH_2]^+$. The other branch corresponds to withdrawal of a ligand, that loses a sulfur atom, and finally produces a species with $m/z=87$, that should correspond to $[SCN–CH_2–CH_3]^+$. However, for palladium compounds similar to those studied here, derivatives of nitrides were obtained [34].

Determination of antimicrobial activity

In this section we carried out a comparative study of the gold salt, ligands, complexes, and a short series of antibiotics such as those shown in Fig. 1. To do so, aqueous solutions of 30 μm ml^{-1} of all the compounds were prepared, with the exception that in the case of the complexes, since these are insoluble in water, the solutions were prepared in a aqueous/ethanolic solution, which had previously been observed to be devoid of activity against any of the microorganisms.

The gold salt showed activity against all nine species, both Gram+ and Gram−. An interesting finding was the absence of a significant difference in $KAuCl_4$ activity in relation with the different cell wall structures, suggesting in this case the lack of appreciable differences in the degree of penetration of the agent into the bacterial cell.

Against ligands and complexes, a significant degree of antibacterial activity was observed, although only against the Gram+ microorganisms: *Micrococcus luteus*

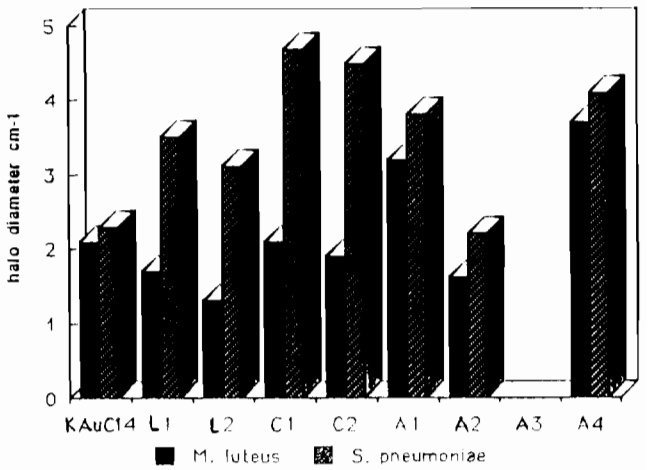


Fig. 1. Comparative study of antimicrobial activity for: L1 = Ba(dtc-DL-Val)·3H$_2$O, L2 = Ba(dtc-DL-Leu)·3H$_2$O, C1 = Au(dtc-DL-Val)$_3$·3H$_2$O, C2 = Au(dtc-DL-Leu)$_3$·3H$_2$O, A1 = Ampicillin, A2 = Norfloxacin, A3 = Colistin and A4 = Cefotaxime.

and *Streptococcus pneumoniae*, this activity being more pronounced – judging by the inhibition halos generated – against the latter microorganism. However, at present it is difficult to establish why the ligands, like the complexes, are active against these two microbial strains but not against the rest.

A possible explanation with respect to the Gram− strains might be the presence in these microorganisms of the outer membrane. Currently, it is known that Gram− microorganisms, as compared with Gram+ ones, show a natural resistance to a series of antibiotics, chemical agents and dyes owing to the innate permeability barrier formed by the outer membrane [37]. However, in the present study the Gram+ microorganisms such as *Bacillus subtilis* and *Staphylococcus*

aureus were also resistant, adding additional complexity when establishing the activity patterns.

Furthermore, it should be noted that in the case of the ligands, after 48–72 h post-inoculation of the antimicrobial agent and the microorganism assayed, a loss in activity of these agents was observed, since after this time a growth of the microorganism was noticed over the inhibition halo that had been generated at 24 h post-inoculation. A possible explanation for such findings would be related to the antimicrobial agent and the microorganism assayed, such that one could speculate that the above agents might exert a bacteriostatic rather than bactericidal effect, either through a decrease in the minimum inhibitory concentration (MIC) or owing to a loss of their activities due to chemical alterations, thus allowing the growth of such microorganisms.

Finally in the light of the results obtained, owing to their marked activity against a microorganism of considerable clinical importance such as *Streptococcus pneumoniae* the use of these complexes is highlighted.

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