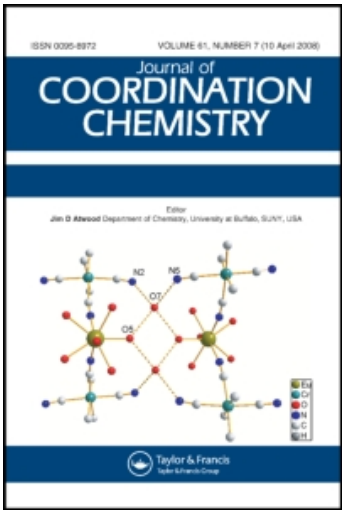

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME METAL COMPLEXES OF BETA-LACTAMIC ANTIBIOTICS

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME METAL COMPLEXES OF BETA-LACTAMIC ANTIBIOTICS

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An overview of the results of the interaction of β-lactamic antibiotics with some transition metal ions is given. Several complexes have been synthesized and characterized by physicochemical and spectroscopic methods. Some exhibit very promising antibacterial activity. Clavulanic acid (L_1), penicillin (L_2), ampicillin (L_3), cephalexin (L_4), cefazolin (L_5) and cephalothin (L_6) were allowed to react with metal ions in methanol under nitrogen. IR spectra of clavulanic acid, penicillin and ampicillin complexes showed strong modifications of the carbonyl group located on the lactamic ring, indicating that this oxygen participates in the coordination to the metal ions along with the carboxylate group. Thus L_1 and L_2 behave as monoanionic bidentate ligands while L_3 behaves as a monoanionic tridentate ligand. The IR spectra of cephalexin, cefazolin and cephalotin chelates show that the beta lactamic carbonyl group does not participate in coordination to the metal ions. A relationship between the structure of the complexes and their antibacterial activity can be observed.

In vitro antibacterial activity of the antibiotics and the complexes were tested using the filter paper diffusion method and the chosen strains include Escherichia coli ATCC 10536, Pseudomonas aeruginosa ATCC 9027, Salmonella typhimorium ATCC 14028, Staphylococcus aureus ATCC 6538, Bacillus cereus ATCC 9634, Proteus mirabilis 35659, Proteus vulgaris ATCC 9920, Klebsiella pneumoniae ATCC 10031, Salmonella sp, Shigella sp ATCC 11126, Streptococcus viridans and Salmonella enteritidis ATCC 497.

Keywords: Antibacterial; Antibiotics; Penicillin; Clavulanic acid; Ampicillin

INTRODUCTION

Clavulanic acid, penicillin and ampicillin are beta-lactamic antibiotics very active against Gram-positive infections but their activity against some

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bacteria such as Klebsiella and P. aeruginosa is not sufficient. Synthesis of metal complexes of these antibiotics should be important to increase effectiveness against some G(−) bacteria for a broad antibacterial spectrum [1−3].

Cephalexin, cefazolin and cephalothin are first generation cephalosporins and the resistance to them may be related to inability of the antibiotic to reach its sites of action, to alterations in the penicillin-binding proteins that are targets of the cephalosporins, or to bacterial enzymes (beta-lactamase) that can inactivate the cephalosporin. Many gram-positive microorganisms release relatively large amounts of beta-lactamase into the surrounding medium and they can destroy the beta-lactamic antibiotics by hydrolysis

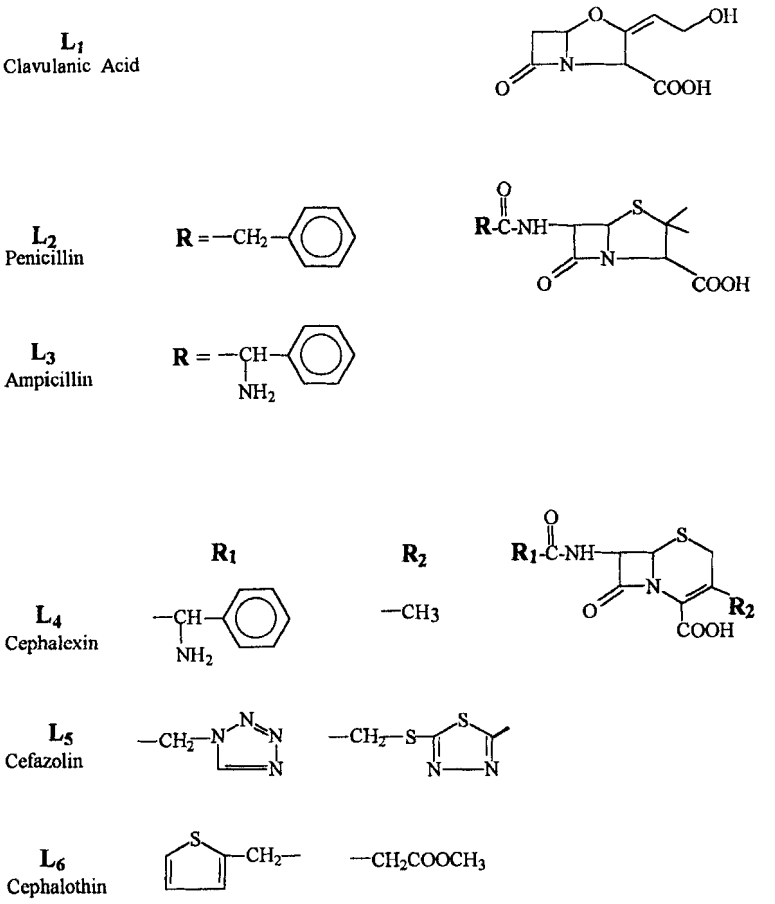

FIGURE 1 Chemical structures of beta-lactamic antibiotics.

of the beta-lactam ring; this is the most prevalent mechanism of resistance [4–6].

Many drugs possess modified toxicological and pharmacological properties in the form of metal complexes; probably the most widely studied in this respect is the copper(II) ion which has proved beneficial in many diseases such as turberculosis, gastric ulcers, rheumatoid arthritis and cancers [7–10]. These results promoted us to investigate the coordination chemistry of antibiotics and Schiff-base compounds with transition and d^{10} metal ions in an attempt to examine its mode of binding in the solid and to study its biological activity [11–13]. As continuation of our work on metal interactions with β-lactamic derivatives we report here the results obtained on the interactions of metal ions with ligands L_1-L_6 [14–19] whose chemical structures are shown in Figure 1.

EXPERIMENTAL

Physical Methods

Fourier transform infrared (FTIR) spectra of the ligand and its metal complexes as KBr pellets were recorded in the spectral range 4000–400 cm^{-1} with a Perkin Elmer Series 2000 apparatus. FTIR spectra as polyethylene pellets were registered between 450–120 cm^{-1} by using Brucker IFS 66V spectrophotometer. Spectra were scanned with resolution of 2 cm^{-1}. Two hundred scans were accumulated for both the mid and far FTIR measurements. EPR spectra were recorded on a Brucker ECS 106 spectrometer by the X-band method (9.76 GHz). α-α'diphenyl-β-picrylhydrazide free radical was used as the g marker.

UV-Visible spectra were recorded using a Perkin Elmer recording spectrometer. The contents of carbon, nitrogen, sulfur and hydrogen were analyzed by the microlabs in the Venezuelan Institute of Scientific Research (IVIC). Magnetic susceptibilities were measured on a Johnson Matthey Susceptibility Balance at room temperature using $HgCo(NCS)_4$ as calibrant.

Antibacterial Activity Test

In vitro antibacterial activity of the ligand and the complexes were tested using the paper disc diffusion method [20]. The chosen strains include G(+) S. aureus ATCC 6538, S. viridans and B. cereus ATCC 9634 and G(−) S. typhimorium ATCC 14028, K. pneumoniae ATCC 10031, P. vulgaris 9920,

P. mirabilis ATCC 35659, P. aeruginosa ATCC 9027, E. coli ATCC 10536, Salmonella sp, Shigella sp ATCC 11126 and S. enteritidis ATCC 497. The liquid medium containing the bacterial subcultures was autoclaved for 20 min at 15 lb pressure before inoculation. The bacteria were cultured for 24 h at 36°C in an incubator. Muller Hinton broth was used for preparing basal media for the bioassay of the organisms. Nutrient agar was poured in a plate and allowed to solidify. The test compounds in DMSO solutions were added dropwise on a 10 mm diameter filter paper disc placed in the center of the agar plates. The plates were then kept at 5°C for 1 h and transferred to an incubator maintained at 36°C. The width of the growth inhibition zone around the disc was measured after 24 h of incubation. Four replicates were taken for each treatment.

Materials and Methods

All reactants and solvents were analytical grade where possible, purchased from Aldrich and used without further purification. All solvents were distilled by standard techniques before use. The beta-lactamic complexes were prepared by mixing sodium antibiotics (2 mmol) and manganese(II), iron(II), iron(III), cobalt(II), nickel(II), copper(II), zinc(II), cadmium(II), mercury(II), palladium(II), lanthanum(III) and silver(I) acetate or chloride salts (1 mmol) in MeOH (40 mL) and the reaction mixture was stirred at room temperature during around 10 h and then left to stand overnight. The volume was then reduced by rotary-evaporation. The precipitated complexes were filtered off, washed with water, MeOH and ether and dried *in vacuo* at room temperature. All syntheses were carried out in nitrogen.

RESULTS AND DISCUSSION

The obtained compounds are indicated in Tables I and II along with the main IR frequencies. The elemental analyses agree well with the formulae of the complexes (Tab. I and Refs. [14–17]). The attempts to form other complexes having a well-defined stoichiometry were unsuccessful.

The complexes formed appear to be air stable solids, soluble in DMSO and DMF, slightly soluble in CH_3CN and insoluble in MeOH and water. The experimental conductivity values measured on 10^{-3} M solutions in DMSO at room temperature, fall in the range of non electrolytes [21], except the ampicillin complexes which are 2 : 1 electrolytes.

TABLE I Elemental analyses[1] for the metal complexes

Compound	*C*(%)	*H*(%)	*N*(%)	*S*(%)
$[Mn(L_4)Cl]\cdot 3H_2O$	38.70(39.04)	3.30(4.50)	8.50(8.53)	7.50(7.60)
$[Co(L_4)OAc]\cdot 3H_2O$	37.00(36.90)	3.09(4.10)	8.10(8.02)	6.10(6.24)
$[Ni(L_4)Cl]\cdot 4H_2O$	37.40(38.28)	4.10(4.72)	15.10(14.80)	6.20(6.33)
$[Mn(L_5)Cl]$	31.17(30.91)	2.89(2.39)	20.61(20.61)	17.25(17.63)
$[Co(L_5)Cl]$	30.22(30.69)	2.75(2.37)	20.29(20.46)	17.92(17.51)
$[Ni(L_5)Cl]$	30.80(30.70)	2.40(2.37)	20.67(20.47)	17.15(17.51)
$[Mn(L_6)Cl]$	39.21(39.55)	2.87(3.09)	5.43(5.77)	12.81(13.18)
$[Co(L_6)Cl]$	39.62(39.23)	2.65(3.07)	5.34(5.72)	13.47(13.08)
$[Ni(L_6)Cl]$	38.78(39.25)	3.42(3.07)	5.28(5.72)	12.75(13.08)

[1] Calculated values are given in parenthesis.

TABLE II The main IR frequencies (cm^{-1}) of β-lactamic antibiotics and their complexes

Compound	*O—H*	*N—H*	*C=O lactam*	*C=O amide*	$\nu_{asym}(COO)$	$\nu_{sym}(COO)$	$\Delta\nu$
$[Na(L_1)]$	–	–	1782	1694	1614	1387	227
$[Cu(L_1)_2(H_2O)_2]$	3400	–	–	1715	1615	1390	225
$[Ni(L_1)_2(H_2O)_2]$	3430	–	–	1715	1622	1390	232
$[Na(L_2)]$	–	3350	1777	1700	1621	1418	203
$[Ni(L_2)_2]\cdot 4(H_2O)$	3403	3285	1654	1639	1610	1386	224
$[Zn(L_2)_2]\cdot 3(H_2O)$	3425	3280	1654	1639	1603	1370	233
$[Cd(L_2)_2]\cdot 4(H_2O)$	3424	3281	1652	1637	1585	1370	215
$[Fe(L_2)_2Cl(H_2O)]\cdot H_2O$	3393	3321	1778	1647	1621	1419	202
$[La(L_2)_2Cl(H_2O)]\cdot H_2O$	3440	3343	1769	1648	1610	1410	200
$[Na(L_3)]$	–	3335	1777	1692	1603	1415	188
$[Ni_2(L_3)_2Cl_2(H_2O)_2]$	3496	3249	1674	1638	1603	1386	217
$[Co_2(L_3)_2Cl_2(H_2O)_2]$	3503	3242	1680	1644	1601	1391	210
$[Cu_2(L_3)_2Cl_2(H_2O)_2]$	3505	3231	–	1656	1630	1390	240
$[Cd_2(L_3)_2Cl_2(H_2O)_2]$	3498	3272	1674	1638	1594	1391	203
$[Zn_2(L_3)_2Cl_2(H_2O)_2]$	3500	3256	1680	1640	1615	1388	227
$[Na(L_4)]$	–	3260	1750	1680	1580	1390	190
$[Mn(L_4)Cl]\cdot 3(H_2O)$	3420	–	–	1660	1615	1380	235
$[Co(L_4)OAc]\cdot 3(H_2O)$	3410	–	–	1660	1610	1390	220
$[Ni(L_4)Cl]\cdot 4(H_2O)$	3400	3240	1750	1640	1610	1380	230
$[Cu(L_4)Cl]\cdot 3(H_2O)$	3420	3220	1750	1660	1610	1360	250
$[Zn(L_4)Cl]\cdot 3(H_2O)$	3400	3260	1750	1640	1620	1380	240
$[Cd(L_4)OAc]$	–	3260	1750	1640	1580	1380	200
$[Hg(L_4)Cl]$	–	3260	1750	1660	1580	1390	190
$[Na(L_5)]$	–	3280	1745	1650	1585	1380	205
$[Mn(L_5)Cl]$	–	3290	1760	1680	1595	1390	205
$[Co(L_5)Cl]$	–	3285	1760	1665	–	1370	–
$[Ni(L_5)Cl]$	–	–	1750	1680	1600	1380	220
$[Cu(L_5)Cl]$	–	3280	1755	1670	1580	1370	210
$[Zn(L_5)Cl]$	–	3285	1755	1665	1600	1380	220
$[Pd(L_5)Cl]\cdot 5H_2O$	3500	–	1770	1690	1620	1400	220
$[Na(L_6)]$	–	3290	1740	1660	1620	1400	220
$[Mn(L_6)Cl]$	3380	–	1730	1680	1630	1390	240
$[Co(L_6)Cl]$	3360	–	1730	1670	1620	1390	230
$[Ni(L_6)Cl]$	3360	–	1730	1700	1630	1390	240
$[Pd(L_6)Cl]$	3380	3260	1780	1745	1655	1400	255

Thermal gravimetric analyses of the L_1 and L_3 metal complexes show a mass loss equivalent to two water molecules in the 150–170°C range, which means that these water molecules are coordinated to the metal ions. Metal complexes of the L_2 ligand and manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II) complexes of the L_4 ligand have lattice water only.

The coordination site and the bonding properties of the ligands are discussed on the basis of spectroscopic analysis and the IR spectroscopy is an important tool to determine the site of coordination. The IR spectra of the ligand and the respective complexes show similarities to one another and were recorded in the region between 4000–200 cm^{-1} (Tab. II).

Infrared spectra of the L_1, L_2 and L_3 antibiotics change in frequency and intensity, when complexed, on the band corresponding to the stretching vibration of the beta lactamic carbonyl group which occurs in the 1777–1782 cm^{-1} range [14–17]. The spectra of the L_1-L_3 metal complexes show this band shifted around 1640–1680 cm^{-1} range suggesting that coordination of the ligands occurs through the oxygen atom of the above mentioned carbonyl group. The exceptions are the Fe(III) and La(III) complexes of L_2 ligand.

Infrared spectra of the L_4, L_5 and L_6 ligands show the band belonging to the stretching vibration of the beta lactamic carbonyl group in the 1740–1750 cm^{-1} range. These bands are not shifted when complexed suggesting that the coordination of the ligands does not occur through this carbonyl group, with the exception of the Pd(II) complex of L_6.

A carboxylate group can bind to the metal atom either as a monodentate or a bidentate ligand distinguished by the relative positions of the antisymmetric and symmetric stretching vibrations [22]. IR spectra for the complexes obtained indicate that the separation value ($\nu_{asym}-\nu_{sym}$) COO is $> 200\,cm^{-1}$ suggesting monodentate bonding for the carboxylate group for all beta lactamic ligands. The presence of M—O stretching vibrations at 270 and 460 cm^{-1} for the metal complexes support coordination by the L_1 and L_2 ligands as bidentate monoanionic chelating agents whereas the L_3, L_4 and L_6 ligands behave as tridentate monoanionic species [22]. It is assumed that L_5 behaves as a tetradentate monoanionic species. A broad diffuse band of medium intensity in the 3360–3503 cm^{-1} region may be assigned to an OH stretching vibration for the coordinated or lattice water.

Corrected magnetic moments have been calculated from the molar magnetic susceptibilities using Pascal's constant [23] and the values for the copper(II) complexes are in the 1.8–2.3 BM range indicating in some cases that orbital contributions could arise. The manganese(II) complexes have

magnetic moment values in the 5.5–5.7 BM range as predicted for high spin systems with five unpaired electrons while the cobalt(II) complexes have magnetic moments in the 4.4–4.6 BM range due to the presence of three unpaired electrons. The nickel(II) complexes have magnetic moment values in the 2.9–3.2 BM range which are characteristic of systems with two unpaired electrons and greater than the spin only value, presumably due to the orbital contribution resulting from the transfer of an electron from the $d_{x^2-y^2}$ orbital to the d_{xy} orbital. Interestingly the $[Fe(L_2)_2Cl \cdot H_2O]$ complex has a magnetic moment value of 3.6 BM at room temperature indicating the presence of a mixture of high-spin and low-spin octahedral complexes [14].

The room temperature EPR spectra of the powder sample of the manganese(II) complexes showed a single broad signal with poor resolution of the hyperfine structure. The calculated g value of 2.03 agrees well with the results obtained previously for high spin manganese(II) complexes. The EPR spectra of the copper(II) complexes showed a single broad band with poor resolution of the hyperfine structure on both sides of the main signal. The calculated $g_{\|}$ and $g_{\perp}$ values were in the 2.14–2.21 and 2.03–2.05 regions, respectively. The existence of $g_{\perp}$ values lower than those of their respective $g_{\|}$ values ($g_{\|} > g_{\perp} > 2.20023$) indicates [24] that the unpaired electron most likely resides in the $d_{x^2-y^2}$ orbital having $^2B_{1g}$ as a ground state term. The axial symmetry parameter, $G > 4$ obtained by the relation $(g_{\|}-2)/(g_{\perp}-2)$ suggests [25] that there is no exchange interaction between the copper centers. The EPR spectrum of $[Fe(L_2)_2Cl \cdot H_2O]$ displays two rather weak resonances with no hyperfine splitting due to nuclear spin. In $S = 3/2$ complexes when the zero-field splitting is large, only one allowed transition is detected with '$g_{\|}$' = 2 and '$g_{\perp}$' = 4 values [14].

The UV-visible spectra of the free ligands and the L_1-L_3 metal complexes in DMSO solution present major absorption maxima assigned to the $\pi \rightarrow \pi^*$ transitions within the organic molecule. The electronic spectra of the manganese(II) complexes show very weak absorptions in the visible region probably due to spin-orbit forbidden transitions. The cobalt(II) complexes present two bands which may be assigned, considering O_h symmetry around the metal, to $^4A_{2g} \rightarrow {}^4T_{2g}$ and $^4A_{2g} \rightarrow {}^4T_{1g}$ (F) transitions, respectively. The nickel complexes also showed two bands which may unambiguously be assigned [26] as $^3A_{2g} \rightarrow {}^3T_{2g}$ and $^3A_{2g} \rightarrow {}^3T_{1g}$ (F) transitions, respectively, arising from the octahedral geometry of nickel(II). The copper(II) complexes exhibit two broad bands also assignable to $^2B_{1g} \rightarrow {}^2E_{2g}$ transitions considering D_{4h} symmetry, which are characteristic of tetragonally elongated octahedral or square planar geometry [27]. The UV-visible spectra of the

L_4 and L_6 ligands and their metal complexes is not very informative but the formula and thermal gravimetric analyses suggest a tetrahedral structure.

Structure of Complexes

Clavulanic acid has several potential donor atoms but due to steric constraints, the ligand can provide a maximum of two donor atoms at any one time to coordinate the metal center. On the assumption that the coordination occurs through the carboxylate and lactamic oxygen atoms to the metal, it behaves as a bidentate ligand. Penicillin also coordinates Fe(III) and La(III) ions as a bidentate ligand through the carboxylate oxygen atom and the amide carbonyl group. Penicillin behaves as a tridentate ligand through the carboxylate and the amide and lactamic carbonyl groups when coordinating Ni(II), Zn(II) and Cd(II) ions. Ampicillin may coordinate metal ions through the carboxylate and the lactamic carbonyl group in the solid state as has been strongly suggested from vibrational spectroscopy. Further coordination of ampicillin ligand through the amino and amide carbonyl groups cannot be discarded. From inspection of molecular models it appear that the binding of two L_1, L_2 or L_3 ligands to metal ions is feasible and that an octahedral or a distorted octahedral configuration around the metal is possible.

On the other hand, L_4 and L_6 cephalosyorins may coordinate as tridentate ligands through the carboxylate, the amide carbonyl group and a further donor atom coming from the R_1 chain substituents. Molecular models suggest that the binding of one L_4 or L_6 ligand to the metal ions is possible with a tetrahedral or a distorted tetrahedral configuration around the metal. Cefazolin L_5 coordinates as a tetradentate ligand through the carboxylate, the amide carbonyl group and a further donor atom coming from the R_1 and R_2 chain substituents. Despite the crystalline nature of the products none proved suitable for x-ray structure determination.

Biological Activity Test

The susceptibility of certain strains of bacterium towards the ligand and metal complexes was judged by measuring the size of inhibition diameter. The results are shown in Table III. The complexes $[Cu(L_1)_2(H_2O)_2]$ and $[Ni(L_1)_2(H_2O)_2]$ when tested against E. coli and P. aeruginosa were found to possess, respectively, higher activity than the antibiotic itself. The L_2 complexes were found to have no activity against S. aureus and B. cereus while Ni(II), Cd(II) and Fe(III) complexes of L_2 show that they have a very

TABLE III Antibacterial activity of β-lactamic antibiotics and their complexes

Compound	(μg/disc)	Zone of inhibition (mm)											
		E.C.	K.P.	P.V.	P.M.	P.A.	Sa.sp	Sh.sp	S.E.	S.T.	S.A.	S.V.	B.C
Amox./(L_1)	200	45	17	45		10				22	57		58
$[Cu(L_1)_2(H_2O)_2]$	200	55	11	39		10				18	56		55
$[Ni(L_1)_2(H_2O)_2]$	200	52	13	40		15				15	53		50
$[Na(L_2)]$	20	–				–					34		11
$[Ni(L_2)_2] \cdot 4H_2O$	20	–				7					–		–
$[Zn(L_2)_2] \cdot 3H_2O$	20	–				–					–		–
$[Cd(L_2)_2] \cdot 4H_2O$	20	–				7					–		–
$[Fe(L_2)_2Cl\ H_2O]H_2O$	20	–				10					–		–
$[La(L_2)_2Cl\ H_2O]H_2O$	20	–				–					–		–
$[Na(L_3)]$	10	13	12			14	12	14			14	15	
$[Ni_2(L_3)_2Cl_2(H_2O)_2]$	10	12	10			15	11	11			11	11	
$[Co_2(L_3)_2Cl_2(H_2O)_2]$	10	15	12			10	10	11			13	12	
$[Cu_2(L_3)_2Cl_2(H_2O)_2]$	10	14	15			15	13	12			13	10	
$[Cd_2(L_3)_2Cl_2(H_2O)_2]$	10	14	13			14	15	13			11	14	
$[Zn_2(L_3)_2Cl_2(H_2O)_2]$	10	15	11			15	15	14			12	14	
$[Na(L_4)]$	400	10	12		13	–			10		22		
$[Mn(L_4)Cl] \cdot 3H_2O$	400	–	–		–	–			–		14		
$[Co(L_4)AcO] \cdot 3H_2O$	400	–	–		–	–			–		–		
$[Ni(L_4)Cl] \cdot 4H_2O$	400	–	–		–	–			–		–		
$[Cu(L_4)Cl] \cdot 3H_2O$	400	13	–		17	–			12		24		
$[Zn(L_4)Cl] \cdot 3H_2O$	400	15	–		8	–			12		25		
$[Cd(L_4)AcO]$	400	12	–		13	–			13		22		
$[Hg(L_4)Cl]$	400	29	25		22	13			28		38		
$[Na(L_5)]$	100	23	19		15	–			21		27		
$[Mn(L_5)Cl]$	100	20	10		13	–			11		18		
$[Co(L_5)Cl]$	100	30	32		20	–			29		35		
$[Ni(L_5)Cl]$	100	40	23		21	–			23		35		
$[Cu(L_5)Cl]$	100	25	19		15	–			22		27		
$[Zn(L_5)Cl]$	100	34	33		24	–			30		38		
$[Pd(L_5)Cl] \cdot 5H_2O$	100	–	–		–	–			–		–		

E.C. Scherichia Coli ATCC 10536, K.P = Klebsiella pneumoniae 10031, P.V = Proteus vulgaris ATCC 9920, P.M = Proteus mirabilis ATCC 35659, P.A. = Pseudomonas aeruginosa ATCC 9027, Sa.sp = Salmonella sp ATCC, Sh.sp = Shigella, sp, S.E. = Salmonella enteritidis ATCC 497, S.T = Salmonella typhimurium ATCC 14028, S.A = Staphilococcus aureus ATCC 6538, S.V = Streptococcus viridans and B.C = Bacillus Cereus ATCC 9634.

good activity as bactericides against P. aeruginosa even though penicillin has no activity at all. The L_3 complexes show similar antibacterial activity to the ampicillin with the best Cd(II) and Zn(II) complexes against Salmonella sp and Cu(II) complex against K. pneumoniae.

The complexes of L_4 and L_5 cephalosporins almost always show better bactericidal activity than the antibiotics themselves with the exception of the Mn(II) complexes. The improvement in antibacterial activity by the cephalosporins complexes in some cases ([Ni(L_5)Cl] and [Zn(L_5)Cl]), is around 70% over the antibacterial activity showed by the respective antibiotics.

Correlation Between Structure and Antibacterial Activity

As shown in Table III, the antibacterial activity of octahedral complexes of clavulanic acid, penicillin and ampicillin were found to possess, in general, similar activity to the antibiotic itself, whereas the non-octahedral complexes of cephalexin and cefazolin show in general, higher activity than the antibiotic itself. In the former the metal is coordinated by the beta-lactamic carbonyl ring which appears to be more amenable to hydrolysis by beta-lactamases due to the weakening of the C=O beta-lactamic bond, whilst in the latter, the beta-lactamic carbonyl group is protected by the chain formed through the coordinated metal with the carboxylate and amide groups.

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