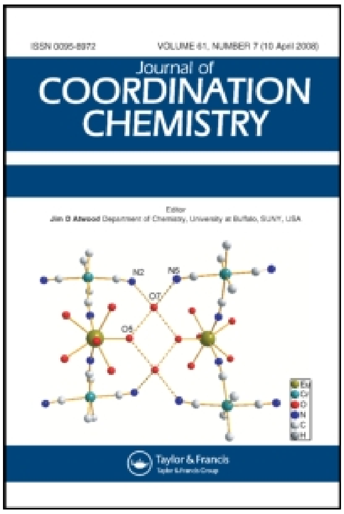

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SYNTHESIS AND CHARACTERIZATION OF METAL COMPLEXES WITH AMPICILLIN

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The reaction, in water, of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) ions with sodium ampicillinate at room temperature has allowed isolation of dimers with the following general formula $[M(amp)Cl]_2 \times nH_2O$ ($n = 1.5\text{-}3.2$). The complexes were characterized by elemental analyses, conductivity measurements, magnetic susceptibilities and spectroscopic methods (IR, Raman, EPR and UV-Visible). A dinuclear structure based on octahedrally coordinated metal ions is proposed.

Keywords: ampicillin; cobalt(II); nickel(II); copper(II); zinc(II); cadmium(II)

INTRODUCTION

The chemical constitution and structure of an antimicrobial compound is clearly a valuable piece of information. Where the structure is known it is always studied carefully to determine whether a structural analogy exists with part or the whole of a biologically important molecule. A structural analogy with a biological molecule may point directly to the site of biochemical action of an inhibitor.

Although ampicillin has special importance among β-lactam antibiotics because of its considerable acid stability and its activity against both G(+) and G(−) bacteria,[1,2] its activity against some bacteria such as Klebsiella and P. aeruginosa is not sufficient.[2,3] Synthesis of metal complexes of ampicillin should be important to increase effectiveness of ampicillin against some G(−) bacteria for a broad antibacterial spectrum.

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Ampicillin in dosage forms has been determined quantitatively by polarographic techniques after acid hydrolysis.[4] More recently,[5] an amperometric study of Ni:(II) and Co(II) complexes of ampicillin has shown that 1:1 complexes are formed and that they undergo reduction at the dropping mercury electrode. Combined pH and spectrophotometric study[6] on the complex of Cu(II) with ampicillin was carried out in water at fixed ionic strength, indicating formation of complexes of the types: $Cu(amp)^+$, $Cu(amp)_2$, $Cu(H_{-1}amp)$, $[Cu(H_{-1}amp)(amp)]^-$ and $[Cu(H_{-1}amp)_2]^{2-}$. Ambidentate nature of the ligand and its possible modes of coordination with Cu(II) at different pH values were suggested on the basis of electronic spectral measurements.

Lastly,[7] the complex formation equilibria involved in the binary and ternary systems, M(II)-amp and M(II)-amp-X where M(II) = Cu, Ni, Co, Zn and Cd, X = 2,2′-bipyridyl and 1,10-phenanthroline, were studied. The mode of chelation was ascertained by conductivity measurements. Spectral characteristics of some ternary complex systems were discussed and it is argued that the ampicillin anion acts as a bidentate ligand. It was suggested that the ampicillin is bound to the metal ion through the carbonyl and the amino group of the side chain.

EXPERIMENTAL

Materials

Sodium ampicillinate (pure powder, 99.9%) was obtained from Calox Labs. $NiCl_2$, $CoCl_2{\cdot}6H_2O$, $CuCl_2{\cdot}2H_2O$, $ZnCl_2$ and $CdCl_2$ along with other chemicals and reagents were of analytical grade.

Physical Measurements

Fourier transform infrared (FTIR) spectra of the ampicillin and its metal complexes as KBr pellets were recorded between 4000-400 cm^{-1} with a Perkin Elmer Series 2000 apparatus. FTIR spectra as polyethylene pellets were registered between 450 and 120 cm^{-1} by using a 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. Raman spectra of metal complexes were scanned from 50 to 3500 cm^{-1} on a Brucker FRA 106 instrument mounted on an IFS 66 FTIR optical bench. UV-Visible spectra were recorded by using a Perkin Elmer recording spectrometer. The metals were determined by atomic absorption spectroscopy after destruction by hot concentrated HNO_3 and $HClO_4$ 1:1 mixture. The contents of carbon, nitrogen, hydrogen and sulphur were analyzed by the microlabs in the

TABLE I Physical data, elemental analyses[1] and magnetic moments for the metal complexes of ampicillin

Compound	*Colour*	*Yield(%)*	*T° Decomp*	*C(%)*	*H(%)*	*N(%)*	*S(%)*	*M(%)*	μ_{eff}*(BM)*
$[Ni_2(amp)_2]Cl_2 \cdot 2H_2O$	Light Green	33.63	170-200	41.37 (41.72)	4.61 (4.35)	9.05 (9.13)	6.72 (6.45)	12.89 (12.76)	3.4
$[Co_2(amp)_2]Cl_2 \cdot 2H_2O$	Rose	48.95	220-235	41.83 (41.70)	4.65 (4.34)	8.95 (9.12)	6.69 (6.95)	12.45 (12.79)	5.2
$[Cu_2(amp)_2]Cl_2 \cdot 2H_2O$	Dark Green	20.96	160-180	40.96 (41.29)	4.15 (4.30)	9.28 (9.03)	7.21 (6.88)	13.91 (13.66)	2.3
$[Cd_2(amp)_2]Cl_2 \cdot 3.2H_2O$	Yellow	65.42	192-200	36.71 (36.59)	3.60 (3.85)	8.32 (8.00)	6.38 (6.10)	21.62 (21.42)	Diam.
$[Zn_2(amp)_2]Cl_2 \cdot 1.5H_2O$	Yellow	20.78	190-210	41.56 (41.52)	4.64 (4.33)	9.10 (9.08)	6.75 (6.92)	14.39 (14.14)	Diam.

[1] Calculated values are given in parenthesis.

Venezuelan Institute of Scientific Research (IVIC). Magnetic susceptibilities were measured on a John Matthey Susceptibility Balance.

Preparation of the Complexes

To a solution of sodium ampicillinate (2 mmol) in water (10 mL) was slowly added a solution of the metal chloride (2 mmol) in water (10 mL) and the mixture was stirred for 1 h. The solid complex which separated was removed by filtration and washed with water, ethanol and ether. The compounds were dried under vacuum at room temperature for 48 h.

RESULTS AND DISCUSSION

Analytical data show that the complexes have the stoichiometries presented in Table I. They are insoluble in water and in common polar and non-polar organic solvents, they decompose around 200°C without melting. The metal complexes are soluble in ethanol at pH 8 where they behave as 2:1 electrolytes.[9]

IR Spectra

The IR spectrum of the sodium ampicillinate shows significant bands at 3325 cm^{-1} ν(N-H), 1777 and 1692 cm^{-1} ν(C=O) from the β-lactam and amide carbonyl groups,[10] respectively, and 1603 and 1415 cm^{-1} bands due to ν_{as}(COO) and ν_s(COO), respectively from the carboxylate group. On the other hand the IR spectra of the metal complexes show as the most relevant bands those at 3231-3272 cm^{-1} ν(N-H) and 1594-1680 cm^{-1} ν_{as}(COO) + $\nu(C{=}O)_{amide}$ + $\nu(C{=}O)_{lactamic}$. These assignments suggest that coordination of the ligand occurs through the O_{carbox}, O_{ceto} and N_{imino} atoms.

A carboxylate ligand can bind to the metal atom either monodentate or bidentate as suggested by Nakamoto.[11] The separation between ν_{as}(COO) and ν_s(COO) vibrational modes was suggested as <200 cm^{-1} for a bidentate ligand and >200 cm^{-1} for a monodentate carboxylate ligand.[12-15] IR spectra of complexes obtained in this study indicate that the separation value (ν_{as} − ν_s)COO is >200 cm^{-1} (Table II), suggesting a monodentate mode of bonding for the carboxylate group of the ampicillinate ligand.

From the infrared data, the presence of water in these complexes can be inferred. These water molecules seem to be structurally well defined as suggested by the sharpness of the bands assigned to the (O-H) stretching vibrations (*ca.* 3500 cm^{-1}). The vibrations of carbonyl groups ($(C{=}O)_{amide}$ and $(C{=}O)_{lactam}$

TABLE II The main IR frequencies (cm^{-1}) and formation constants of sodium ampicillinate and its complexes

Compounds	*O-H*	*N-H*	*C=O (lactam)*	*C=O (amide)*	v_{as} *(COO)*	v_s*(COO)*	Δv	*log* K^a	*log* K^b
Na(amp)	3500	3335	1777	1692	1603	1415	188	-	-
$[Ni_2(amp)_2]Cl_2 \cdot 2H_2O$	3496	3249	1674	1638	1603	1386	217	3.66	3.78
$[Co_2(amp)_2]Cl_2 \cdot 2H_2O$	3503	3242	1680	1644	1601	1391	210	3.12	3.12
$[Cu_2(amp)_2]Cl_2 \cdot 2H_2O$	3505	3231	^{c}	1656	1630	1390	240	4.79	6.38
$[Cd_2(amp)_2]Cl_2 \cdot 3.2H_2O$	3498	3272	1674	1638	1594	1391	203	-	2.79
$[Zn_2(amp)_2]Cl_2 \cdot 1.5H_2O$	3500	3256	1680	1640	1615	1388	227	2.98	3.17

[a] Formation constants of binary complexes were taken from Ref 16 [b] From Ref 7 [c] overlapped

stretching vibrations) appear to be shifted to lower wavenumber with respect to the IR spectrum of sodium ampicillinate; they are partial or totally overlapped with the antisymmetric COO stretching frequency, as can be seen in Figure 1. This could indicate that these carbonyl groups are also involved in the metal-ligand bond. New absorptions were observed in the range of 550-620 cm^{-1}, which were characterized as absorptions of M-O bonds.[11]

In order to identify bands corresponding to either metal-ligand or metal-water vibration modes, the far infrared and Raman spectra of compounds were investigated. Unfortunately, the IR and Raman spectra of the sodium ampicillinate show a higher number of bands than in the IR and Raman spectra of the metal complexes making study difficult. In all spectra, the lack of coincidental infrared and Raman frequencies in the mid- and far-IR region for the ampicillinate complexes may suggest a center of inversion.

In order to examine the effect of coordination and hydrogen bonding Nakamoto *et. al.*[11] have made extensive measurements of the COO stretching frequencies of various metal complexes of amino acids and related ligands. It was found that separation between the two frequencies (υ_{as} - υ_s)COO can be related with the covalent character of the M-O bond, which in turn, has been related to stability constants in acetylacetonate and oxalato complexes.[11] Following this criteria, we have found that the separation value (υ_{as} - υ_s)COO bears a direct relation with the stability constant values of the respective mono adducts for the metal complexes, further supporting our proposition of coordination around two metal ions with two ampicillin molecules. The frequency difference ($\Delta\upsilon$) and log K values are given in Table II and the data show that they follow the order Zn(II) < Cu(II) > Co(II) > Ni(II) > Cd(II) which is in agreement with the order given by Irving and Williams.[17]

NMR and Mass Spectra

The ^{13}C and ^{1}H NMR spectra of the Zn(II) and Cd(II) complexes have been recorded. However, due to the poor solubility of compounds in DMSO-d_6 these spectra have a very low signal/noise ratio. The mass spectra of metal complexes were not helpful in determining the molecular weights due to decomposition.

Electronic and Magnetic Properties

The UV-visible spectrum of the free ampicillinate in ethanolic solution presents two bands at 27397 and 30030 cm^{-1} which can also be observed in all metal complexes; for Ni(II), Co(II) and Cu(II) complexes the absorptions were blue shifted (2400-1000 cm^{-1}) in comparison with free ampicillinate. These

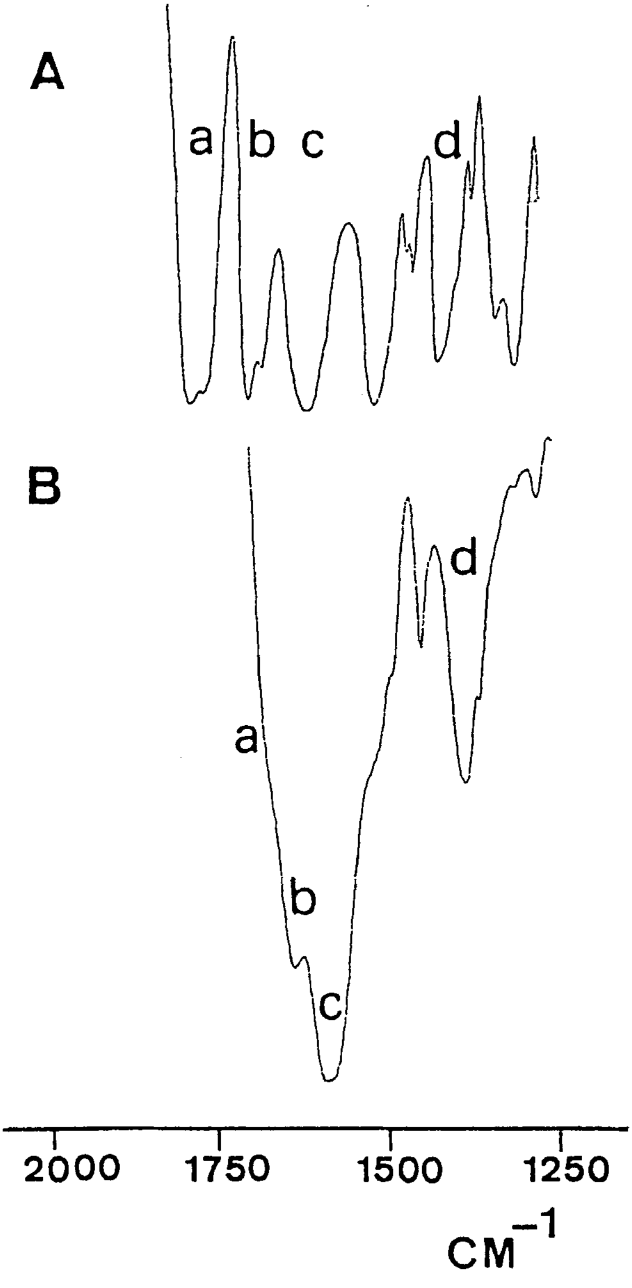

FIGURE 1 Infrared spectra of Na(amp) (A) and $Cd_2(amp)_2Cl_2$ (B) in the solid state. Stretching CO_{lactam} (a), stretching CO_{amide} (b), antisymmetric COO stretching (c) and symmetric COO stretching (d).

complexes also show bands at 25707, 25844 and 24695 cm^{-1} respectively, that may correspond to charge transfer or to *d-d* transitions. The copper complex also has a *d-d* transition at 15151 cm^{-1}.

The magnetic moment values per ion in binuclear complexes show that the complexes of Ni(II), Co(II) and Cu(II) are high spin with S = 1, 3/2 and 1/2 ground states respectively, and they fall in the ranges associated with high spin ions in octahedral fields. The Ni(II) complex has a magnetic moment of 3.4 BM, a value typical for d^8 systems with two unpaired electrons. The Co(II) complex has a magnetic moment of 5.2 BM which is characteristic of high spin d^7 systems. The rather high value of the magnetic moment for the freshly prepared Cu(II) complex (2.3 BM) could be explained, in part, by the fact that spin-orbital coupling in the ion can mix the ground state representing no orbital momentum with higher levels of identical multiplicity, resulting in a small orbital contribution;[18] however, the presence of impurities cannot be discarded. The

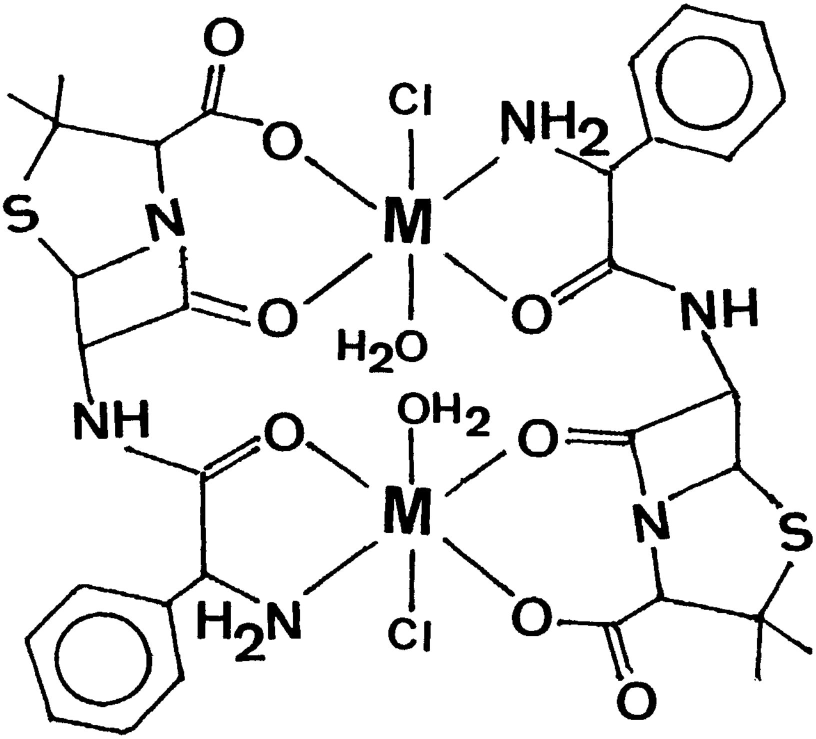

FIGURE 2 The tentative structure of complexes $[M_2(amp)_2]Cl_2$.

powder EPR spectrum of $[Cu_2(amp)_2]Cl_2{\cdot}2H_2O$, displays two g values, $g_{\|} = 2.21$ and $g_{\perp} = 2.05$ ($G = 4.2$) which is consistent with an elongated tetragonal octahedral geometry.[19] The G value indicates that the local tetragonal axes are aligned in a parallel fashion or only slightly misaligned.[20]

The Structure of the Complexes

It is well known that ampicillin exists as a zwitterionic species and the -COOH and the $-NH_3^+$ groups are successively deprotonated in the pH ranges 2-4 and 6-8, respectively. At physiological pH, ampicillin remains in the fully deprotonated amp^- form, which,[6,21] coordinates metal ions as a bidentate ligand in the pH range $5 < pH < 8$ using the amino nitrogen and the amide carbonyl oxygen atoms. The thiazolidine S atom is unlikely to coordinate in this mode due to angle strain. Ampicillin may also coordinate metal ions through carboxylate and the β-lactamic carbonyl groups in the solid state as has been strongly suggested in the present study from vibrational spectroscopy. We suggest that the complexes take structures shown in Figure 2. However, the Zn(II) complex might present a different structure as it does not have the two water molecules required to complete the coordination sphere around the metal centers. There is no relevant spectroscopic evidence to support such a difference.

Since none of these complexes have been analyzed by X-ray methods there is no structural information concerning them. From an inspection of molecular models it appears that binding of two ampicillins to two metal ions is feasible and that a octahedral or distorted octahedral configuration around the metals is possible.

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