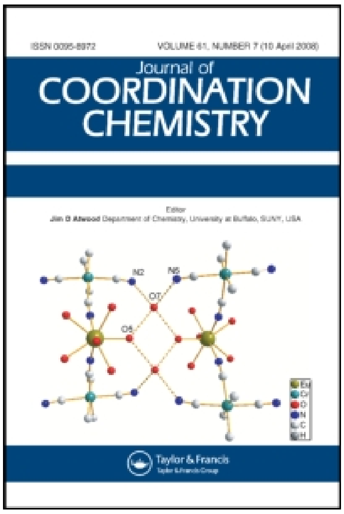

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SYNTHESIS AND CHARACTERIZATION OF METAL COMPLEXES WITH PENICILLIN

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The reaction of Ni(II), Zn(II), Cd(II), Fe(III) and La(III) ions with sodium penicillinate at room temperature has allowed the isolation of two types of complexes with the following general formulae: $M(pen)_2 \cdot nH_2O$ (M = Ni(II), Zn(II), Cd(II); $n = 3,4$) and $M(pen)_2 \cdot Cl \cdot nH_2O$ (M = Fe(III), La(III); $n = 2$). The complexes were characterized by physicochemical and spectroscopic methods. A monomeric structure is proposed with octahedrally coordinated metals ions. The divalent ions are coordinated through the amide and β-lactam carbonyls and a carboxylate group from penicillin while the trivalent ions are coordinated through the carboxylate group and the amide carbonyl only.

Keywords: Penicillin; nickel(II); iron(III); zinc(II); cadmium(II)

INTRODUCTION

The chemical constitution and structure of an antimicrobial compound is 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 all of a biologically important molecule. A structural analogy with a biological molecule may point directly to the site of biochemical action of an inhibitor.

Penicillin is a broad spectrum β-lactam antibiotic drug that is used as the first medicine in the treatment of the majority of infectious diseases because

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of its activity against both G(+) and G(−) bacteria,[1,2] although its activity against some bacteria appears to be insufficient.[2,3] It is known to inhibit protein synthesis on a ribosome by causing misreading of the genetic codes.[4]

The transfer of genetic information for the synthesis of specific proteins is influenced by metal ions which bind with nucleotide fragments, with the enzyme protein or with the drug itself.[5,6] Coordination of the drug with the enzyme-bound metal ions may cause selective denaturation of the enzyme protein.[7]

There are many reports in the literature of penicillin metal complexes and most of these are solution studies in which no compounds were isolated. With a view to getting some idea about the nature of metal–drug interactions, we have studied complex formation of Ni(II), Zn(II), Cd(II), Fe(III) and La(III) with penicillin.

EXPERIMENTAL

Materials

Anhydrous sodium penicillinate (pure powder, 99.9%) was obtained from Calox Labs. $NiCl_2$, $FeCl_3$, $LaCl_3$, $ZnCl_2$ and $CdCl_2$ along with other chemicals and reagents used were of analytical grade. All solvents were distilled using standard techniques before use.

Physical Measurements

Fourier transform infrared (FTIR) spectra of the penicillin 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 and 120 cm^{-1} by using a Bruker IFS 66V spectrophotometer. Spectra were scanned with 2 cm^{-1} resolution. 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 Bruker FRA 106 instrument mounted on an IFS 66 FTIR optical bench. UV–Visible spectra were recorded 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 sulfur 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. EPR spectra were recorded on a Brucker ECS 106 spectrometer by the X-band method.

Preparation of Complexes

To a solution of sodium penicillinate (2 mmol) in water (10 mL) was added slowly 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 nonpolar organic solvents and they decompose around 200°C without melting. The metal complexes are soluble in DMSO and ethanol at pH 8 where they behave as nonelectrolytes.[8]

IR spectra

The IR spectrum of the sodium penicillinate shows as the most significant bands those at 1777 and 1700 cm^{-1} corresponding to stretching vibrations ν(C=O) from the β-lactam and amide carbonyl groups,[9] respectively, and 1621 and 1418 cm^{-1} bands due to asymmetric ν_{asym}(COO) and symmetric ν_{sym}(COO) vibrations, respectively, from the carboxylate group.

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

Compound	*T° decomp.*	*Yield* (%)	*C* (%)	*H* (%)	*N* (%)	*S* (%)	$\mu_{eff.}$ (*BM*)
$Ni(pen)_2 \cdot 4H_2O$	255	60	48.08 (48.20)	5.38 (5.27)	6.84 (7.03)	7.87 (8.03)	2.86
$Zn(pen)_2 \cdot 3H_2O$	250	75	48.61 (48.69)	5.36 (5.09)	6.98 (7.13)	8.06 (8.15)	
$Cd(pen)_2 \cdot H_2O$	248	68	45.27 (45.16)	4.72 (4.94)	6.58 (6.59)	7.31 (7.53)	
$Fe(pen)_2Cl \cdot 2H_2O$	270	80	48.54 (48.50)	5.11 (4.79)	6.96 (7.06)	8.35 (8.07)	3.60
$La(pen)_2Cl \cdot 2H_2O$	264	50	42.64 (42.93)	4.65 (4.47)	6.03 (6.26)	7.17 (7.16)	

[a] Calculated values are given in parenthesis.

In the spectra of the complexes changes in frequency and intensity are observed on the bands corresponding to the stretching vibrations mentioned above. The IR spectra of the metal (II) complexes show as the most relevant bands those at 1652–1654 cm^{-1} ν(C=O) lactam and 1637–1639 cm^{-1} ν(C=O) amide groups, suggesting that coordination of the ligand occurs through the oxygen atoms from the carbonyl groups. On the other hand the IR spectra of the metal (III) complexes show as the most prominent bands those at 1769–1778 cm^{-1} ν(C=O) lactam and 1647–1648 cm^{-1} ν(C=O) amide stretching vibrations, suggesting that the lactam carbonyl oxygen atom does not coordinate to the metal ions.

A carboxylate ligand can bind to the metal atom either as a monodentate or a bidentate ligand as suggested by Nakamoto[10] and the separation value between ν_{asym}(COO) and ν_{sym}(COO) vibrations has often been used to diagnose the coordination modes of carboxylate groups. It was suggested a difference < 200 cm^{-1} for bidentate ligand and > 200 cm^{-1} for monodentate carboxylate ligand.[11–14] IR spectra for the complexes obtained presently (Table II) indicate that the separation value ($\nu_{asym} - \nu_{sym}$)COO is > 200 cm^{-1} suggesting monodentate bonding for carboxylate group of the penicillinate ligand. From the infrared data, the presence of water in these complexes can be inferred but there is no evidence about coordination of water. These water molecules seem to be structurally well defined as suggested by the sharpness of the bands assigned to the (O–H) stretching vibrations around 3400 cm^{-1}. The vibrations of carbonyl groups of metal(II) complexes have the (C=O) amide and the (C=O) lactam stretching vibration bands partially or totally overlapped with the antisymmetric COO stretching frequency, as shown in Figure 1.

In order to identify bands corresponding to either metal–ligand or metal–water vibration modes, the far infrared (FIR) and Raman spectra of compounds were investigated. Unfortunately, the FIR and Raman of the sodium penicillinate show a higher number of bands than in the FIR and

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

Compound	*O–H*	*N–H*	*C=O lactam*	*C=O amide*	ν_{asym} *(COO)*	ν_{sym} *(COO)*	$\Delta\nu$
Na(pen)	3450	3350	1777	1700	1621	1418	203
$Ni(pen)_2 \cdot 4H_2O$	3403	3285	1654[a]	1639	1610	1386	224
$Zn(pen)_2 \cdot 3H_2O$	3425	3280	1654[a]	1639	1603	1370	233
$Cd(pen)_2 \cdot 4H_2O$	3424	3281	1652[a]	1637	1585	1370	215
$Fe(pen)_2Cl \cdot 2H_2O$	3393	3321	1778	1647	1621	1419	202
$La(pen)_2Cl \cdot 2H_2O$	3440	3343	1769	1648	1610	1410	200

[a] Suggested values, attending that the bands are partially overlapped.

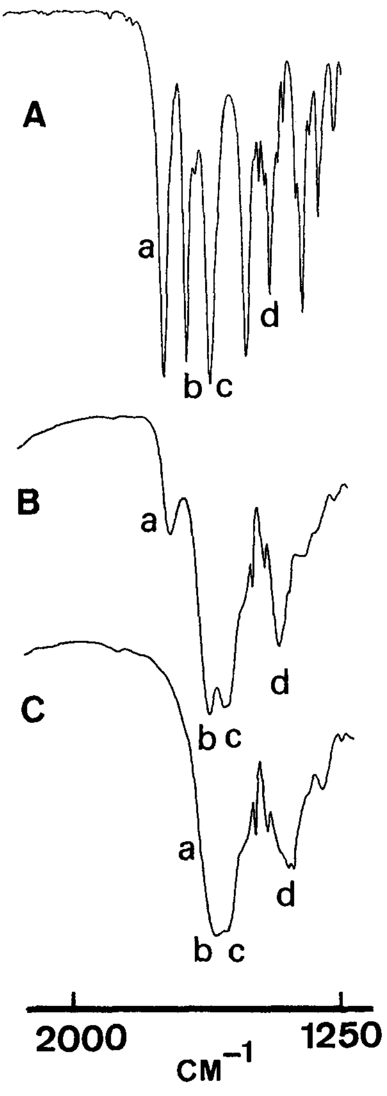


FIGURE 1 Infrared spectra of Na(pen) (A), $La(Pen)_2Cl \cdot 2H_2O$ (B), and $Zn(pen)_2 \cdot 3H_2O$ (C) in the solid state. Stretching CO lactam (a), stretching CO amide (b), antisymmetric COO stretching (c), and symmetric COO stretching (d).

Raman spectra of the metal complexes which makes study difficult and conclusions cannot be made. In all spectra, the lack of coincident infrared and Raman frequencies in the mid and FIR region for the metal(II) penicillin complexes may suggest center of inversion.

In order to examine the effect of coordination and hydrogen bonding, Nakamoto *et al.*[10] have made extensive measurements of the COO stretching frequencies of various metal(II) complexes of amino acids and related ligands. It was found that the separation between the two frequencies $(\nu_{asym} - \nu_{sym})$COO can be related with the covalent character of the M–O bond. The difference frequency $(\Delta\nu)$ is given in Table II and the data show that they follow the order Zn(II) > Ni(II) > Cd(II) which is in agreement with the order given by Irving and Williams.[15] Similar behavior has been previously described for the metal(II) complexes of ampicillin.[16]

Electronic and Magnetic Properties

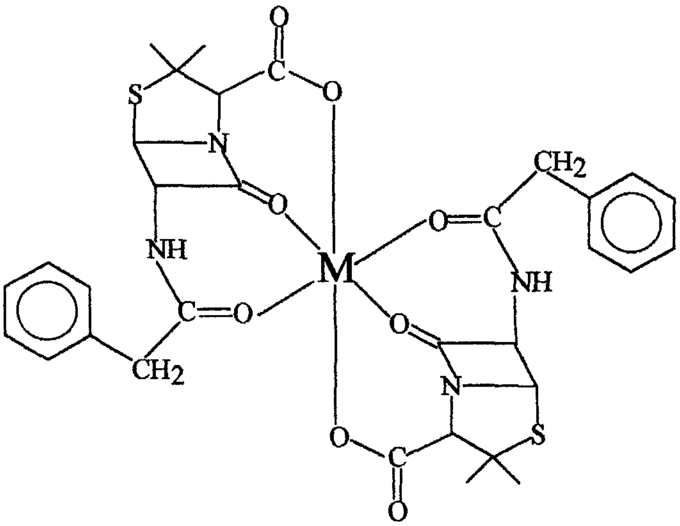
The UV–Visible spectra of free penicillinate and the metal complexes in DMSO solutions present two major absorption maxima in two distinct regions: 36240–39100 and 30300–31250 cm^{-1}, presumably due to intraligand excitation. The diamagnetic complexes of Cd(II) and La(III) also display intense charge transfer transitions in the visible region at 28700 and 23300 cm^{-1}, respectively. The Ni(II) complex also exhibits a weak absorption band at 25200 cm^{-1} that arises from a *d-d* transition.

The magnetic moment value shows that the complex of Ni(II) is high spin with $S = 1$ and falls in the range associated with high spin ions in octahedral fields. The nickel(II) complex has a magnetic moment of 2.86 BM, a value typical for high d^8 systems with two unpaired electrons. The magnetic moment of the Fe(III) complexes has a value of 3.6 BM at room temperature, which lies between the expected spin-only value of 5.92 BM for a high-spin complex and 2.3 BM for a low-spin complex. This anomalous value may be due to the presence of a mixture of high-spin and low-spin octahedral complexes, or to an antiferromagnetically-coupled binuclear complex. However, the IR spectral data suggest the absence of bridged OH group.[17] Therefore, this anomalous behavior may be due to the existence of a spin-crossover equilibrium. The existence of bridging carboxylate groups has been discounted from the IR results.

A powder EPR spectrum of $Fe(pen)_2 \cdot Cl \cdot 2H_2O$ displays two rather weak resonances near $g = 4$ and $g = 2$ (g is defined as $h\nu/\beta H$). No hyperfine splitting due to nuclear spin (^{57}Fe, $I = 1/2$, 2.8% natural abundance) was observed. The EPR spectrum of the iron (III) complex is similar to ferric phthalocyanine chloride in the solid state which has been variously reported as having a g value of 3.8[18] and 2.5[19] and it is thought to have a spin $S = 3/2$ since its magnetic moment is 3.22 BM. In $S = 3/2$ complexes when the zero-field splitting is large, only one allowed transition is detected having 'g' values between 2 and 4, with '$g_{\|}$' = 2 and '$g_{\perp}$' = 4.[20]

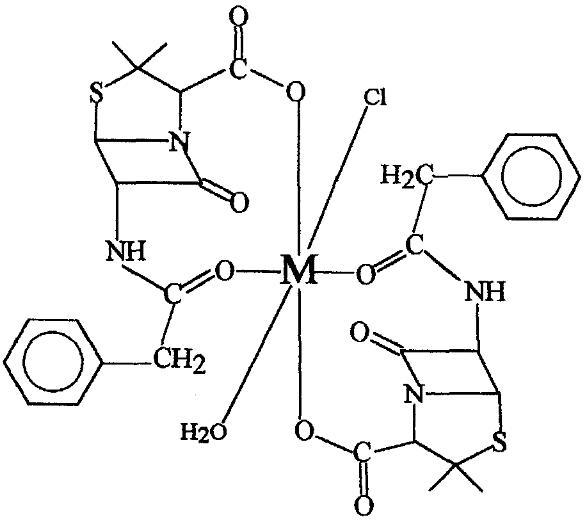
The Structure of the Complexes

At physiological pH, penicillin remains fully deprotonated and coordinates Ni(II), Zn(II) and Cd(II) ions as a tridentate ligand using the amide and the β-lactam carbonyl groups and the carboxylate oxygen atom as suggested in the present study by vibrational spectroscopy. The thiazolidine S atom and the amide N atom are unlikely to coordinate in this mode, due to angle strain. On the other hand, penicillin coordinates Fe(III) and La(III) ions as a bidentate ligand through the carboxylate oxygen atom and the amide carbonyl group. Complexes of Fe(III) generally have covalent bonds, but in the case of La(III) complexes, bonds are essentially electrostatic with the ionic radius for La(III) greater than that of Fe(III). This means that greater coordination numbers should be expected for La(III) but, in the absence of further evidence, the same structure has been proposed for both, although La(III) may involve coordination of two water molecules. The possibility that a chloride ion is in the outer sphere and that one of the ligands is tridentate and the other bidentate has been discarded from the conductivity measurements,



M = Ni(II), Zn(II), Cd(II)

FIGURE 2 The tentative structure of metal(II) complexes of penicillin.



M = Fe(III) , La(III)

FIGURE 3 The tentative structure of metal(III) complexes of penicillin.

which show that they are nonelectrolytes. On the basis of the above evidence and analyses, we suggest that the complexes have structures in the solid state as shown in Figures 2 and 3 for the metal(II) and metal(III) complexes respectively.

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

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