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Studies of transition metal (II) complexes with β-lactam ring

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Abstract
The complexes of Ni (II) and Cu (II) with β-Lactam-amoxicillin have been synthesized. The structures of these newly synthesized complexes were substantiated by elemental analysis, molar conductivities, infrared, electronic absorption spectra and magnetic moment measurements. On the basis of these analyses it has been confirmed that direct reaction of metal salts with amoxicillin-suspension leads to formation of complexes. The tridentate nature of ligand and square planar geometry of the complexes has been established. The ligation centers of the amoxicillin as NH_2, NH and hydroxyl groups have also been confirmed. Solubility of the complexes has been determined by using different solvents. Melting point of the complexes was determined by the open capillary tube and hence is uncorrected.

Keywords: Antibiotic, amoxicillin, β-Lactam

Introductions
Antibiotics that possess the β-lactam ring structure are predominant class of agents currently used for the chemotherapy of bacterial infections. In addition to a broad spectrum of antibacterial action, two properties contribute to the unequaled importance of β-lactam antibiotics in chemotherapy: a potent and rapid bactericidal action against bacteria in the growth phase and a very low frequency of toxic and other adverse reactions in the host. The uniquely lethal antibacterial action of these agents has been attributed to a selective inhibition of bacterial cell wall synthesis [1] specially; the basic mechanism involved is inhibition of the biosynthesis of the peptidoglycan that provides strength and rigidity to the cell wall.
It is 6-[D-(–)-α-amino-p-hydroxyphenylacetamido] penicillanic acid, a semisynthetic penicillin introduced in 1974, is simply the p-hydroxy analogue of ampicillin, prepared by acylation of 6-APA with p-hydroxyphenyl glycine [2, 3]. The antibacterial spectrum of amoxicillin is nearly identical with that of ampicillin and like ampicillin, it is resistant to acid, susceptible to alkaline and β-lactamase hydrolysis and weakly protein bound. Early clinical reports indicated that orally administered amoxicillin possesses significant advantages over ampicillin, including more complete gastrointestinal absorption to give higher plasma and urine levels, less diarrhea, and little or no effect of food on absorption [4-8]. Thus amoxicillin has largely replaced ampicillin for the treatment of certain systemic and urinary tract infections for which oral administration is desirable. Amoxicillin is reportedly less effective than ampicillin in the treatment of bacillary dysentery, presumably because of its greater gastrointestinal absorption. Considerable evidence suggests that oral absorption of α-aminobenzyl substituted penicillins and cephalosporins is carrier mediated [9], thus generally explaining their generally superior oral activity.
Amoxicillin is a fine, white to off-white, crystalline powder that is sparingly soluble in water. It is available in a variety of oral dosage forms. Aqueous suspensions are stable for one week at room temperature [10-11].

Experimental
Complexes of amoxicillin Ni (II) and Cu (II) ions
All chemicals such as amoxicillin, Ni (II) chloride and Cu (II) chloride, methyl alcohol, ethyl alcohol, n-pentane, acetone, DMF and DMSO used in this study were of analytical grade. These chemicals were purchased from CDH or Merck.

Preparation of solution
A 0.18 g of ligand amoxicillin, as required for making 0.01 M solution was taken in a dry and clean conical flask containing 50 ml of redistilled water.

The flask was fitted with cork and stirred vigorously with glass rod for two hours. To make it clear solution it was again vigorously stirred with an electrical stirrer for three hours. But I failed to get its clear solution. So its suspension was used as such for complexation.
A 0.01 M solution of metal salts were prepared by dissolving appropriate amount of metal salt in 10 ml of redistilled water in a dry and clean conical flask. The solution was filtered to remove any insoluble residue.

Preparation of complex
The complex was prepared by the slow addition of 10 ml of 0.01 M metal salt solution to the magnetically stirred 50 ml of 0.01 M of ligand amoxicillin suspension at room temperature. As the amount of metal cation was increased amoxicillin dissolved. The solution was attained coloured syrupy state. The concentration of final solution gave rise to colour precipitates, which were filtered and washed with distilled water, ethanol and ether regularly and repeatedly three times. The precipitates were dried in a desiccator over calcium chloride, and then solid complexes were obtained.
Solubility tests of these complexes were performed. The thin layer chromatography of this complex was performed by using aluminium plates coated with silica gel-60GF254 as the stationary phase. The solvent system was consisted of butyl acetate: glacial acetic acid: methanol: water (5:2.5:2.5:1, V/V) as mobile phase. The R_f value was found 0.59±0.03.
Its melting point was determined using open capillary tube in kjeldal flask filled with concentrated sulphuric acid. Its melting point was greater than 300 ^{0}C.
The elemental analysis of the complex was carried out at Central Drug Research Institute (CDRI), Lucknow. The elemental analysis of the complex is given as:

Elemental analysis

	% of metal ion Cal/(found)	% of C Cal/(found)	% of H Cal/(found)	% of N Cal/(found)
[Ni(amox)Cl]	12.80/(12.68)	41.86/(41.52)	3.92/(3.88)	9.16/(8.98)
[Cu(amox)Cl]	13.71/(13.53)	41.52/(41.28)	3.92/(3.88)	9.06/(8.91)

Complexes of amoxicillin
The complexes of amoxicillin, with lanthanide metal and transition metal ions (Ni^{2+} and Cu^{2+}) are anhydrous as evident from analytical, spectral studies. All these complexes are quite stable at room temperature. The complexes are generally soluble in common organic solvents such as alcohol, benzene, DMF, DMSO but partially soluble in diethyl ether, and in water.
The molar conductance values are too low to account for any dissociation. Thus complexes are non electrolytes. The molar conductance of these complexes in nitrobenzene is given in following table.

Complexes	M.Pt. (°c)	Insoluble	Conductance ($\Omega^{-1}cm^2mol^{-1}$)	μ_{eff}	Colour
[Ni(amox)Cl]	192	Water and alcohol	11.28	Diamagnetic	Emerald green
[Cu(amox)Cl]	210	Water and alcohol	13.34	1.74	Light green

Spectral Studies transition metal Complexes with amoxicillin
The infrared, [1] H NMR and electronic spectra of the complexes were obtained from external agency C.D.R.I., Lucknow. The IR spectral data and the assignment of the ligand and its metal complexes are given in following table.

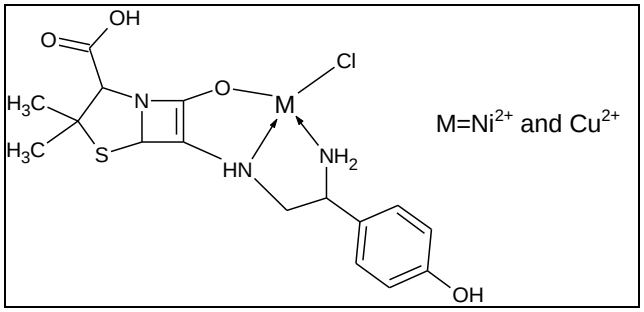
Compound	ν_{OH} Str.	ν_{CO} of Carboxyl	$\nu_{(CO)}$ quinolone	ν_{OH} bending	$\nu_{(C)}$ of oxo group
amoxicillin	3050	1713	1622	1400	1150
[Ni(amox)Cl]	.....	1625	1570	.....	1190
[Cu(amox)Cl]	.....	1640	1585	.....	1225

The infrared spectra of complexes of amoxicillin with transition metal (II) ions and the ligand amoxicillin were recorded in the range of 400–4000 cm^{-1}. The highest frequency of the bands of the ligand at ~3050 cm^{-1} can be assigned [14] to the stretching ν_{NH} vibration of the –NH group in the ligand amoxicillin. This band is disappear in the all complexes of metal (II) ions indicates that the complexation [15] of the NH group through metal ions. The infrared spectra of the ligand amoxicillin shows a peat at 1713 cm^{-1} due to stretching frequency of the C=O of carboxyl group. This peak is reduced to the range of 1625-1670 cm^{-1}. It also indicates the participation of the carboxyl group in the complexation [8] with metal ions. The frequency at 1622 cm^{-1} in IR spectra of the ligand due to the carbonyl group present in the β-lactam ring reduced to 1585-1605 cm^{-1} in the metal complexes. It also indicates the participation of the l group in the complexation.
Thus, on account of infrared spectral properties one can say that amoxicillin acts as tridentate ligand. The electronic spectral data for the solution of these complexes investigated in acetonitrile are recorded in CDRI, Lucknow and presented in the following table.

Table 1: Electronic spectral data of complexes in cm^{-1}

Complexes	Spectral bands	Transitions
[Ni(amox)Cl]	8800, 14550, 25350	$^3A_{2g} \longrightarrow {}^3T_g$, $^3T_{1g}$ (F), $^3T_{1g}$ (P).
[Cu(amox)Cl]	625	$^2T_g \longrightarrow {}^2E_g$

On the basis of structures of the complexes are as below:



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