

Synthesis And Characterization Of Mixed Sulphadiazine - Ampicillin Complexes

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Abstract: Three metal complexes of $[\text{Cu}(\text{Su})(\text{Amp})\text{Cl}_2]$, $[\text{Co}(\text{Su})(\text{Amp})\text{Cl}_2]$, and $[\text{Cd}(\text{Su})(\text{Amp})\text{Cl}_2]$ were synthesized using concentrating and mixing methods. The complexes formed were characterized by melting point, conductivity and infrared spectroscopy. An octahedral geometry was assigned for all the synthesized complexes. The ligands used were found to be bidentate. In sulphadiazine, coordination occurs through the nitrogen of the pyrimidine group and Sulphone group while in Ampicillin, coordination occurs through oxygen of the carbonyl group shown on the Infrared spectra. Investigation of the antimicrobial study was also carried out which indicates that the synthesized complexes exhibits higher activities than their parent ligands. The aim of the research work is to synthesized new alternative drugs which will be more effective than their parent ligands.

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1. Introduction

Previous reports have shown that efficacy of a therapeutic agent (such as sulphadiazine) increased upon coordination to transition metals, [Ajibola, 1990 and Akanji *et al.*, 1993]. Sulphadiazine is an antimalarial drug and is used in treatment of malarial due to its esquizonticide effect, [Craig *et al.*, 1982]. The short half-life of antibiotics (such as ampicillin), has proved to provide the benefits of therapy in rapid clearing bacterial disease that results in the release of harmful metals into blood, [Calvin *et al.*, 1953]. Ampicillin is an antibiotic and it plays an important role in maintaining the level of bacterial causing disease in the body, [Hershko *et al.*, 1994]. Key Pour *et al.*, 1986 reported the use of ascorbic acid as a possible antidote for iron overload in reaction of ferric iron with ascorbic acid. Bessman *et al.*, 1954 reported the use of calcium-EDTA as an effective remedy for lead poisoning. The non-toxic penicillamine is effectively used to remove excess copper in patients suffering from Wilsons disease, [Adrien *et al.*, 1985].

Few reports regarding metal complexes of mixed sulphadiazine and ampicillin as possible antidotes for metal overload in the body appeared in literature. It is in line with this observation that we investigate the metal-chelating ability of mixed sulphadiazine and ampicillin ligands, and to report the antimicrobial activities for possibility regarding their usage as metal-chelator therapy.

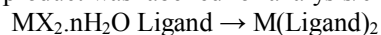
2. Experimental

Materials and Instrumentation: All reagents and chemicals were of analytical grade and used as obtained from Aldrich. Sulphadiazine and Ampicillin were obtained as gift from Sam Pharmaceutical Ltd,

Ilorin, Nigeria. Metal salts used include Copper chloride dehydrate $[\text{CuCl}_2 \cdot 2\text{H}_2\text{O}]$, Cobalt chloride hexahydrate $[\text{CoCl}_2 \cdot 6\text{H}_2\text{O}]$ and Cadmium (II) chloride $[\text{CdCl}_2 \cdot 2\frac{1}{2}\text{H}_2\text{O}]$. IR spectra of the samples in KBr pellets were obtained in the ranges of 4000-400 cm^{-1} using FTIR spectrometer. Metal Analyses were determined by atomic absorption spectroscopy with Perkin-Elmer Spectrometer, model 3110. UV-Vis spectra were obtained on Aquamate v4.60 spectrophotometer.

Experimental Procedure

Synthesis of $[\text{Cu}(\text{Su})(\text{Amp})\text{Cl}_2]$ complex: 2mmol of each of sulphadiazine and ampicillin were dissolved in 10ml of each of acetone and methanol in one conical flask and 1mmol of $[\text{CuCl}_2 \cdot 2\text{H}_2\text{O}]$ in 10ml of ethanol in another flask. The clear solution observed after mixture was concentrated at 50°C. Precipitate formed was allowed to cool, was filtered, washed and dried. The product was labelled for analysis/characterization.



Synthesis of $[\text{Co}(\text{Su})(\text{Amp})\text{Cl}_2]$ complex: 2mmol of each of sulphadiazine and ampicillin were dissolved in 10ml of each of acetone and methanol in separate conical flasks and 1mmol of $[\text{CoCl}_2 \cdot 2\text{H}_2\text{O}]$, in 10ml of ethanol in another flask. The clear solution observed after mixture was concentrated at 50°C. Precipitate formed was allowed to cool, filtered, washed and dried. The product was labelled for analysis/characterization.

Synthesis of $[\text{Cd}(\text{Su})(\text{Amp})\text{Cl}_2]$ complex: 2mmol of each of sulphadiazine and ampicillin were dissolved in 10ml of each of acetone and methanol in separate conical flasks and 1mmol of $[\text{CdCl}_2 \cdot 2\text{H}_2\text{O}]$, in 10ml of ethanol in another flask. After mixing a clear solution of the mixed ligand, and metal salt, was left to stand

for 24hrs. Precipitate formed was allowed to cool, filtered, washed and dried. The product was labelled for analysis/characterization.

3. Antimicrobial Test: The inhibitory action of all the complexes was tested against *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumonia*.

4. Results And Discussion

The Cu (II), Co (II) and Cd (II) complexes of sulphadiazine-ampicillin ligands were synthesized by reaction of metal salts with mixed sulphadiazine and ampicillin. The complexes were characterized by AAS, Conductivity, TLC, infrared, UV-Vis spectroscopy and antimicrobial studies was

investigated. The complexes are generally soluble in methanol, ethanol, acetone and DMSO but insoluble in non-polar organic solvents. The complexes are non-hygroscopic solids with melting points higher than the parent drug. The physical properties of the various complexes are collected in Table 1. The molar conductance values measured in DMSO solution (10^{-3} M) for these complexes are 7.31×10^{-6} , 6.58×10^{-6} , and 6.46×10^{-6} for the Cu, Co and Cd complexes respectively (Table 1). Similarly, from the results, the complexes are non-electrolytes. Determination of stoichiometric ratio using job's method [Hubel., 2000] suggests a 1:2 metal to ligand stoichiometry for the complexes. The proposed structures of the mixed complexes are shown below.

TABLE 1: Analytical Data of Sulphadiazine and Ampicillin metal complexes

Ligand/mixture	Colour	Melting point°C	Conductivity $\Omega^{-1} \text{ mol}^{-1} \text{ cm}^2$	% Metal	TLC Rf
Sulphadiazine (ligand)	White	230	6.4×10^{-6}		0.34
Ampicillin (ligand)	White	237-238	2.8×10^{-6}		0.37
[Cu(Su)(Amp)Cl ₂]	Blue	247	6.46×10^{-6}	10.30	0.35
[Co(Su)(Amp)Cl ₂]	Pink	270	6.58×10^{-6}	15.60	0.34
[Cd(Su)(Amp)Cl ₂]	White	251	7.31×10^{-6}	17.70	0.36

UV-Visible Spectroscopy Results

Table 2: UV-Visible spectra of Sulphadiazine and Ampicillin metal complexes

Ligand/mixture	Wavelength(nm)	Energies(cm^{-1})	Assignment
Sulphadiazine (ligand)	268325244	37313.430769.240983.6	$\pi - \pi^*$ LCTn- π^*
Ampicillin (ligand)	229325	43668.130769.5	n- π^* n- π^* n- π^*
[Cu(Su)(Amp)Cl ₂]	821	12180	2Eg - 2T _{2g}
[Co(Su)(Amp)Cl ₂]	367585850	272471223911764	MLCT4T _{1g} -4A _{2g} 4T _{1g} - 4T _{2g}
[Cd(Su)(Amp)Cl ₂]	193256	51813.538940.8	n- π^* n- π^*

The UV-Vis. Spectra of sulphadiazine in methanol present three absorption bands maxima at 268 and 325 which is assigned to $\pi - \pi^*$ transition, 325 is assigned to LCT and 244 is assigned to n- π^* transitions. The UV-Vis spectra of ampicillin in acetone present two absorption band maxima at 229 and 325 which is assigned to n- π^* transitions respectively. Copper(II) complex exhibits one band centered at 821 which may be tentatively assigned to 2Eg - 2T_{2g} transitions respectively. The cobalt (II)

complex exhibits 3 bands at 367, 585 and 850 nm. These bands are assigned to MLCT, 4T_{1g} - 4A_{2g} and 4T_{1g} -4T_{2g} transitions respectively. Cadmium (II) exhibits two absorption bands centered at 193 and 256 which may be assigned to n- π^* transition respectively. All these characteristic bands observed in the UV-Vis. spectra confirm octahedral configuration for Co(II), Cd(II) and Cu(II) complexes respectively.

Infrared Spectroscopy Results

Table 3: Infrared spectra result for mixed Su-Amp metal complexes

Ligand/Complexes	N-H	(SO ₂)	(C=O)	(C-O)	(C-N)	C=N	C-S
Sulphadiazine (ligand)	3424.02s	1325.76w,b	1262.31s	1187.79s	1157.77b	1681.04s	-
Ampicillin (ligand)	3525.80 m,b	-	1396.79s	874.19w,b	1373.60s	1684.29s	-
[Cu(Su)(Amp)Cl ₂]	3538.68s,s	1384.82s,b	1268.55s	1126.52m,b	1368.67s	1629.94s	697.52
[Co(Su)(Amp)Cl ₂]	3413.14s	1325.93m,b	1156.61s	-	1387.76s	1652.17w	687.45b
[Cd(Su)(Amp)Cl ₂]	3403.53s	1326.55s	1557.77s	1157.77s	1387.56s	1641.04s	689.10b

Sulphadiazine and Ampicillin can provide two donor atoms to the central atom due to steric constraints. The coordination of sulphadiazine occurs through the nitrogen of the pyrimidine group and Sulphone group while in Ampicillin, coordination occurs through oxygen of the carbonyl group shown on the Infrared spectra. The values of IR spectra of both ligands and their complexes have been assigned mainly for those specific frequencies directly involved in complex formation, (Table 3). The vibrational band at 1681.04cm^{-1} C=N Sulphadiazine is shifted to lower wave number 1629.94cm^{-1} for Cu (II) complex, 1652.17cm^{-1} for Co (II) complex, and 1641.04cm^{-1} for Cd(II) complex, thus indicating coordination through C=N at 3424.02cm^{-1} N-H in sulphadiazine shifted to higher wave number (3538.68cm^{-1}) in $[\text{Cu}(\text{Su})(\text{Amp})\text{Cl}_2]$ complex; and finally shifted to lower wave numbers (3413.14cm^{-1} and 3403.53cm^{-1}) in $[\text{Co}(\text{Su})(\text{Amp})\text{Cl}_2]$ and $[\text{Cd}(\text{Su})(\text{Amp})\text{Cl}_2]$ complexes; this is probably due to coordination of metal via Nitrogen of N-H group of sulphadiazine in the complexes.

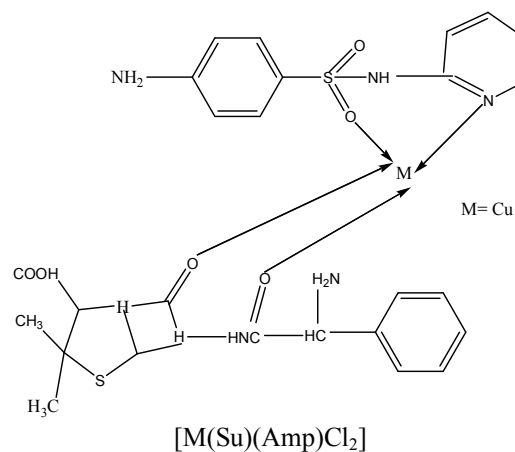
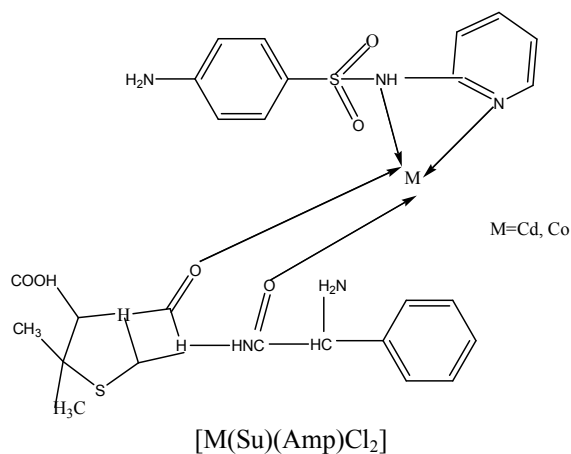
Special attention is also paid to the bands at 1325.76cm^{-1} assigned to sulphone group $\nu(\text{S}=\text{O})$ in sulphadiazine which shifted to higher wave number (1384.82cm^{-1}) for Cu(II) complex while the bands at (1325.93cm^{-1} and 1326.55cm^{-1}) assigned to (S=O) shows slight regularity as well for Co(II) and Cd(II)

complexes, thus indicating that this group may or may not be involved in coordination with the Cu(II), Co(II) and Cd(II) complexes. Spectra changes observed from 1373.60cm^{-1} in ampicillin to (1368.67cm^{-1} , 1387.76cm^{-1} and 1387.56cm^{-1}) corresponding to $\nu(\text{C}-\text{N})$ of the nitrile group in Cu(II), Co(II) and Cd(II) is so insignificant, indicating that this group is not involved in coordination of all the complexes. Similarly, the insignificant spectra changes observed at (697.52cm^{-1} , 687.45cm^{-1} and 689.10cm^{-1}) corresponding to $\nu(\text{C}-\text{S})$ for all the complexes and for which none appeared in ampicillin, suggests there is no possibility of coordination at this site to the Cu(II), Co(II) and Cd(II) ions. However, the band at 1396.79cm^{-1} corresponding to $\nu(\text{C}=\text{O})$ in ampicillin shifted to higher wave numbers (1268.55cm^{-1} , 1156.61cm^{-1} and 1557.77cm^{-1}) in all the complexes thus, indicating that this group is possibly involved in coordination of all complexes.

From the result in Table 4 above, it is evident that the overall zone of inhibition against bacterial species is highest in Co(II) complex, followed by Cu(II) complex while Cd(II) complex appears to have the least zone of inhibition. It is also evident that nearly all the metal complexes possess significant zone of inhibition acting against bacterial species than their parent ligands thus, giving the metal-chelators potentiality as antidotes for metal-overload.

Table 4: Antimicrobial Activity of Sulphadiazine and Ampicillin metal complexes

Ligand/Complex	Escherichia coli (nm) (-ve)				Staphylococcus (nm) (-ve)				Klebsiella (nm) (-ve)			
	20	40	50	100	20	40	50	100	20	40	50	100
Sulphadiazine (ligand)	0	0	0	7.8	0	9.7	0	3.50	0	4.5	0	0
Ampicillin (ligand)	0	3.4	0	0	2.5	0	0	0	4.5	0	0	0
$[\text{Cu}(\text{Su})(\text{Amp})\text{Cl}_2]$	26.8	22.2	13.5	37.0	0	0	0	0	15.5	17.09	7.8	17.09
$[\text{Co}(\text{Su})(\text{Amp})\text{Cl}_2]$	23.4	25.6	14.4	38.5	0	0	0	0	16.5	15.7	7.2	15.3
$[\text{Cd}(\text{Su})(\text{Amp})\text{Cl}_2]$	0	0	34.9	35.6	0	0	0	3.1	15.7	16.98	8.9	16.9



Proposed Structure

The results obtained from spectroscopic analysis for this study revealed that coordination of sulphadiazine, occurs through the nitrogen of the pyrimidine group and Sulphone group while in Ampicillin, coordination occurs through oxygen of the carbonyl group for all the metal complexes of [Cu(Su)(Amp)Cl₂], [Co(Su)(Amp)Cl₂], and [Cd(Su)(Amp)Cl₂] synthesized to give an octahedral geometry, with ligand acting as bidentate. This mode of coordination correspond to those in literature [Keypour et al., 1986 and Bessman et al 1954].

Evidence of formation of complex was demonstrated by examining the IR and UV spectra carefully.

5. Conclusion

The metal complexes of [Cu(Su)(Amp)Cl₂], [Co(Su)(Amp)Cl₂], and [Cd(Su)(Amp)Cl₂] have been synthesized by carefully mixing two ligands (sulphadiazine and ampicillin) in suitable solvents and adding suitably dissolved inorganic salts of Cu(II), Co(II) and Cd(II) into solution of ligands respectively. The structure of the product formed was characterized by AAS, conductivity, TLC, infrared and UV-Vis spectroscopy. In all the complexes formed, sulphadiazine coordinated through the nitrogen of the pyrimidine group and Sulphone group while Ampicillin coordinated through oxygen of the carbonyl group. The mixed ligands being bidentate is assumed to coordinate with the three metal ions (copper, cobalt and cadmium) thus, forming an octahedral geometry. Two donors atom (Nitrogen atom of pyrimidine group and sulphur atom of sulphone group in sulphadiazine and oxygen atom of

carbonyl group in ampicillin) are involved in coordination of sulphadiazine-ampicillin with the three metal ions. In summary, it is evident that the overall antimicrobial activity is high for the [Cu(Su)(Amp)Cl₂], [Co(Su)(Amp)Cl₂], and [Cd(Su)(Amp)Cl₂] complexes thus giving the three complexes potentiality as antidotes for metal-overload/poisoning.

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