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Synthesis, Characterization and Antibacterial Activity of Co^{2+} and Ni^{2+} Mixed Drug Metal (II) Complexes of Sulfamethoxazole and Ampicillin Trihydrate

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Abstract: *The emergence of new infectious diseases, the resurgence of several infections that appeared to have been controlled and the increase in bacterial resistance have created the necessity for studies directed towards the development of new antimicrobials. Mixed drug metal (II) complexes of Co and Ni with Sulfamethoxazole (SMX) and ampicillin trihydrate (AMP) as ligands were synthesized and characterized by standard procedures i.e. (elemental chemical analysis C.H.N.S, FTIR, Molar conductivity, melting point and decomposition temperature and solubility test). On the basis of these studies, a six coordinated octahedral geometry for all these complexes has been proposed. The standard drugs and its mixed complexes were also tested for their antibacterial activity using agar diffusion method against Salmonella typhi (gram negative bacteria) and Staphylococcus aureus (gram positive bacteria). The results of the zones of inhibition showed that the complexes of Co and Ni at 20 µg/disc has antibacterial activity on Staphylococcus aureus (24.3 and 22.3 mm) and S.typhi (15.3 and 14.0) respectively.*

Keywords: *synthesis, sulfamethoxazole, ampicillin trihydrate, Salmonella typhi, Staphylococcus aureus.*

1. Introduction

Metals have an esteemed place in medicinal chemistry. First row transition metals represent the d-block elements which lie between group IIA and IIIA of the periodic table. Their d-shells are in process of filling. This property of transition metals resulted in the foundation of coordination complexes. Metal complex or coordination compound is a structure consisting of a central metal atom, bonded to a surrounding array of molecules or anions (ligands) (Rafique *et al*., 2010). Transition metal complexes are cationic, neutral or anionic species in which a transition metal is coordinated by ligands (Cox, 2005). Mixed ligand complexes with metal ion bound to two different and biochemically important ligands have aroused interest as model for metallo-enzymes. The physiologically interesting mixed ligand complexes of transition metals with amino acids play an important role in biological systems and have been a subject of great interest for researchers (Shivankar *et al*., 2003). Metals not only provide templates for synthesis, but they also introduce functionalities that enhance drug delivery vectors (Obaleye *et al*., 2012). Many organic drugs require interaction with metals for activity. They interact with metals at their target site or during their metabolism or disturb the balance of metal ion uptake and distribution in cell and tissue. The unique properties of metal complexes tend to offer advantages in the discovery and development of new drugs (Obaleye *et al*., 2012).

Thus, our aims are to synthesize and characterize novel metal (II) mixed ligands complexes of sulfamethoxazole and ampicillin trihydrate. Furthermore, the metal (II) complexes potentials as broad spectrum antibacterial agents *in-vitro* will be verified. (Ekennia *et al*., 2014; Osowole *et al*., 2015).

Here in this paper we are describing synthesis and characterization of cobalt (II), nickel (II) and copper (II) complexes with Schiff base of sulfamethoxazole [4-amino-N-(5-methyl-3-isoxazolyl) benzenesulfonamide]

2. Materials and Methods

(a) Reagents and Instruments:

All chemicals and solvents used were of analytical grade. Pure sample of Sulfamethoxazole, molecular formula $C_{10}H_{11}N_3O_3S$ and molecular weight 253.28, was obtained from Bristol Scientific Company, Lagos Ampicillin trihydrate from Central Drug House, New Delhi. Metal salts $CoCl_2.6H_2O$ and $NiCl_2.6H_2O$ were of Merck chemicals.

Analytical Reagent grade hydrated metal chlorides from Bristol Scientific Chemicals were used for the preparation of the complexes.

Elemental analysis (C, H, N and S) were carried out using micro analytical technique on C,H,N,S,O Elemental analyzer at Universiti Technologi Petronas (UTP) Malaysia. The Infrared spectra of ligand and metal complexes were recorded on KBr pellets in the range 4000-450 cm-1 on Perkin Elmer FTIR spectrophotometer. Melting points were recorded using melting point apparatus.

(b) Synthesis

To a hot ethanolic solution (20 cm^3) containing 2.0 mmole (0.506 g) of sulfamethoxazole, ethanolic solution (20 cm^3) containing 2.0 mmole, (0.806 g) of ampicillin trihydrate were added to ethanolic solution (20 cm^3) 2.0mmole of a metal chloride (hydrate) under constant stirring. The pH of the reaction mixture was adjusted to 7.5–8.5 by adding 10 % alcoholic ammonia solution and refluxed for about 3 h. The precipitated solid metal complex was filtered off under hot conditions and washed with hot ethanol, petroleum ether (40–60 °C) and dried over anhydrous $CaCl_2$ in a vacuum desiccator (Munde *et al* 2010).

2.1. Antibacterial Activities

The antibacterial activity of the ligand and metal complexes were tested *in vitro* against

Bacteria: *Staphylococcus aureus* and *Salmonella typhi* by the paper disc plate method. The compounds were tested at the concentration 0.50 and 1.0 mg mL^{-1} in DMSO and compared with known antibiotics *viz.* ciprofloxacin.

2.2. Results and Discussion

The physical characteristics and molar conductance data of the ligands and its metal complexes are given in Table 1. The analytical data of the complexes revealed 1:1 mole ratio (metal:ligand) and corresponds well with the general formula [ML] (M= Co(II), Ni(II)) Cu(II). The magnetic susceptibilities of the Cu (II) and Ni (II) complexes at room temperature were found to be consistent with square-planar geometry and that of the Co (II) complexe with high-spin octahedral structures having two water molecules coordinated to the metal ion. The presence of two coordinated water molecules was confirmed by TG/DT analysis.

The metal chelate solutions in DMSO showed low conductance, supporting the non-electrolyte nature of the complexes.

Table1. *Analytical Data of the Complexes and Ligands*

Complexes	Yield (%)	Colour	M.P.(°C)	□□□□□□□Λ S cm2 mol-1	Molar conductance
[Co(SMX)(AMP)]	59.50	Pink	245 (D)	18.20	**6.08**
[Ni(SMX)(AMP)]	61.90	Yellow	238 (D)	28.71	6.72
(AMP)	ND	White	198-199	-	4.10
(SMX)	ND	White	169-171	-	4.19

Key SMX = Sulfamethoxazole, AMP = Ampicillin trihydrate, ND: Not determined, D = decomposed

From Table 1, the percentage yield of the [Co (SMX)(AMP)], [Ni(SMX)(AMP)] and [Cu(SMX)(AMP)] are 59.50, 61.90 and 58.33 and all the complexes decomposed at a temperature range of 234 ^oC to 245 ^oC.

2.3. IR Spectra

FTIR spectral data of the complexes and standard drugs in Table 3.2 showed the most important absorption bands. The presence of strong absorption bands at 3507 cm^{-1} in the spectrum of ampicillin trihydrate was attributed to *v*(O-H) vibration frequencies (Waziri *et al*., 2014). This absorption band shifted to 3477 cm^{-1}, 3460 cm^{-1} and 3445 cm^{-1} in cobalt (II), nickel (II) and copper (II) complexes respectively indicating the formation of coordination bond between the central metal atom and (O-H) of the ampicillin trihydrate. These bands shifted to The appearances of such spectral bands suggest the coordination to the respective metals as reported by (Ahmed *et al.*, 2011) in which the band at 1633 cm^{-1} was assign to v(C=O) in free sulfamethoxazole. This band is observable in the spectra of three complexes at 1639 cm^{-1}, 1620 cm^{-1} and 1657 cm^{-1} confirming the coordination of sulfamethoxazole to the respective metals. The strong absorption in the range of 550-595 cm^{-1} and 420-500 cm^{-1} of the metal complexes have been assigned to v(M-N) and v(M-O) stretching frequencies respectively, supporting the coordination of the ligands to respective metal ions through Nitrogen and oxygen atoms respectively (Osowole *et al*., 2015).

Table2. *Infrared Spectral Data of the Complexes and the Ligands (cm^{-1}).*

Complexes(cm^{-1})	*v* (O-H)	*v*(N-H)	*v*(C=O)	*v*(S=O)	*v*(M-N)	*v*(M-O)
[Co(SMX)(AMP)]	3477	3386	1639	1134	588	476
[Ni(SMX)(AMP)]	3460	3173	1620	1125	576	428
AMP	3507	3445	1773	-	-	-
SMX	3470	3015	1633	1337	-	-

It was therefore suggested, based on the chelate theory (Chang *et al.*, 2010, that increasing the number of chelate rings may improve the antimicrobial activities of the complexes.

The strong absorption bands at 3445 cm^{-1} and 3015 cm^{-1} in AMP and SMX were assigned as *v*(N-H) band (Khan and Asnani, 2011; Gulcan *et al.*,2012). On coordination, these bands shifted to 3386 cm^{-1}, 3173 cm^{-1} and 3339 cm^{-1} in the spectra of Co (II), Ni (II) and Cu (II) complexes respectively indicating the coordination of the amino group's nitrogen to the metal (II) ions without deprotonation (Beyrambadi *et al*., 2011). This is in closed agreements with the bands obtained by (Osowole *et al*., 2015).

Table3. *Antibacterial Activities of the complexes and the ligands against S. aureus and S. typhi*

Complexes/Ligands	zone of inhibition (S.aureus)		(*S.typhi*)	
	10 µg/cm^3	**20 µg/cm^3**	**10 µg/cm^3**	**20 µg/cm^3**
[Co(SMX)(AMP)]	19.7 ± 0.58	24.3±0.58	11.6 ± 0.58	15.3±1.15
[Ni(SMX)(AMP)]	18.0 ± 0.00	21.3±1.15	13.7± 0.58	14.0±0.00
[(SMX)(AMP)]	15.2 ± 0.60	20.0±0.00	8.2 ± 0.58	8.6±0.58
(SMX)	12.7 ± 1.15	16.3±0.58	6.3 ± 0.58	7.6±0.58
(AMP)	14.0 ± 0.00	17.7±0.58	8.0±0.00	9.3± 1.15

2.4. Antibacterial Activity

The measured zone of inhibition of the complexes as well as the ligands against *Staphylococcus aureus* and *Salmonella typhi* were presented in Table 3. The comparison of the biological activity of the *Salmonella typhi* (gram negative) bacteria and *Staphylococcus aureus* (gram positive) the biological activities of the metal complexes are higher than the free ligands towards the gram positive and gram negative bacteria, in addition, the antibacterial activity of the complexes follow the order [Co(SMX)(AMP)] > [Ni(SMX)(AMP)] > (SMX)(AMP) > (SMX) > (AMP) against *Staphylococcus aureus*. But with *Salmonella typhi*, the antibacterial activities of the complexes reduced in the following order (AMP) < (SMX) < (SMX)(AMP) < [Ni(SMX)(AMP)] < [Co(SMX)(AMP)]. It is evident from the above data that the antibacterial activity significantly increased on coordination.

It was suggested that suggested that the ligands with nitrogen and oxygen donor systems inhibit enzyme activity (Fayad *et al*., 2012) Coordination reduces the polarity of the metal ion mainly because of the partial sharing of its positive charge with donor groups within the chelate ring system (Raja *et al.*, 2011). The increase in the antibacterial activities of the complexes as compared to the free ligands may be due to to the electropositive nature of metals, ultimately enhancing their antibacterial (Nazir *et al.*, 2013).

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