International Journal of Scientific Engineering and Applied Science (IJSEAS) - Volume-1, Issue-8, November 2015
ISSN: 2395-3470
www.ijseas.com

Coordination Behavior and Antibacterial Studies of Ni(II) and Zn(II) Cremothalidine Complexes

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Abstract

Cremothalidine is a synthetic opioid and strong analgesic medication. It is a nacrotic pain reliever used to treat moderate to severe pain. Cremothalidine is used for the management of pain (systematic) and as an anesthesia adjunct. Ni(II) and Zn(II) complexes cremothalidine have been synthesized. The melting point, solubility, colour and yield were determined. The metal complexes were characterized based on electonic and infrared spectroscopy. Metal:ligand ratios were determined using Job's method of continuous variation. Electronic spectrum of cremothalidine showed intraligand charge transfer transition (ILCT). The electronic spectra of the metal complexes showed intraligand charge transfer transition (ILCT), ligand to metal charge transfer (LMCT) and d-d transition. Infrared spectra studies suggested coordination through the C=O and OH functionalities in Zn(II) complexes. For Ni(II) cremothalidine complex, complexation occurred through C=O, OH and C=N functional groups. Metal:ligand ratio for Zn(II) and Ni(II) complexes suggested 1:1 and 1:2 ratio respectively. Cremothalidine showed no inhibitory activity against *Escherichia coli, Stapylococcus aureus, Klebsiella pneumoniea and Salmonella enterica.* Nickel (II) cremothalidine complex showed inhibition of 22.00 ±0.00 for *Escherichia coli* and 30.00 ± 0.00 for *Salmonella entrica* . Zinc (II) cremothalidine complex inhibited *Escherichia coli* , *Staphylococcus aureus* and *Klebsiella pneumoniae.* The inhibition zone diameters were 22.67 ± 19.63, 34.00± 0.00 and 11.33± 19.63 respectively. Zinc (II) cremothalidine showed higher inhibition . This showed that both metal ions were able to introduce a new feature into the ligand. The high inhibition of zinc (II) cremothalidine complex can be attributed to the biological importance of zinc.

Keywords: Cremothalidine, complexes, ligand, infrared, electronic, antibacterial.

1. Introduction

The field of medicinal inorganic chemistry can be divided into two main classes: firstly, chelating agents as drugs which target metal ions, whether free or protein-bound; and secondly, metal-based drugs that target receptors where the central metal ion is usually the key feature of the mechanism of action[1]. Silver and mercury complexes have been reported as antibacterial agents [2 – 4]. Silver sulfadiazene [5] finds use for treatment of severe burns; the polymeric compound slowly releases Ag ion. In many countries silver nitrate is still used to prevent ophthalmic disease in newborn babies [6]. The mechanism of action of Ag and Hg is through slow release of the active metal ion. These metal ions inhibit thiol in bacterial cell walls. The medicinal uses of coordination compounds are of increasing biological, clinical, pharamaceutical and industrial importance. Colorectal cancer has been treated with fluorouracil-oxaliplatin complex in Europe and the USA[7, 8].Peptic ulcer and ulcers associated with Helicobacter pylori has been managed with ranitidine-bismuth citrate complex, marketed in the USA as ranitidine bismutrex [9]. The use of complexing agents in the treatment of Wilson's disease is a good example of how excess (CuII) toxicity may be ameliorated by chelating agents [10] Antiparasitic activity of gold and ruthenium complexes of chloroquine and clotrimazole have been investigated [11,12]. Furthermore, it was found that some chloroquine complexes are useful even in chloroquine-resistant cases. It has been reported [13] that copper–cephalexin complex exhibited a good anti-inflammatory activity and had more antibacterial effect than the free cephalexin. The effect of metal ions on drug activity

was confirmed by several studies [14, 15]. Fe(II) and Mn(II) complexes of 2-[({4-[(1,3-thiazol-2ylamino) sulfonyl]phenyl}amino)carbonyl]benzoic acid have been investigated to be more potent than the free ligand againt *Escherichia coli* and *Stapylococcus aureus* [16]. Transition metal complexes offer advantages over common organic base drugs because the transition metal ion provides an alternative route in the drug receptor machanism. Cisplatin, a platinum complex is one of the world's best selling anticancer drug [17].

Based on the therapeutic properties of metal complexes, we have decided to synthesize, characterize and determine the antibacterial activity of Ni(II) and Zn(II) cremothalidine complexes.

2. Materials and methods

2.1 All reagent used were of analytical grade. Cremothalidine , Zn (II) chloride and Ni(II) tetraoxosulphate (VI) were purchased fron BDH Chemical Ltd Poole England. UV-visible 2500PC Series Spectrophotometer was used for electronic studies while SHIMADZU FTIR-8400S Fourier Transform Infrared Spectrophotometer was employed for the functional group studies.

2.2 Synthesis of Nickel (II) cremothalidine complex: Methanolic solution (50ml) of cremothalidine (8.066g, 0.02mol) was added to (50 ml) methanolic solution of nickel(II)sulphate (3.093, 0.02 mol). The reaction mixture stirred gently for 45 minutes. The mixture was refluxed for 4 hours. The precipitate was dried in a desiccator. The yield was recorded.

2.3 Synthesis of zinc (II) cremothalidine complex: Methanolic solution (50ml) of cremothalidine (8.066g, 0.02mol) was prepared and added to a prepared (50ml) methanolic solution of zinc(II)chloride (2.73g, 0.02). The reaction mixture was stirred gently for 45 minutes. The mixture was refluxed for 4 hours. The precipitate was dried in a desiccator. The yield was recorded.

2.4 Media preparation: The media used for the antimicrobial sensitivity testing was Muller Hinton agar. It was prepared by weighing out 38g of the powdered agar into 100ml of distilled water in a conical flask. This was sterilized in an autoclave at 121^{o}C for 15 minutes, after autoclave, the media was poured into sterile petri dish and allowed to gel (cool).

2.5 Determination of antimicrobial activity.The organisms used are *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniea and Salmonella enterica* gotten from stock culture in Michael Okpara University of Agriculture's microbiology laboratory. Organisms were inoculated into the already prepared Muller Hinton agar. Using a cork borer, well (7mm in diameter and 2.5mm deep) was bored into the inoculated agar and 50µl of each of the complex at a concentration of 1g/ml was delivered into the wells. The plates were incubated and read after 18 - 24 hours. The diameter zone of inhibition produced by the complexes were measured with a transparent meter rule in mm

2.6 Determination of minimum inhibitory concentration (MIC): The minimum inhibitory concentration (MIC) is the lowest concentration of antimicrobial extract that can be able to inhibit the visible growth of a microorganism after overnight incubation. To determine the MIC 0.95 mL of Mueller Hinton Broth was transferred into 9 test tubes.1ml of the complex at 50mg/ml was pipetted into the first tube and properly mixed.1ml was taken from the first test tube into the second test tube and mixed. This was continued up to the 7th tube to give concentrations of 50, 25, 12.5, 6.25, 3.12 and 0.78mg/ml. The 8th tube was labeled the organism control which contained only the organisms and Mueller Hinton Broth but no complex. The 9th tube was labeled antibiotic control which contained the organism, Mueller Hinton Broth and antibiotic. 0.05ml (50ul) of the organism suspension was transferred into each test tube using a micropipette. The tubes were incubated and result read after 18-24 hours. The MIC was the tube that prevented visible growth of the organism after the period of incubation.

2.7. Stoichiometric determination: Metal: ligand ratio was determine using Job's method of continuous variation method [16]

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3. Results and discussion

3.1 Physical data of the ligand and complexes are shown in Table 1. The solubility data is shown in Table 2. Antibacterial activity and minimum inhibition concentration are presented in Tables 3 and 4 respectively. Infrared and elctronic spectra are shown in Figures 1 – 6.

Table 1: Physical data for the ligand and complexes.

Properties	L	[NiL]	[ZnL]
Appearance	Solid	Solid	Solid
Melting point (^oC)	272-277	200-202	289-291
Color	White	Light green	Light brown
Yield (%)	-	83.2	65.0

L = cremothalidine

Table 2: Solubility data for the ligand and metal complexes

Compound	C_2H_5OH	C_6H_{14}	CH_3OH	H_2O	$C_2H_5OC_2H_5$
L	IS	IS	PS	PS	IS
[NiL]	IS	IS	S	SS	IS
[ZnL]	IS	PS	IS	IS	IS

IS = insoluble, PS = partially soluble, SS = sparingly soluble, S= Soluble
L = cremothalidine

Table 3: Antibacterial studies of the ligand and complexes

	L	[NiL]	[ZnL]
Bacteria Strain	IZD(mm)	IZD(mm)	IZD(mm)
Escherichia coli	0.00 ±0.00	22.00 ± 0.00	22.67±19.63
Staphylococcus aureus	0.00±0.00	30.00±0.00	34.00±0.00
Klebsiella pneumoniea	0.00 ± 0.00	0.00 ± 0.00	11.33±19.63
Salmonella enterica	0.00 ± 0.00	15.00±0.00	0.00±0.00

Values are written as Mean±S.D L = cremothalidine

Table 4: Minimum inhibition Concentration (MIC) of the ligand and complexes

	L	[NiL]	[ZnL]
Bacteria Strain	MIC(mg/ml)	MIC(mg/ml)	MIC(mg/ml)
Escherichia coli	0.00 ± 0.00	10.04 ± 6.00	1.22±0.77
Staphylococcus aureus	0.00 ± 0.00	13.50 ± 0.00	2.12±0.00
Klebsiella pneumoniea	0.00 ± 0.00	0.00 ± 0.00	20.00±0.00
Salmonella enterica	0.00 ± 0.00	0.00±0.00	0.00±0.00

Values are written as Mean±S.D L = cremothalidine

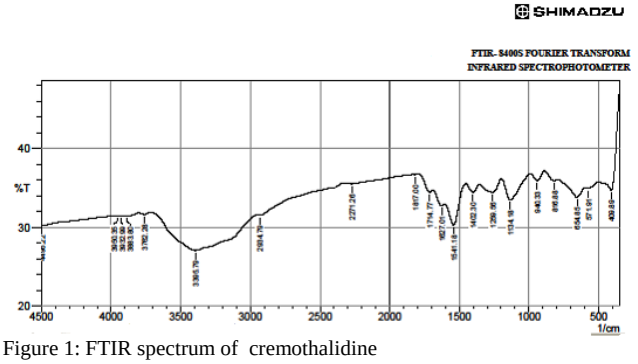

Figure 1: FTIR spectrum of cremothalidine

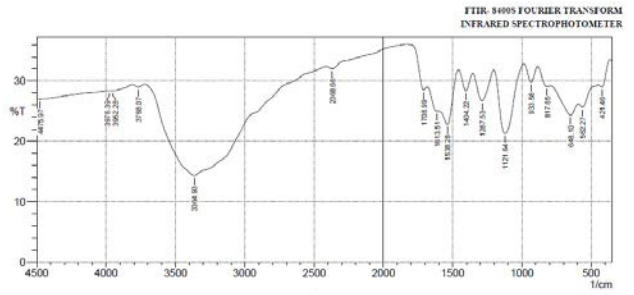

Figure 2: FTIR spectrum of Ni(II) cremothalidine complex

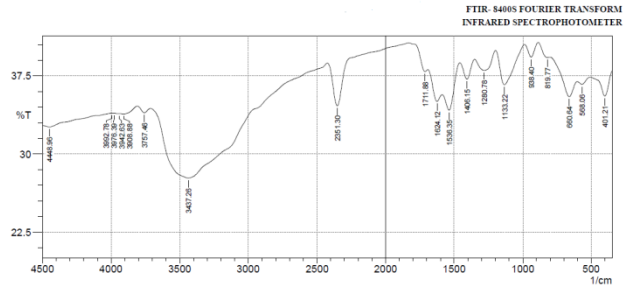

Figure 3: FTIR spectrum of Zn(II) cremothalidine complex

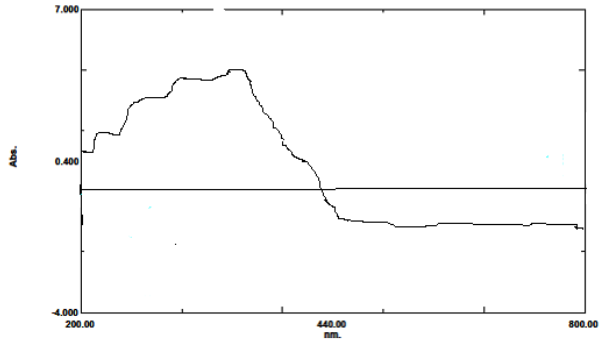

Figure 4: UV-visible of cremothalidine

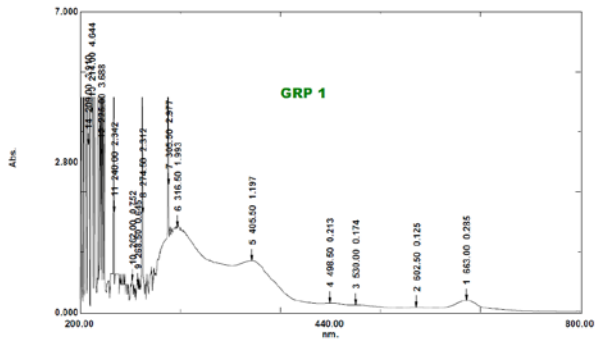

Figure 5: UV-visible of Ni(II) cremothalidine complex

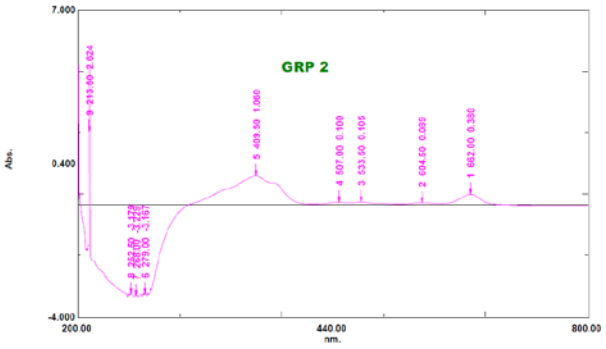

Figure 6: UV-visible of Zn(II) cremothalidine complex

3.2 The colour of the Ni(II) complex is light green while that of Zn(II) complex is light brown. The colour change is as a result of metal-ligand interaction which indicates complexation; since transition metal complexes are coloured [17]. The melting point range of cremothalidine is 272 – 277°C, the melting of Ni(II) cremothalidine complex is 200 -202°C while that of Zn(II) cremothalidine complex is 289 -291°C. The change in melting point is an indication that complexation occurred. The C-O vibrational stretch of the ligand was found to be 1259.56cm^{-1}. This C-O vibrational frequency shifted in the metal complexes (1287.53 cm^{-1} in Ni complex and 1280.72 cm^{-1} in Zn). These shifts suggest the involvement of C-O in coordination which is as a result of decrease in electron density which decreases the C-O bond length and consequently increase the vibration frequency. In the FTIR spectrum of the ligand, the -OH stretch of the carboxylic acid was found to be 3395.75cm^{-1}. In the spectra of the metal complexes, the -OH vibrational frequency shifted. In zinc (II) complex, it shifted upfield (3437.26 cm^{-1}) while in the nickel (II) complex, it shifted downfield (3364.93 cm^{-1}). These shift suggest the involvement of -OH group of cremothalidine in complexation. C=N vibrational frequency appeared at 1627.01cm^{-1} in the ligand. In Zn(II) complex, there was no significant shift. FTIR spectrum of Ni(II) complex showed that C=N vibrational frequency shifted to 1613.51cm^{-1}. This shift suggests the involvement of C=N in coordination with Ni(II). In the electronic spectrum of the ligand, the λ maximum was found at 365nm. This band has been assigned $\pi - \pi^*$ transition. This transition could be as a result of chromophores in the ligand. The chromophores are C = O, S = O, C = C and C = N. There was no transition in the visible region (400 – 800 nm). Electronic spectra of the metal complexes showed three types of transitions. The transitions are intra ligand charge transfer transition (ILCT), the ligand to metal charge transfer (LMCT) and d – d transition. λ maximum in nickel (II) complex appeared at 409.50 and 662.00 nm. Thses bands have been assigned ligand to metal charge transfer and d – d transition respectively. In zinc (II) complex, λ maximum appeared at 405.00 and 665.00 nm. These bands have been attributed to ligand to metal charge transfer and d – d transition respectively.

Antibacterial activity is shown in Table 3. Cremothalidine could not inhibit the selected bacteria; *Salmonella entrica, Klebsiella pneumoniae, Staphylococcus aureus and Escherichia coli*. Nickel (II) cremothalidine complex showed inhibition of 22.00 ±0.00 for *Escherichia coli* and 30.00 ± 0.00 for *Salmonella entrica* . Zinc (II) cremothalidine complex inhibited *Escherichia coli* , *Staphylococcus*

aureus and *Klebsiella pneumoniae.* The inhibition zone diameters were 22.67 ± 19.63, 34.00± 0.00 and 11.33± 19.63 respectively. Zinc (II) cremothalidine showed higher inhibition . This showed that both metal ions were able to introduce a new feature into the ligand. The high inhibition of zinc (II) cremothalidine complex can be attributed to the biological importance of zinc. Minimum inhibition concentation(MIC) have been reported in Table 4. Minimum inhibition concentation (MIC) of nickel (II) cremothalidine complex was10.04 ± 6.00 mg/ml and 13.50 ± 0.00 mg/ml for *Escherichia coli and Staphylococcus aureus* respectively . Minimum inhibition concentation (MIC) of zinc (II) cremothalidine was 1.22±0.77 mg/ml, 2.12±0.00 mg/ml and 20.00±0.00 mg/ml for *Escherichia coli, Staphylococcus aureus* and *Klebsiella pneumoniea* respectively.

Stoichiometric ratio base on Job's method of continous varation [16] showed that the metal:ligand ratios of 1:1(ZnL) and 1:2(NiL).

The structure of the ligand is shown in Figures 7.

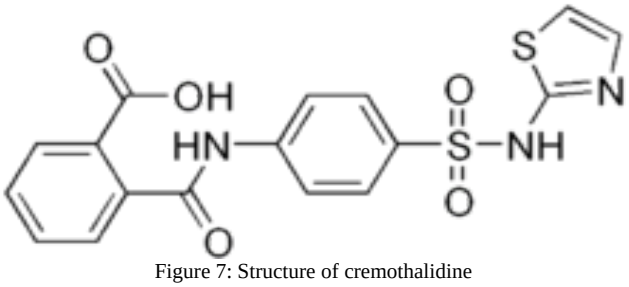

Figure 7: Structure of cremothalidine

Based on the electronic, infrared characterization, and Job's method of continuous variation, the following structures, Figures 8 and 9 have been proposed for the metal complexes.

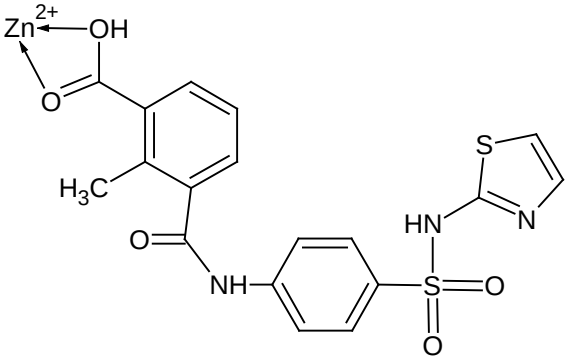

Figure 8: Suggested structure for Zn(II) cremothalidine complex

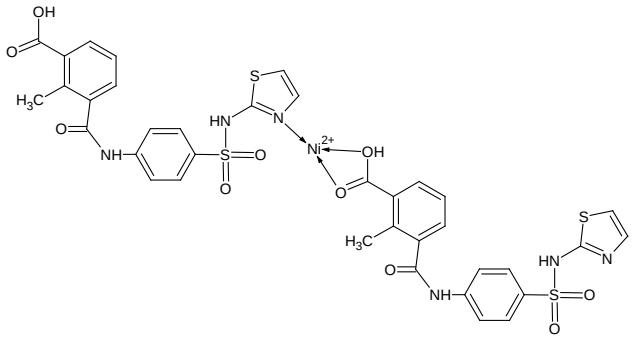

Figure 9: Suggested structure for Ni(II) cremothalidine complex

4. Conclusions

Ni(II) and Zn(II) complexes of cremothalidine have been synthesized. Tentative structures were proposed based on FT-IR, electronic characterization, and stoichiometric determination. The ability of cremothalidine to coordinate Ni(II) and Zn(II) have been assured.. The complexes were more potent than cremothalidine

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