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Chelating and Antibacterial Potentials of Benzylpenicillin and its Ni(II) Complex

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Abstract: *The ligand, benzylpenicillin (BPEN) is an antibacterial therapy used in the treatment of bacteria. Infections. Ni(II) complex of (BPEN) was synthesized. The physical properties such as melting point, solubility and colour of BPEN and [Ni(BPEN)] were determined. BPEN and its Ni complex were characterized using spectroscopic methods. [Ni(BPEN)] has a light green shade. The molar conductivity of (BPEN) and [Ni(BPEN)] were 218.2 and 126.0 Sm^2mol^{-1}. The conductivity parameters suggested that BPEN and its Ni complex are ionic. Spectroscopic results suggested that BPEN coordinated to Ni ion through hydroxyl, carbonyl of amide, carbonyl of carboxylic acid, carbonyl of β-lactam and amine functional groups. BPEN coordinated through five sites to the Ni ion. A pentadentate geometry was proposed for the complex. The antibacterial activity of BPEN and [Ni(BPEN)] were studied against four-gram negative bacterial strains (Escherichia coli, Enterobacter cloacae, Pneumonia aeruginosa and Campylobacter fetus) and four-gram positive bacterial strains (Staphylococcus aureus, Bacillus substilis, Bacillus cereus and Enterococcus faecalis). The results suggested that [Ni(BPEN)] exhibited better antibacterial activity than (BPEN]. It was concluded that metal complexation enhanced the antibacterial activity of the ligand by increasing the inhibitory potential against the bacterial strains used.*

Keywords: *Benzylpenicillin, ligand, chelation, spectra, bacteria, inhibition. complexes*

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1.0 Introduction

There is increasing demand for new antimicrobial compounds that can combat the growing threat of widespread antibiotic resistance. Metal complexes are currently in clinical development for the treatment of microbial infections (Angelo *et al*., 2020). Metal complexes have a unique mode of action and exist in a wider range of three-dimensional geometries than purely organic compounds (Angelo, 2020). Advances in inorganic chemistry have provided better opportunities of using metal complexes as therapeutic agents (Rafique *et al*., 2010; Thompson and Orgiv, 2004; Thompson and

Orgiv, 2006; Otuokere and Chinweuba, 2011; Onyenze *et al*., 2016; Otuokere and Amadi, 2017; Otuokere *et al*., 2021; Otuokere and Robert, 2020; Otuokere *et al*., 2017; Ikpeazu *et al*., 2017). Several metal complexes are known to accelerate the drug action and the efficacy of the organic therapeutic agent. The efficacies of the various organic therapeutic agents can be enhanced through coordination with a suitable metal ion.

The pharmacological activity of metal complexes is highly dependent on the nature of the metal ions and the donor sequence of the ligands because different ligands exhibit different biological properties. Generally, drug combinations have proven to be an essential feature of antimicrobial treatment due to several important considerations including (i) they increase activity through the use of compounds with synergistic or additive activity; (ii) they thwart drug resistance; (iii) they decrease required doses, reducing both cost and the chances of toxic side effects; (iv) they increase the spectrum of activity. Various biological aspects of the metal-based drugs/ligands entirely depend on the ease of cleaving the bond between the metal ion and the ligand. Pahontu *et al*. (2013) synthesized Ni(II) complexes with salicylidene thiosemicarbazones. These Ni(II) salicylidenem thiosemicarbazones complexes showed higher antimicrobial activities than the standard Furacillinum towards *Staphylococcus* and *Streptococcus* bacteria. The minimum inhibitory concentration (MIC) and minimum bactericide concentration (MBC) were influenced by the nature of thiosemicarbazone and amine of the inner sphere coordination compound. New Ni(II) complex derived from N-Isonicotinoyl- N1-(3-methoxy-2-hydroxybenzaldehyde)-hydrazine were synthesized and screened for in vitro antimicrobial activity against *Escherichia coli, Klebsiella pneumonia and Staphylococcus aureus strains*. The results obtained from the quantitative antimicrobial activity tests indicated that both the ligand and the complex combinations exhibited specific antimicrobial activity that varied with the tested species of microorganism (Pahontu *et al*., 2017). Islam *et al*. (2007) synthesized new Ni(II) tyrosine complex. The Ni(II) tyrosine complex was screened as a potential antimicrobial agent against several medically important bacteria (*Bacillus subtillis, Streptococcus β-haemolytica, Escherichia coli* and *Shigella dysentarae*). It was observed that the metal chelates exhibited more inhibitory effects than the parent ligands. The observed increase in the lipophilic character of these complexes was responsible for their enhanced biological potency. In continuation, Islam *et al*. (2015) synthesized a new Ni(II) pyridine complex and its antibacterial effect was evaluated against human pathogenic bacteria (Salmonella typhi, Shigella dysentarae, Escherichia coli and Bacillus cereus). Ni(II) pyridine complex was more effective against *Salmonella typhi, Shigella dysentarae, Escherichia coli* and *Bacillus cereus* than the free ligand. This research aims to investigate the chelating and antibacterial potentials of BPEN and [Ni(BPEN)] with the intention of enhancing access to their pharmacological properties.

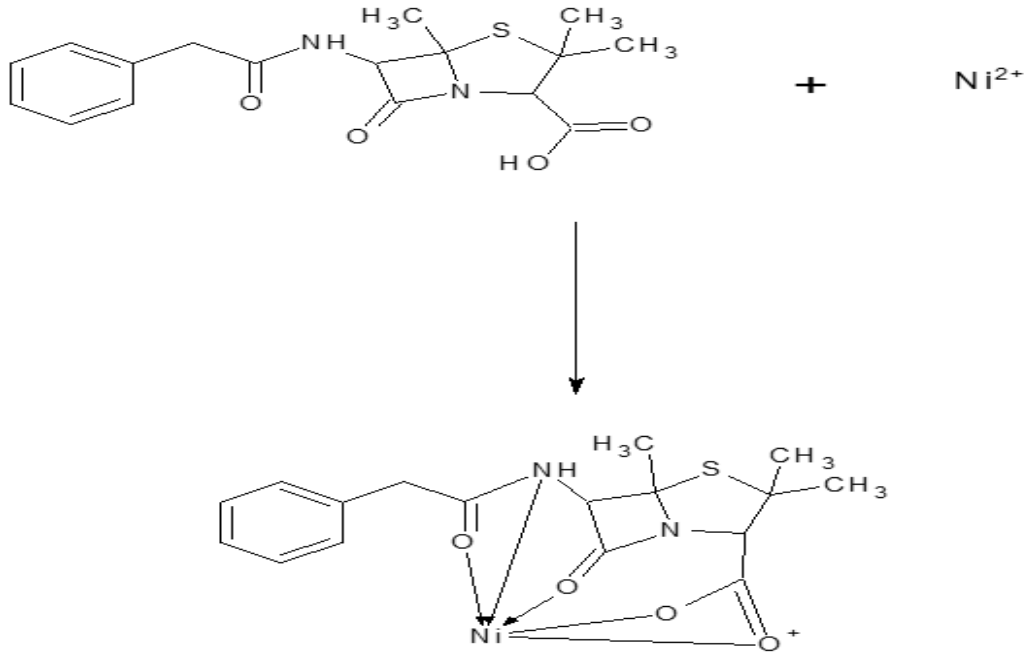
2.0 Materials and Methods

All the chemicals used in this study were of analytical grade. The ligand, BPEN was obtained from Shanxi Federal Pharmaceutical Company limited, Shanxi, China. Melting points of both the ligand and the complex were determined using Gallenkamp melting point apparatus. The solubility of the ligand and the metal complex were tested using various organic solvents at 25^{o}C. Conductivity measurements of the ligand and its nickel (II) complex (10^{-3} M) were recorded at room temperature using Jenway conductivity Meter 4510. DMSO was used as the solvent.

Nickel analyses were carried out on AAS spectrophotometer (bulk 210). The elemental analysis for C, N, H and S were obtained using a Perkin-Elmer 240B elemental analyzer. The liquid state UV-Vis spectra of the ligand and its nickel complex were recorded on Uv-1800 series using Dimethylsulfoxide as the solvent in the range 200-800 nm. The solid state FTIR spectra of the ligand and its nickel complex were recorded on a Perkin Elmer Spectrum BX FTIR spectrophotometer (4400-350 cm^{-1}) in KBr pellets. The NMR spectral measurement was recorded on a nuclear magnetic resonance Bruker spectrophotometer using tetramethylsilane internal standard and DMSO-d6 as solvent.

The complex was prepared following reported procedure by Anacona and Figueroa, (1999). Ni(II) solution was prepared by dissolving 3.09g (0.013mole) $NiCl_2.6H_2O$ in 10 ml of water. The metal solution was added to a solution of BPEN (0.013 mol). The mixture was stirred for 1 hour and the solid complex which separated was removed by filtration and washed with water, ethanol and ether. The compound was dried under vacuum at room temperature for 48 hours. The complex was then stored in a neatly labelled container after determining its percentage yield. The proposed synthetic route for the metal complex is shown in Scheme 1

2.1 Synthesis of [Ni(BPEN)]



Scheme 1: Proposed synthetic route for the metal complex

2.2 Antibacterial activity test

The organisms used were Gram-negative *Escherichia coli*, *Enterobacter cloacae*, *Pneumonia aeruginosa*, and *Campylobacter fetus*. The Gram-positive bacterial strains were *Staphylococcus aureus*, *Bacillus substilis*, *Bacillus cereus*, and *Enterococcus faecalis*. They were obtained from Federal Medical Centre, Umuahia, Abia State. Antibacterial activity of the sample was determined by using the agar well diffusion method and bacterial growth was subcultured on nutrient broth for their in vitro testing which was prepared by dissolving (24 g) of nutrient broth. The

mixture was autoclaved for 15 minutes at 120 °C. Stock solution for in vitro antibacterial activity was prepared by dissolving 5 mg of the compound in 9 cm^3 of DMSO to make the stock solution of 100 g/mL. Exactly 1.15 cm^3 of liquid nutrient agar was prepared separately for tested target microorganism cultures and 1 cm3 of nutrient broth for antibacterial activity. Inoculation was done with the help of a micropipette with sterilized tips and 100 µL of activated strain was placed onto the surface of agar plate. It spread over the whole surface and then two wells having diameter of 10 mm were dug in media and incubated at 37°C for 48 hours. The zone of inhibition was measured around the disc and has been expressed in mm.

2.3 Statistical analysis

Statistical significance was determined using Duncan Multiple Range Test. Results were considered statistically significant at $P<0.05$ and were expressed as mean ±SD.

3.0 Results and Discussion

Some physical and analytical data of BPEN and [Ni(BPEN)] are shown in Table 1. Table 1 reveals that the % yield of [Ni(BPEN)] was 75%. The complex is air and photostable. The high decomposition temperature from 209 to 212 ^oC associated with the change in colour from white (BPEN) to light green [Ni(BPEN)] suggest that coordination occurred since transition metal complexes are known to exhibit colour as one of their characteristics (Najlaa et al., 2020). The measured conductivity of BPEN and [Ni(BPEN)] are 236.0 and 218.2 $Sm^2.mol^{-1}$ respectively. This suggested that the ligand and complex are electrolytes (Geary, 1971). Data obtained from % elemental analysis were compared with the calculated data and were found to be in good agreement with the calculated data. This suggested a metal-ligand ratio of 1:1.

Table 2 shows the solubility of BPEN and [Ni(BPEN)] in various solvents. BPEN was found to be soluble in distilled water, n-hexane, ethanol, methanol, petroleum ether and DMSO. However, the complex was found to be insoluble in n-hexane and petroleum ether. It was slightly soluble in ethanol and methanol but completely soluble in DMSO. The solubility data indicated that the complex is highly polar.

Fig. 1 shows FTIR spectra of DPTA and [Ni(BPEN)]. FTIR spectrum of the complex was compared with that of the free ligand to determine the coordination sites that were involved in the bonding. In the FTIR spectrum of BPEN, the carbonyl of amide stretching frequency was observed at 1697.66 cm^{-1} but in the FTIR spectrum of [Ni(BPEN)], the band was observed at 1642.00 cm-1. This indicates the existence of interaction and that C=O of amide was involved in coordination to nickel. In the FTIR spectrum of BPEN, carbonyl of β-lactam was observed at 1178.04 cm^{-1} but this vibration frequency was absent in the spectrum of the complex indicating this functional group participated in coordination. It is hereby proposed that C=O is converted to C-O during complexation. C-O stretching frequency was observed at 1134.00 cm^{-1} in the spectrum of the metal complex. Also, the vibration frequency of hydroxyl group was observed at 3542.26 cm^{-1} in the spectrum of the ligand but was absent in the spectrum of the metal complex. This suggested deprotonation of OH during complex formation. N-H stretching frequency was observed at 3351.50 cm^{-1} in the spectrum of the ligand. This vibration frequency was shifted to lower wavenumber 3300.00 cm^{-1} in the spectrum of the complex, indicating the participation of N-H functional group in complex formation. An increase in electron density can increase N-H bond length and consequently slows down the vibration frequency as observed in this study.

Table 1: Some physical and analytical data of BPEN and [Ni(BPEN)]

Ligand /complex	BPEN	[Ni(BPEN)]
Colour	White	Light green
M.P (ºC)	209	212
Yield (%)	-	75
Conductance ($Sm^2.mol^{-1}$)	236.0	218.2
C (%) Found Calc.	57.42(57.47)	48.99 (49.01)
H (%) Found Calc.	5.41 (5.43)	4.35(4.37)
N (%) Found Calc.	8.37(8.38)	7.15 (7.14)
S (%) Found Calc.	9.59(9.58)	8.14(8.18)
Ni (%) Found Calc.	-	14.95 (14.97)

Table 2: Solubility data of BPEN and [Ni(BPEN)] in some selected solvents

Ligand/ complex	n-Hexane	Distilled water	Petroleum ether	Ethanol	Methanol	DMSO
BPEN	**S**	**S**	**S**	**S**	**S**	**S**
[Ni(BPEN)]	**IS**	**IS**	**IS**	**SS**	**SS**	**S**

Key: S-Soluble, SS-Slightly Soluble, IS-Insoluble

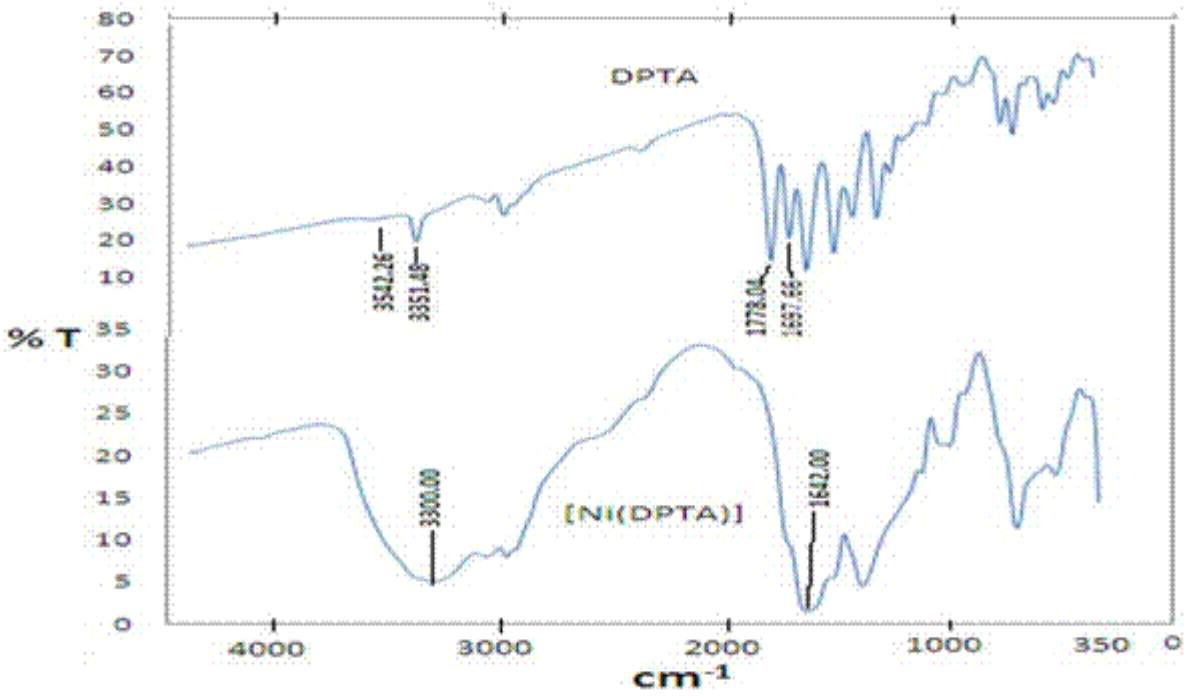


Fig. 1: FTIR spectra of BPEN and [Ni(BPEN)

Fig. 2 shows UV-Vis spectra of BPEN and [Ni(BPEN)]. The ligand and its nickel (II) complex absorbed maximally at λmax = 97.50, 203.50,209.50, 215.50, 226.50, 238.50,

255.50, 259.50, 270.50, 278.50, 284.50 and 317.50 nm.

These absorption bands are assigned to π–π* and n–π* transitions. These bands are known as Intra-Ligand Charge Transfer (ILCT). Similarly, the UV-Vis spectra of [Ni(BPEN)] showed an absorption band at λmax= 389.00 nm. This absorption band is due to ligand to metal charge transfer (LMCT).

Figs. 3 and 4 show the 1H NMR spectra of BPEN and [Ni(BPEN)]. The 1H NMR spectrum of BPEN shows a singlet at 11.00 ppm. This chemical shift was assigned to OH proton of carboxylic acid. The shift was absent in the spectrum of [Ni(BPEN)]. The absence of OH chemical shift in the complex indicated deprotonation of OH during coordination. A doublet observed at 8.72 ppm in 1H NMR spectrum of BPEN was assigned to NH proton.

Multiplets observed in the 1H NMR spectrum of the ligand at 7.12-7.32 ppm were assigned to aromatic protons and it appeared at 7.25 ppm in the 1H NMR spectrum of the nickel (II) complex. Multiplets observed at 3.39 ppm in the 1H NMR spectrum of the ligand were attributed to CO-CH2 of the thiazolidine ring and were observed at 3.52 ppm in the spectrum of the nickel complex. A singlet observed at 1.46 and 1.59 ppm was assigned to protons of the methyl group of the thiazolidine ring.

However, in the 1H NMR spectrum of [Ni(BPEN)], these were observed at 1.55 b 1.15 ppm respectively. Fig. 5 and 6 show the 13C NMR spectra of BPEN and [Ni(BPEN)]. A comparison of the 13C NMR

(DEPT 135) the spectrum of BPEN and [Ni(BPEN)] were made. In the 13C NMR (DEPT 135) spectra of BPEN, the chemical shift of C=O amide was observed at173.73 ppm.

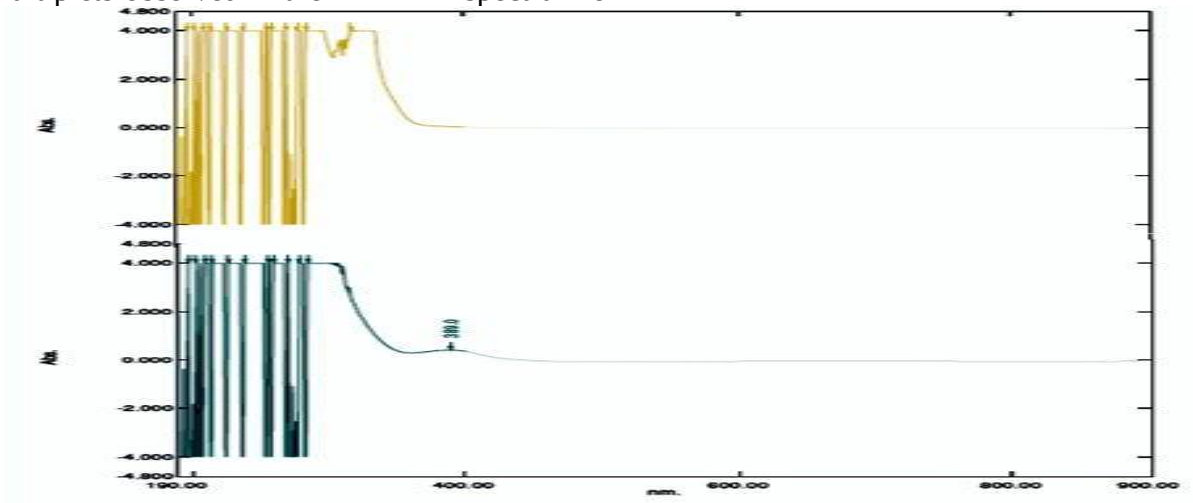


Fig. 2: Uv-Visible spectra of BPEN and [Ni(BPEN)]

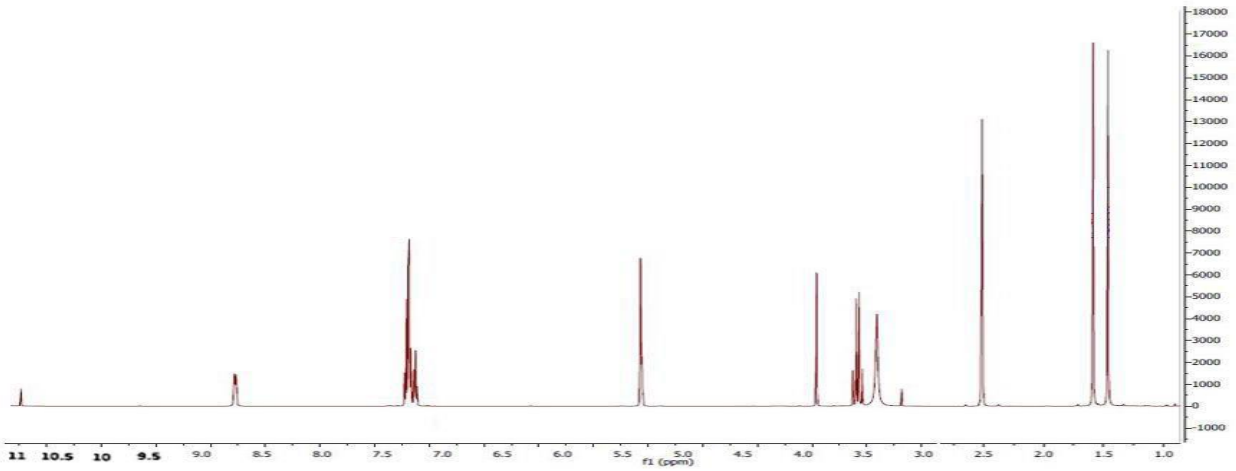


Fig. 3: ^{1}H NMR Spectrum of BPEN

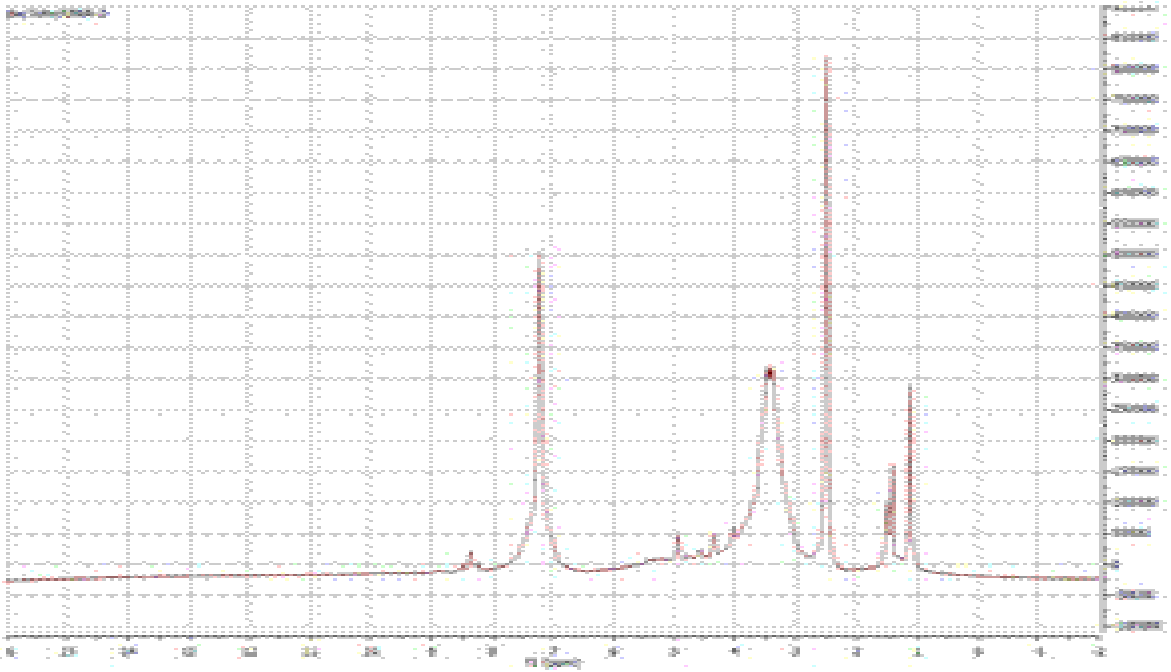


Fig. 4: ^{1}H NMR spectrum of [Ni(BPEN)]

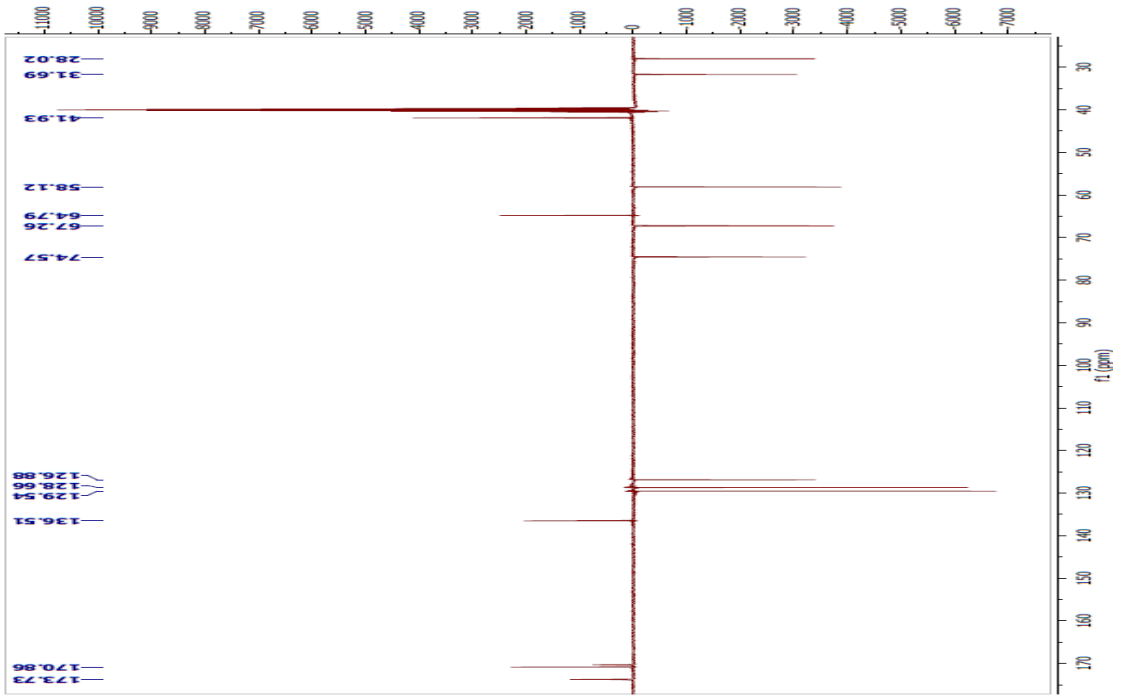


Fig. 5 : ^{13}C NMR (DEPT 135) spectrum of BPEN

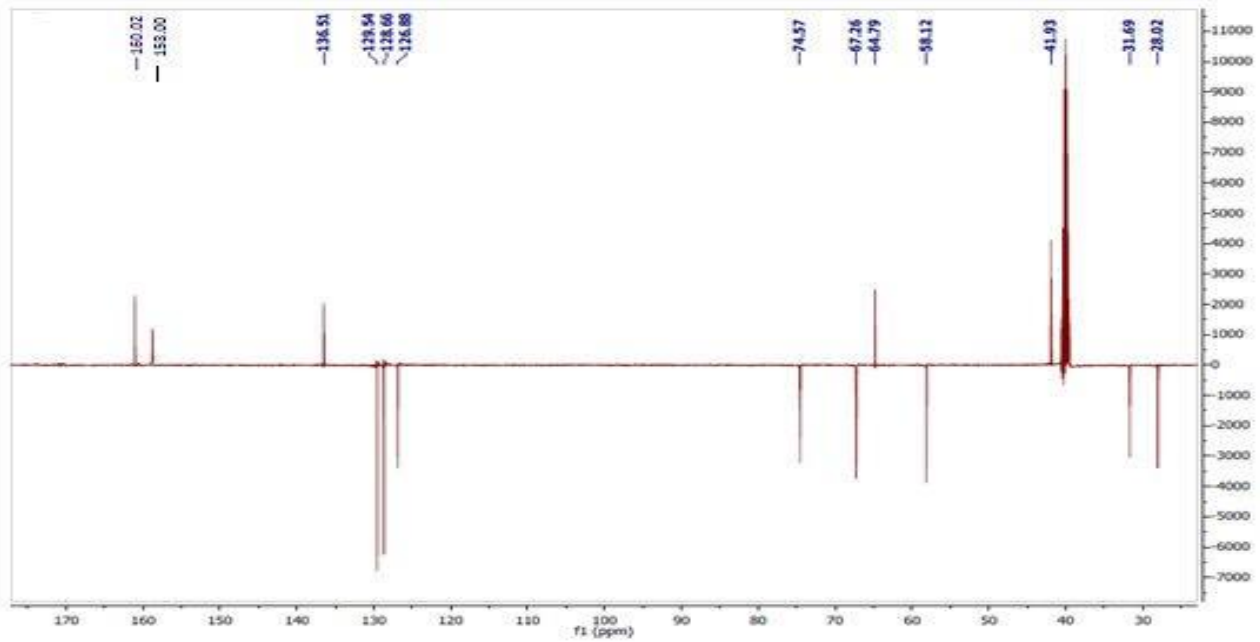
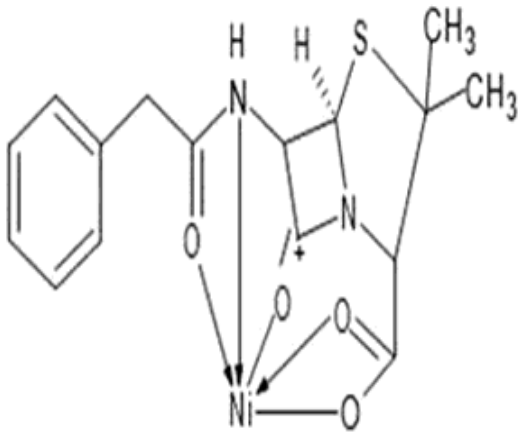


Fig. 6: ^{13}C NMR (DEPT 135) spectrum of [Ni(BPEN)]

This functional group was observed at 158.00 ppm in the ^{13}C NMR (DEPT 135) spectrum of [Ni(BPEN)]. This suggests that C=O of amide was involved in the complexation of nickel ions. The chemical shift of C=O carboxylic acid and β-lactam was observed at a chemical shift at 170.86 and 170.05 ppm in the spectrum of BPEN. In the spectrum of [Ni(BPEN)], the chemical shift corresponding to C=O of carboxylic acid was observed at 160.02 ppm. This shift suggests that C=O of carboxylic acid was involved in coordination with the nickel ion. The absence of C=O of β-lactam in the ^{13}C NMR(DEPT) spectrum of [Ni(BPEN)] suggests that C=O was transformed to C-O during complexation. The aromatic carbons were observed at 126.88 and 29.54 ppm in the spectra of the ligand and complex respectively.

Based on elemental analysis, FTIR, UV/Visible, ^{1}H NMR and ^{13}C NMR(DEPT) spectroscopic analysis, the structure in Figure 7 was proposed for [Ni(BPEN)]. Table 3 shows the antibacterial activity of DPTA and [Ni(BPEN)] complex against four-gram negative bacterial strains (*Escherichia coli, Enterobacter cloacae, Pneumonia aeruginosa,* and *Campylobacter fetus*) and four gram-positive bacterial strains (*Staphylococcus aureus, Bacillus substilis, Bacillus cereus*, and *Enterococcus faecalis*). The zone of inhibition of the metal complex was significantly higher ($P<0.05$) compared to the free ligand against the bacterial strains used.



Metal complexes coordinatively saturate the bacterial strains and operate by physical

interactions. From the above, it was concluded that the process of chelation affected the biological behavior of the compound which in turn increased the inhibitory potential against the bacterial strains.

Table 3: Percentage zone of inhibition (mm) of BPEN and [Ni(BPEN)]on the bacterial population

Bacteria		Ligands	
Type	**Name**	**DPTA**	**[NiOPTA]**
Gram positive	Staphylococcus aureus	2.52 ± 0.3^{a}	6.9 ± 0.02^{b}
Gram positive	*Bacillus substilis*	6.12 ± 0.03^{a}	12.83 ± 0.04^{b}
Gram positive	*Bacillus cereus*	4.96 ± 0.01^{a}	7.70 ± 0.01^{b}
Gram positive	*Enterococcus*	2.12 ± 0.03^{b}	8.12 ± 0.03^{b}
Gram negative	*Escherichia coli*	10.43 ± 0.03^{a}	11.94 ± 0.06^{b}
Gram negative	*Enterobacter cloacae*	1.32 ± 0.03^{a}	6.52 ± 0.06^{b}
Gram negative	*Pneumonia aeruginosa*	6.82 ± 0.03^{a}	13.11 ± 0.01^{b}
Gram negative	*Campylobact*	7.32 ± 0.02^{a}	12.63 ± 0.04^{b}

****Values are mean ±SD of 3 replicates. Values carrying superscripts different from their parent**

4.0 Conclusion

The nickel (II) complex of BPEN was synthesized and characterized using techniques such as elemental analysis, conductivity measurement, FTIR, UV-Vis, ^{1}HNMR,^{13}CNMR (DEPT 135).The ligand coordinated to the nickel ion through OH, NH, C=O of amide, C=O of β-lactam and C=O of carboxylic acid. Hence, BPEN behaved as a pentadentate ligand towards nickel ion. The antibacterial activity of BPEN and [Ni(BPEN)] against four-gram negative bacterial strains (*Escherichia coli*, *Enterobacter cloacae*, *Pneumonia aeruginosa*, and *Campylobacter fetus*) and four gram-positive bacterial strains (*Staphylococcus aureus, Bacillus substilis, Bacillus cereus,* and *Enterococcus* antibiotics for each micro-organism are significantly different ($P<0.05$) *faecalis*) was studied. It was observed from the result that [Ni(BPEN)] has more inhibitory potential than the uncomplexed BPEN. From the above, it was concluded that the process of chelation affected the biological behavior of the compound which in turn increased the inhibitory potential against the bacterial strains.

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