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Synthesis, Characterization and Antibacterial Studies of 4-[(E)-benzylideneamino]-N-thiazoyl-2-yl-benzenesulfonamide and its Fe(III) Complex

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ABSTRACT

Schiff bases represent an important class of pharmacologically active molecules which have triggered the interest of medicinal chemist as they possess a variety of pharmacological properties. A new Schiff base 4-[(E)-benzylideneamino]-N-thiazoyl-2-yl-benzenesulfonamide (BATS) was prepared by equimolar reaction between benzaldehyde and sulphathiazole in the ratio 1:1. Its iron complex was also prepared by the action of the (BATS) Schiff base and Fe(III) ion. The BATS ligand and its iron complex were characterized by melting point, solubility, colour, conductivity, elemental analysis, infrared, UV/Visible, ^{1}HNMR and ^{13}CNMR spectroscopy. The spectral data showed that the Schiff base ligand (BATS) behaved as a tridentate ligand coordinating to the metal ion through -NH group and two C=N groups. The complex is coloured, non-ionic and non-electrolytic. Similarly, it has been found that Fe(III) complex has a trigonal geometry. The (BATS) and [Fe(BATS)] have been screened for their*in vitro* antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus and Salmonella typhi*. In conclusion, [Fe((BATS)] showed enhanced antibacterial activity than (BATS). This enhanced activity might be due to chelation process, which reduces the polarity of metal ion by coordinating with ligands.

Keywords: Schiff base, chelation, complex, bacterial

INTRODUCTION

Schiff bases are among the most important ligands used in modern coordination chemistry [1, 2], due to their well-known coordinative capability. They play an important role in revealing the preferred coordination geometries of metal complexes due to their preparative accessibility, diversity and structural variability. The huge research on Schiff base coordination complexes in the past few decades has given rise to several new molecules that have been of biological importance [3].

Schiff base compounds had been shown to exhibit a variety of applications including biological, clinical, analytical and industrial in addition to their important roles in catalysis and organic synthesis [4-6]. Schiff's bases are considered as an important class of compounds in the medical and pharmaceutical fields [7-9]. They have also been found to exhibit a broad range of biological activities including anti-fungal, anti-bacterial, anti-malarial, anti-proferative, anti-inflammatory, anti-viral, and anti-pyretic properties [9, 10].

Schiff bases play an important role as intermediates for the synthesis of some bioactive compounds such as β-lactams [11] and it has been confirmed that some drugs exhibit increased activity when administered as metal complexes [12]. Schiff bases have the ability to form coordinate bonds with many metal ions through azomethine, enolic or thiolic groups, and so they have been used for synthesis of metal complexes due to their easy formation and strong metal binding ability. The azomethine nitrogen in Schiff base, not only provides binding site for metal ions but also makes attachment with various substrates of bio-molecules like proteins and amino acids in biological systems and that of diseases-causing germs.

In recent years, there has been a continued interest in synthesizing Schiff base ligands [13] and coordination compounds [14-16] because of their biological activities [17–20]. Transition coordination compounds with a Schiff base (HL) derived from the condensation of cephalexin antibiotic with sulphathiazole have been reported [21] and was tested against *Staphylococcus aureus* as a Gram-positive bacterium and *Escherichia coli* as a Gram-negative bacterium. The Schiff base and its complexes were found to be better bacterial inhibitor than the parent antibiotics [22]. It has been reported that metal complexes can effectively inhibit a number of gram-positive and gram-negative bacteria [23, 24].

On the other hand, the antibacterial activities of the rifampicin metal(II) complexes investigated exhibited higher activity than the standard, rifampicin especially those of Fe(II), Co(II) and Cu (II). A similar trend was observed for clofazimine metal(II) complexes, particularly those of Fe (II), Co(II) and Zn(II), showing remarkably higher activity than the standard, clofazimine [25]. Literature survey reveals that not much work has been carried out on Schiff base ligand derived from sulfathiazole with benzaldehyde. In view of the above findings, we hereby report the synthesis, characterization and antibacterial activity of a novel Schiff base ligand 4-[(E)-benzylideneamino]-N-thiazoyl-2-yl-benzenesulfonamide and its Fe(III) complex.

MATERIALS AND METHODS

All the chemicals used were of analytical grade and were used without further purification. The melting points and decomposition temperature of the novel Schiff base ligand and the Fe(III) complex were determined using melting point apparatus (Gallen Kamp). Infrared spectra of solids (in a KBr pellets) were recorded in the 4400–350 cm^{-1} region on a Perkin Elmer spectrum Bx FT-IR spectrophotometer. ^{1}H and $^{13}CNMR$ spectra were determined using Bruker NMR spectrophotometer (tetramethylsilane was used as internal standard and DMSO-d6 as solvent). UV spectra were obtained on a UV-1800 series spectrophotometer. Microanalysis (C, H, S and N) of the synthesized ligand and complex were carried out using Perkin-Elmer 240B elemental analyzer. The conductivity of the Schiff base ligand and its corresponding Fe(III) complex were measured by Jenway Conductivity Meter 4510 at room temperature in a concentration of 10^{-3} M DMSO solution. The bacteria used in the antimicrobial test were obtained and confirmed at the Microbiology Laboratory of the Federal Medical Center, Umuahia, Abia State, Nigeria, and were used as test organism.

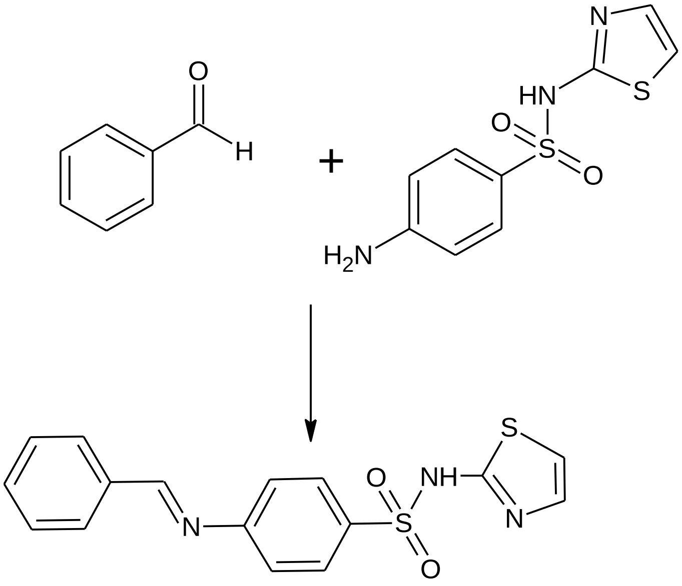
Synthesis of 4-[(E)-benzylideneamino]-N-thiazoyl-2-yl-benzenesulfonamide (BATS)

The synthesis was prepared according to the procedure reported in the literature [20] with slight modification. Equimolar solutions of sulphathiazole (5.11 g; 2 mmol) in ethanol (45 cm^3) solution was added to 2.03 cm^3 (2 mmol) of benzaldehyde with constant stirring. The solution was stirred and refluxed for 3 hours. The product was filtered off, washed several times with H_2O, ethanol and dried in a desiccator. The equation of reaction is shown in Scheme 1. The yield was calculated.

Preparation of Fe(III) complex of 4-[(E)-benzylideneamino]-N-thiazoyl-2-yl-benzenesulfonamide, [Fe(BATS)]

To hot solution of BATS (6.87 g; 2 mmol) in ethanol (45 cm^3), 45 cm^3 aqueous solution of $FeCl_3.2H_2O$ (3.96 g; 2 mmol) was added and refluxed for 2 hours. The solution obtained were filtered and evaporated to half of its volume. The concentrated solutions were left overnight at room temperature for precipitation to take place. The product was filtered off, washed several times with H_2O, ethanol for purification and dried in a desiccator. The yield was calculated

The general synthesis of the Schiff base BATS is proposed in Scheme 1.



Scheme 1: Synthesis of 4-[(E)-benzylideneamino]-N-thiazoyl-2-yl-benzenesulfonamide (BATS) Schiff base ligand

Antibacterial Activity Test

The organisms used were gram-negative *E. coli and P. aeruginosa*. The gram-positive bacterial strains were *S. aureus and S. typhi*. The organisms were clinical isolates obtained from Federal Medical Centre, Umuahia, Abia State. Antibacterial activity of the samples were determined by using agar well diffusion method while bacterial growth were subcultured on nutrient broth for their *in vitro* testing which were 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 compound in 9 cm^3 of DMSO. Inoculation was done with the help of micropipette with sterilized tips in which 100 μL of activated strain was placed onto the surface of agar plate. It was 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. Penicillin and distill water were used for positive and negative control. The diameters of the zones of inhibition were measured to the nearest mm.

RESULTS AND DISCUSSION

Table 1: Some physicochemical properties of BATS and [Fe(BATS)] complex

Ligand/ Complex	Colour	M.P. (dec.) (°C)	Yield %	Conductance ($Sm^2.mol^{-1}$)	Carbon % Found (Calc.)	Hydrogen % Found (Calc.)	Nitrogen % Found (Calc.)	Sulphur % Found (Calc.)
BATS	Greenish-brown	244-246	96.1	10.5	55.92 (55.96)	3.79 (3.82)	12.21 (12.24)	18.63 (18.67)
[Fe(BATS)]	Brick red	277-279	71.8	17.2	48.20 (48.25)	3.00 (3.04)	10.49 (10.55)	16.09 (16.10)

Table 1 shows that BATS ligand and [Fe(BATS)] complex are all colored compounds and were microcrystalline solids which decomposed at 244-246 °C and 277-279 °C. Since the complexes are colored, it indicates that complexation occurred. The measured conductance values of BATS and [Fe(BATS)] were 10.5 and 17.2 Sm^{2}mol ^{1}respectively are too low to account for their electrolytic behavior. Geary [26], reported that coordination compounds with molar conductance above 100 Ohm^{-1}mol^{1}cm^{1}are electrolytes, indicating that those below this threshold value are weak electrolyte. The elemental analysis results were in good agreement with the calculated value and give evidence of the formation of ligand and [Fe(BATS)] complex. The high percentage yield of the BATS ligand and its [Fe(BATS)] complex indicates the high purity of the compounds. The analytical data of the complex indicated a 1:1 metal: ligand stoichiometry.

Table 2: Solubility data of the BATS and [Fe(BATS)] complex in various solvents

Ligand/Complexes	n-Hexane	Methanol	Petroleum ether	DMSO
BATS	SS	IS	SS	VS
[Fe(BATS)]	SS	IS	S	VS

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

Table 2 shows that BATS ligand and [Fe(BATS)] complex were insoluble in methanol, slightly soluble in n-hexane and soluble in DMSO. [Fe(BATS)] was soluble in petroleum ether. This suggested that BATS ligand and [Fe(BATS)] complex were moderately polar.

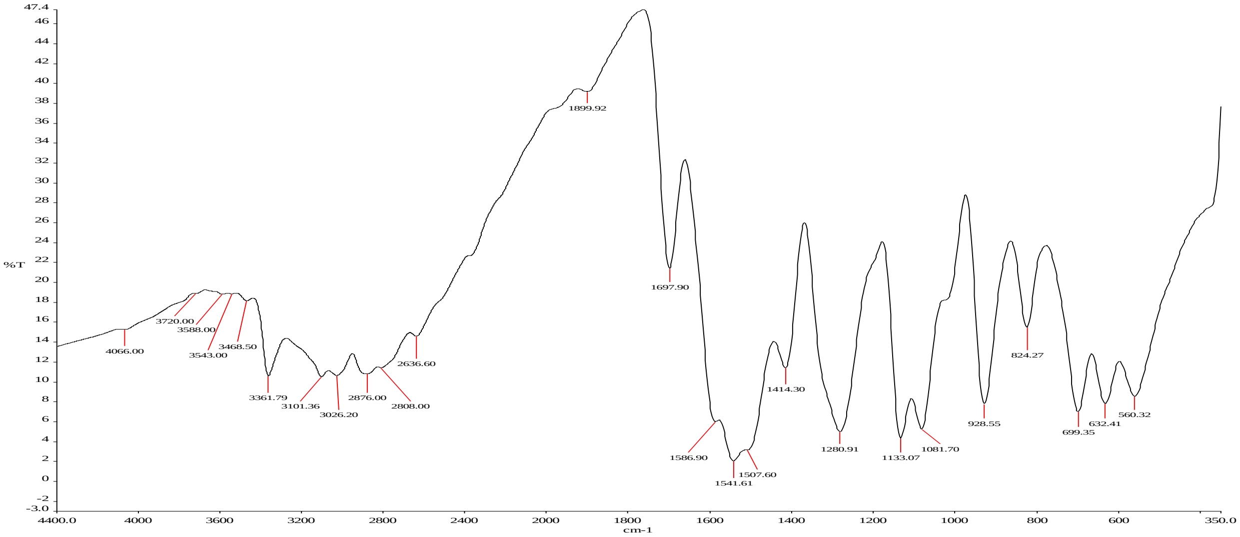


Figure 1: IR spectrum of BATS ligand

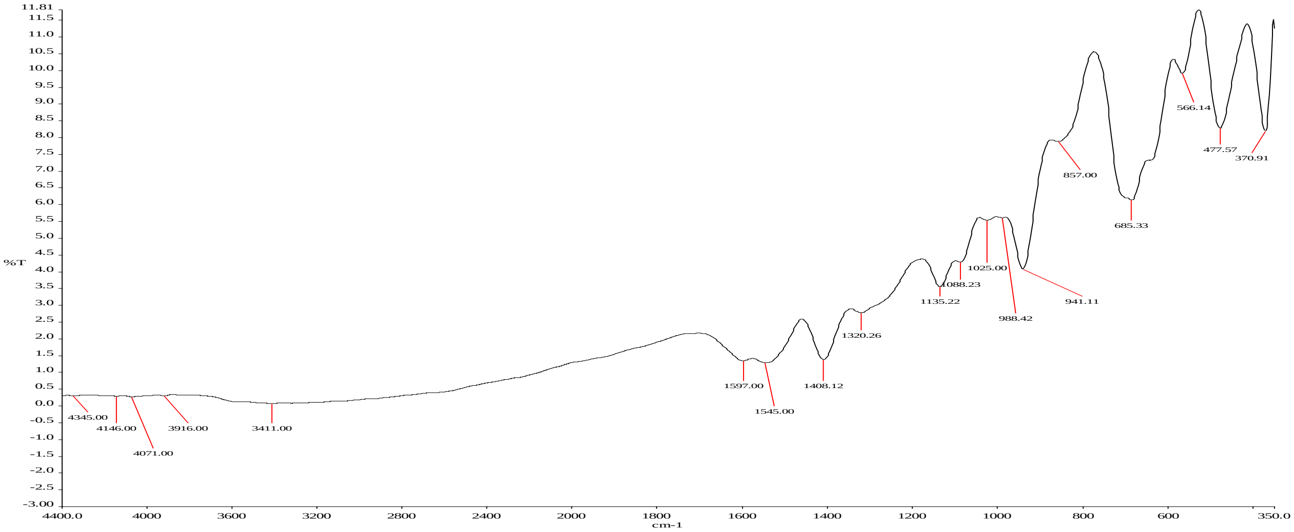


Figure 2: IR spectrum of [Fe(BATS)] complex

The FTIR of Schiff base BATS and [Fe(BATS)] are shown in Fig.1 and Fig. 2 respectively. The IR spectral data was studied to show evidence for complex formation and also for the determination of the mode of coordination of ligands with the metal ion during complex formation. The FTIR of the BATS Schiff base showed absorption band at 1697.90 cm^{-1} which was assigned to azomethine υ(C=N) stretching mode. On comparison with [Fe(BATS)], this band was shifted to lower wave number 1597.57 cm^{-1}. This indicated the participation of the azomethine nitrogen in coordination with Fe during complexation. Similar shift was reported in previous publications [20]. The absence of band characteristics of υ(C=O) confirmed the formation of the proposed Schiff base framework. The characteristic ring vibrations at 3026.20 cm^{-1}and 2876.00 cm^{-1} in the spectrum of the ligand have been assigned as aromatic and aliphatic rings. The band at 3361.79 cm^{-1} was assigned to υ(N-H) stretch in the BATS ligand. In the [Fe(BATS)] complex, the υ(N-H) stretch shifted to a higher wave number 3411.00 cm^{-1} . This suggested the involvement of υ(N-H) in coordination with Fe. The FTIR vibration band observed at 1133.07 cm^{-1} in the spectrum of the Schiff base was assigned υ(S=O). This functional group remained unchanged 1135.22 cm^{-1} in the complex [Fe(BATS)]. This suggested that S=O group was not involved in coordination with iron.

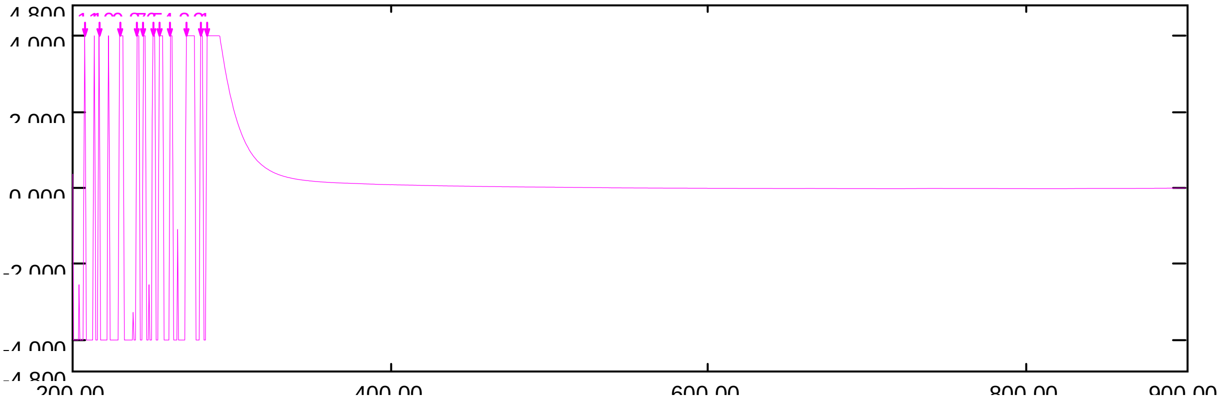


Figure 3: Uv/Vis spectrum of BATS ligand

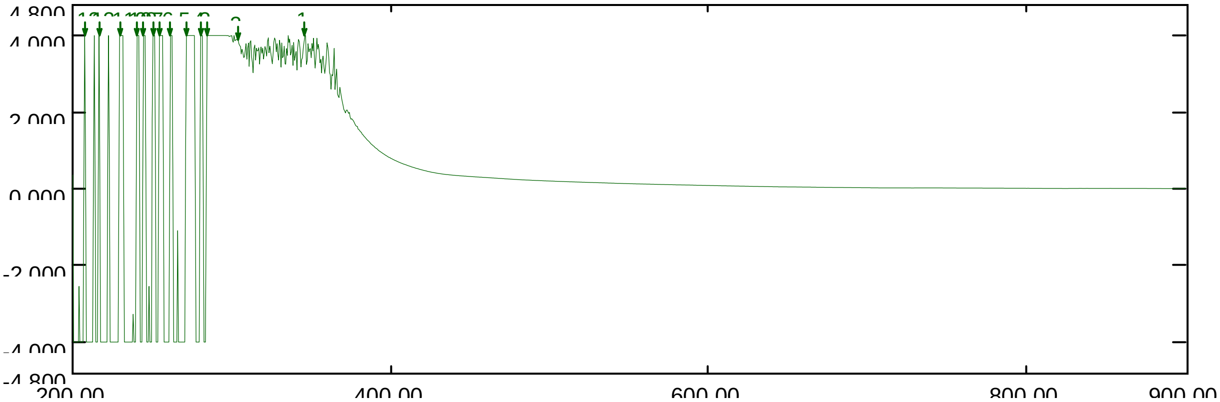


Figure 4: Uv/Vis spectrum of [Fe(BATS)] complex

The UV-Vis spectra of BATS and [Fe(BATS)] absorbed at λ maxima = 207.50, 216.50, 229.50, 244.50, 250.50, 254.50, 261.50, 271.50, 280.50 and 284.50 nm and these absorptions were as a result of the chromophores presents in the PTSA. These transitions have been assigned π- π* and n- π*. These transitions are known as Intra-Ligand Charge Transfer (ILCT). In the Uv/Vis spectra of the complex, the ligand to metal charge transfer (LMCT) was observed at 390.50 nm. This suggested that complexation occurred.

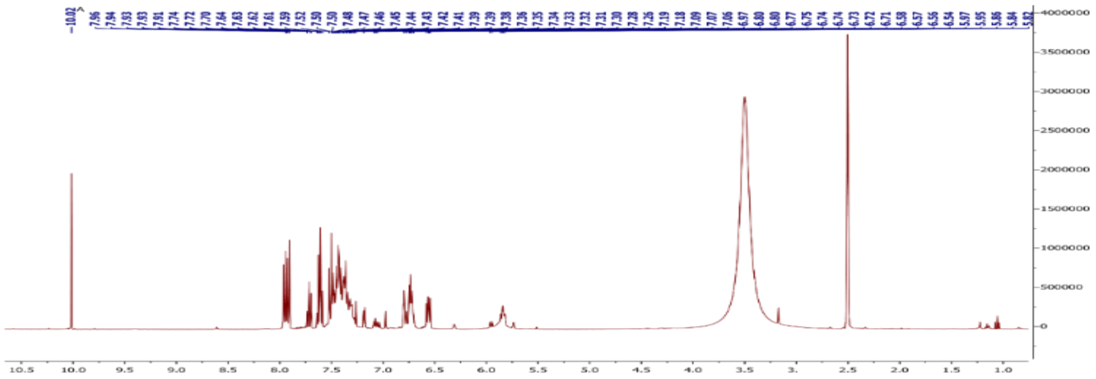


Figure 5: ^{1}H NMR spectrum of BATS

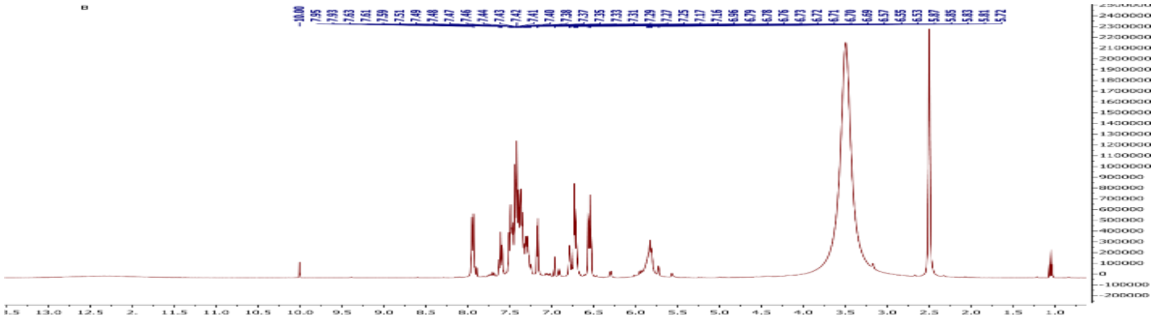


Figure 6: ^{1}H NMR spectrum of [Fe(BATS)]

The ^{1}H NMR spectra of BATS ligand and its Fe complex are represented in Figures 5 and 6 respectively. The resonance peak at 10.02 ppm in ^{1}H NMR spectrum was assigned to the protons of -SO_2NH group. This chemical shift was absent in the ^{1}H NMR spectrum of the complex [Fe(BATS)], indicating complexation. The chemical shift which was observed at 5.82-6.58 ppm was assigned as thiazole protons. This remained unchanged in the complex. The peaks, which appeared as multiplets in the spectrum of the ligand at 6.71-7.59 ppm, were assigned phenyl group. This also remained unchanged in the complex [Fe(BATS)]. Similar shift was reported in our previous publications [20, 27]. The peaks of the azomethine protons observed at chemical shift 8.60 ppm in the spectrum of the ligand was absent in the spectrum of the metal complex. This is suggestive that deprotonation occurred during complexation [20, 27].

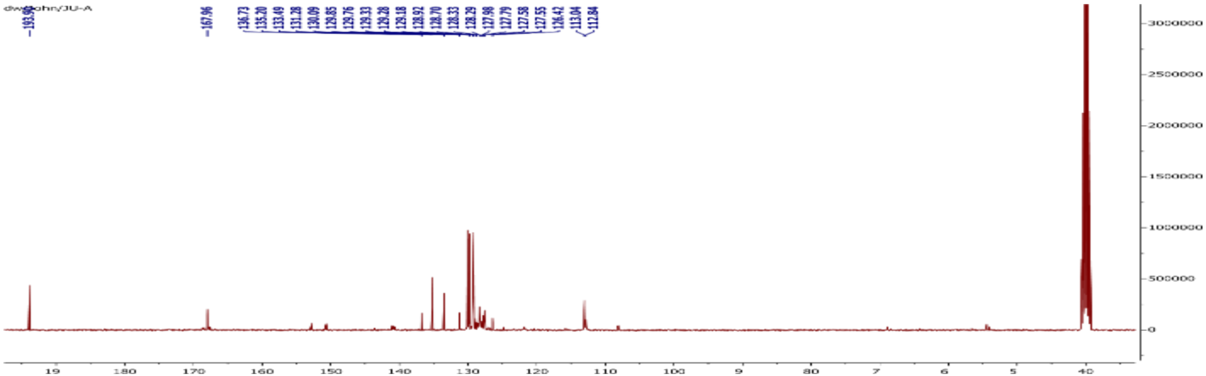


Figure 7: ^{13}C NMR spectrum of BATS

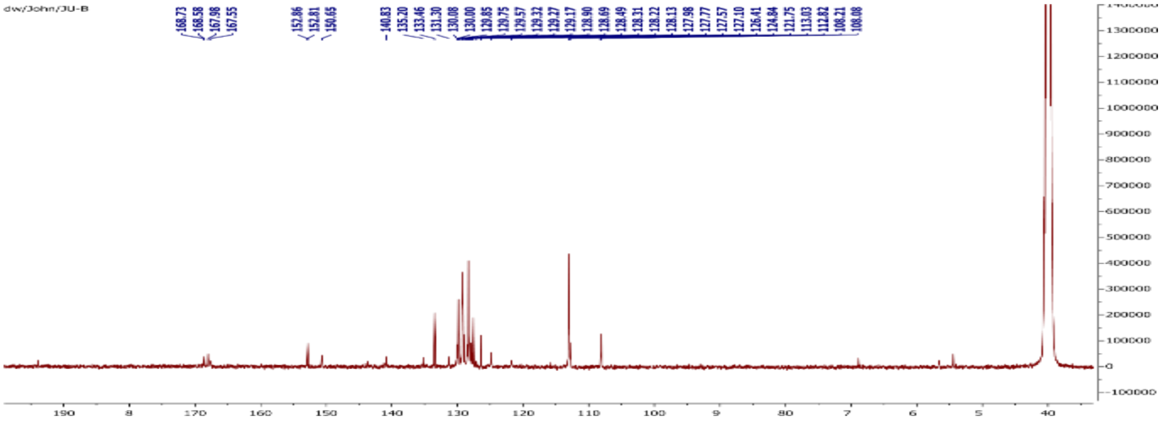


Figure 8: ^{13}C NMR spectrum of [Fe(BATS)] complex

The ^{13}C NMR spectra of BATS and [Fe(BATS)] are shown in Figures 7 and 8 respectively. The ^{13}C NMR spectrum of the ligand showed azomethine resonance peak at 167.96 ppm. In the spectrum of the complex, azomethine resonance peak was also observed at168.00 ppm.

Furthermore, based on the spectroscopic studies, the structure in Figure 9 is proposed for the newly synthesized [Fe(BATS)].

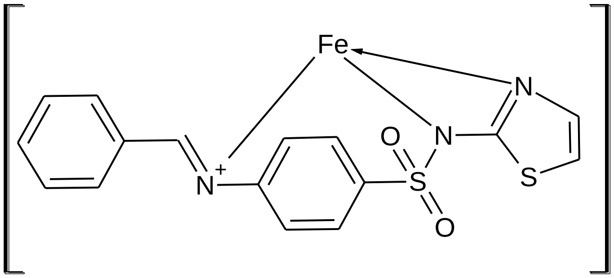


Figure 9: Proposed structure for [Fe(BATS)]

Table 3 shows the antibacterial activity results obtained for BATS ligand and [Fe(BATS)] complex.

Table 3: Zone of inhibition (mm) of BATS and [Fe(BATS)] on some bacterial organisms

Ligand/complex	*E. coli*	*P. aeruginosa*	*S. typhi*	*S. aureus*
BATS	13.00 ±0.02	16.00±0.04	14.00±0.01	17.00±0.03
[Fe(BATS)]	16.00± 0.03	9.00±0.04	16.00± 0.05	17.00±0.01
Distilled water	00.00± 0.00	0.00±0.00	00.00± 0.00	00.00±0.00
Penicillin	37.00± 0.03	37.00±0.04	36.00± 0.05	38.00±0.01

*>15: Significant, 10-14: Moderate, <10 Weak

It was observed from the data that the ligand showed significant (>15 mm) activity against *P. aeruginosa* and *S. aureus* bacterial strains while showing a moderate activity against *E. coli* and *S. typhi* bacterial strains. [Fe(BATS)] complex showed better activity against *E. coli*, *S. typhi* and *S. aureus.* The zone of inhibition for the positive control were significantly >15 mm for all the bacterial strains used. It was concluded that the antibacterial activity of the complex could be due to the reduction of the polarity of the metal ion by partial sharing of the positive charge with the ligand's donor atoms so that there is electron delocalisation within the metal complex. This may increase the lipophilic character of the metal complex, enabling it to permeate the lipid layer of the organism killing them more effectively [28].

CONCLUSION

In the light of above discussion, we synthesized a new N, N, N donor type Schiff base (BATS) which was further complexed with Fe to produce a new metal complex, [Fe(BATS)]. We also established that they are all coloured compounds and were microcrystalline solids which decomposed at 244-246 ^{o}C and 277-279 ^{o}C. Similarly, the melting point of the complex was higher than that of the ligand and their low conductivity value indicated the non-ionic as well as non-electrolytic nature. The elemental analysis and the observed spectral data agreed with their structures. The mode of coordination of BATS to Fe ion was ascertained to be through the -NH group and two C=N groups. A trigonal geometry has been proposed for the metal complex. Furthermore, BATS ligand and its [Fe(BATS)] complex were screened for antibacterial activity against three gram-negative (*S. typhi*, *E.* coli and *P. aeruginosa*) and one gram-positive (*S. aureus*) bacterial strains. The ligand showed significant activity against two gram-negative and one gram-positive bacterial strains. The metal complex showed enhanced antibacterial activity. Finally, they were proved to be active against all bacterial strains.

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