

Research Article

Nonfunctionalized Cation of an Ionic Liquid as a Ligand in the Synthesis of a New Coordination Compound and Assessment of Its Biological Activity

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Literature evidences reveal the affinity of ionic liquids for biomembranes that they are readily absorbed into the cell, resulting in a variety of biological effects, including broad antibacterial potential and anticancer activity. Recent research directions considered the ions of this class of compounds as a new choice of ligands in the synthesis of transition metal complexes for various applications. Based on this, the present work reports the synthesis, structural characterization, and *in vitro* antibacterial activities of a tetrahedral hexacationic Co(II) complex formed by coordinating with the cation of an ionic liquid, *N*-butyl-4,4'-bipyridinium bis(trifluoromethylsulfonyl)amide ($[\text{C}_4\text{Bip}][\text{TF}_2\text{N}]$). It has been demonstrated by the isolation and characterization of tetrakis-(*N*-butyl-4,4'-bipyridinium)cobalt(II)dichloride-tetrakis-(bis(trifluoromethylsulfonyl)amide), $[(\text{C}_4\text{Bip})_4\text{Co}]\text{Cl}_2(\text{TF}_2\text{N})_4$. The ligand and complex are characterized spectroscopically (^1H , ^{13}C , and ^{19}F NMR, ESI MS, ICP OES), and by CHNS elemental analysis, halide estimation, and conductivity studies. The antibacterial activities of the compounds against two bacteria, *Klebsiella pneumoniae* (*K. pneumoniae*) and *Staphylococcus aureus* (*S. aureus*), are screened using the agar well-diffusion method and were compared with a reference (gentamicin). The metal complex demonstrated better inhibition than the ionic liquid and the reference.

1. Introduction

Ionic liquids (ILs) are salts with a melting point of less than 100°C . Many of them are liquids at and/or below room temperature and are thus called room temperature ionic liquids (RTILs) [1]. The choice of appropriate cation-anion combinations enables to design an IL with a set of desired properties for a specific application [2]. This makes them a class of materials for a wide spectrum of applications that academia and industries are attracted to [3–5]. Recently, these liquids are attracting increasingly the attention of inorganic and material chemists for the synthesis of zeolites and nanoparticles [6–12], in electrochemical applications such as electrolytes in batteries and in photovoltaic devices, a medium for electrodeposition or electropolishing of metals [13–17], in pharmaceuticals synthesis, and in drug delivery since the ions from this family could represent a new choice

of versatile ligands, able to interact with lipids and proteins, affecting the structure, dynamics, and activity of biomembranes [18–20]. The permutation between the large number of cations and anions allows a large number of ionic liquids with a corresponding amount of properties which can offer unique possibilities to the inorganic chemist. For instance, their application in coordination chemistry is important that their coordination tendency to metal ions and the property of the combination need investigation. In this regard, a number of reports disclosed that typical ionic liquids do not extract metal cations because of their poor coordination. Even if they do, the coordination takes place between the metal ion and the poorly coordinating anions of the ionic liquid [21–23]. This required the use of some extractants or functionalized ionic liquids incorporating some functional groups in their cations and/or anions which makes them both solvent and extractant [2, 24]. However,

these strategies require further amount of synthetic work and render the final application more laborious, expensive, and less environmental friendly. Thus, the objective of this work was to investigate the coordination ability of a non-functionalized cation of an ionic liquid to a metal ion. The outcome of the investigation was a hexacationic coordination compound. The result introduces a promising new material which contains the combined features of ionic liquids and metal ions such as medicinal, magnetic, spectroscopic, and catalytic properties.

2. Materials and Methods

4,4'-Bipyridine and 1,4-dioxane were obtained from Sigma-Aldrich; 1-bromobutane and lithium bis(trifluoromethylsulfonyl) amide were purchased from Alfa Aesar. All solvents were purified employing standard drying agents prior to use.

CHNS elemental analyses were made using a 5E-CHN2200 elemental analyzer taking 20 mg sample. ^1H and ^{13}C NMR, using a Bruker AM-270 (270 MHz) and Bruker 400 MHz spectrometers, and ^{19}F NMR using a Bruker AV-400 (376.5 MHz) spectrometer were employed to confirm the structures and check the purity of the synthesized ligand salt and complex. ESI MS was used to determine the molecular ion mass of the ligand and complex using Bruker Micro TOF. Bromide and chloride estimation was conducted taking 30 mg sample and dissolving in 40 mL distilled water. Excess AgNO_3 solution was added for the formation of AgBr and AgCl precipitate. Then, the cruddy white precipitate formed was filtered and dried in an oven, and the amount of bromide and chloride was calculated from the weight difference. Conductivity of 3×10^{-4} M ethanolic solution of the complex was also investigated using a Bante901P portable pH/conductivity/TDS meter at room temperature.

2.1. Synthesis. *N*-Butyl-4,4'-bipyridinium bromide [C_4Bip]Br and *N*-butyl-4,4'-bipyridinium bis(trifluoromethylsulfonyl) amide [C_4Bip][Tf_2N] were prepared following literature report [25] (Scheme 1).

2.2. *N*-Butyl-4,4'-bipyridinium Bromide [C_4Bip]Br. Four grams (0.0256 mol) of 4,4'-bipyridine was dissolved in 30 mL dry 1,4-dioxane in a two-necked 100 mL round-bottomed flask fitted with a condenser. 3.52 g (0.0257 mol, 2.45 mL) of 1-bromobutane dissolved in 10 mL dry 1,4-dioxane was added from a dropping funnel, and the mixture was allowed to stir at 65°C for 24 h and a white precipitate was filtered (yield: 5.48 g, 73%).

2.3. *N*-Butyl-4,4'-bipyridinium Bis(trifluoromethylsulfonyl) Amide [C_4Bip][Tf_2N]. To a 80 mL aqueous solution of [C_4Bip]Br (2.5 g, 8.5 mmol) in a double-neck round bottomed flask fitted with a condenser being stirred in an oil bath at 65°C , slightly excess molar equivalent (2.53 g, 8.8 mmol) of $\text{Li}(\text{Tf}_2\text{N})$ dissolved in 80 mL of distilled water was added dropwise. Consequently, oily droplets formation

was started and the stirring continued for an hour. The mixture was left to stand overnight, and a yellowish separate, denser phase was obtained. The oily phase was decanted and dissolved in methanol and stirred with activated charcoal for 30 min and filtered. A colorless solution was obtained. The methanol was removed under vacuum, and a colorless viscous mass was collected (yield: 3.56 g, 84.73%).

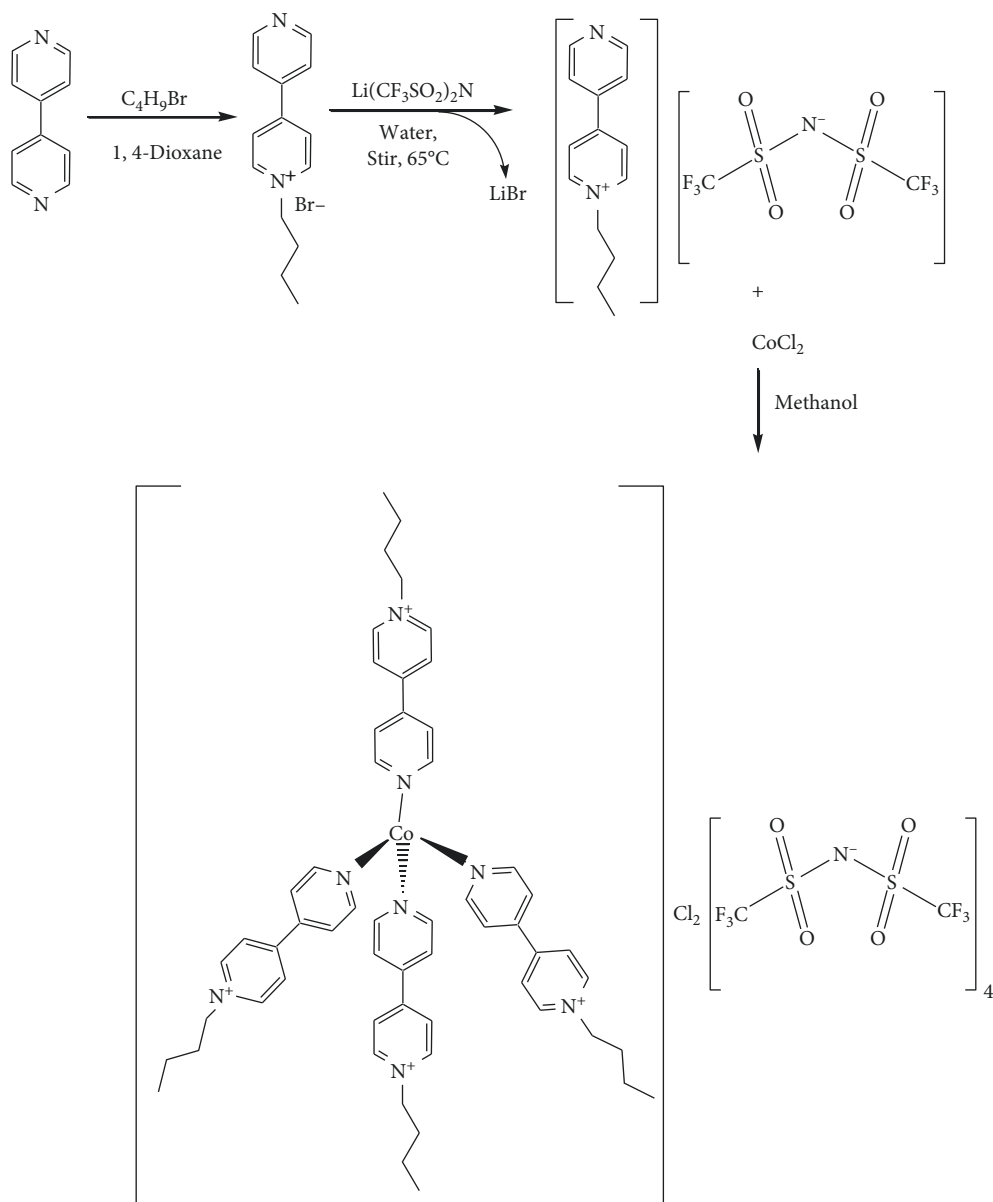
2.4. Tetrakis-(*N*-butyl-4,4'-bipyridinium)cobalt(II) Dichloride Tetrakis-(bis(trifluoromethylsulfonyl) Amide [$\text{Co}(\text{C}_4\text{Bip})_4$] $\text{Cl}_2(\text{Tf}_2\text{N})_4$. To a methanolic solution of CoCl_2 (0.025 g, 1.925 mmol) being stirred magnetically in a water bath at room temperature, a methanolic solution of *N*-butyl-4,4'-bipyridiniumbis (trifluoromethylsulfonyl) amide (0.380 g, 7.702 mmol) was added from a dropping funnel and stirred for 90 min until the addition of the reagent was completed. Then, the mixture was further stirred for 1 h at 35°C . A light pink colored homogenous solution was obtained. The methanol was removed in vacuum. Blue powder was collected and washed three times with acetone to remove any excess *N*-butyl-4,4'-bipyridinium (bis(trifluoromethylsulfonyl) amide. It was recrystallized from methanol to remove any unreacted CoCl_2 (yield: 0.374 g, 92.3%). The synthesis path is indicated in Scheme 1.

2.4.1. Antibacterial Activity Testing. The ionic liquid (ligand) and its $\text{Co}(\text{II})$ complex were evaluated for *in vitro* antibacterial activities against strains of *S. aureus* and *K. pneumoniae*. The strains were maintained in the appropriate blood agar base at 4°C . Gentamicin was used as reference. The experiments were repeated three times to obtain consistent results. The antibacterial tests were carried out at Bahir Dar University, Department of Biology, Microbiology Laboratory, Bahir Dar, Ethiopia.

2.4.2. ^1H , ^{13}C , and ^{19}F NMR. The ^1H , ^{13}C , and ^{19}F NMR of the ligand and complex are indicated in Figure 1.

3. Results and Discussion

The synthesis of the ligand is evident from NMR and ESI MS data (Figures 1(a)–1(e) and 2(a) and 2(b)). The appearance of four and eight peaks in ^1H NMR and ^{13}C NMR in the aromatic region, respectively, and the up-field appearance of the appropriate number of peaks representing alkyl protons and carbon are strong confirmations for the occurrence of monoquaternization. Moreover, the molecular positive ion peak ($m/z = 213.1379$) obtained from ESI MS spectra confirmed the synthesis of the intended structure (Figure 2(a)). Furthermore, the complete anion exchange performed to acquire pure ionic liquid is also confirmed from the appearance of only one peak at $\delta = -78.75$ ppm in the ^{19}F NMR (Figure 1(e)) and molecular negative ion peak ($m/z = 279.9171$) in the ESI MS of $(\text{CF}_3\text{SO}_2)_2\text{N}^-$ (Figure 2(b)). This evidence was compounded with the appearance of quartet peaks in the range $\delta = 112.92$ – 127.14 ppm of ^{13}C NMR (Figure 1(b)). The latter is the characteristic of carbon



SCHEME 1: Synthesis strategy of the complex.

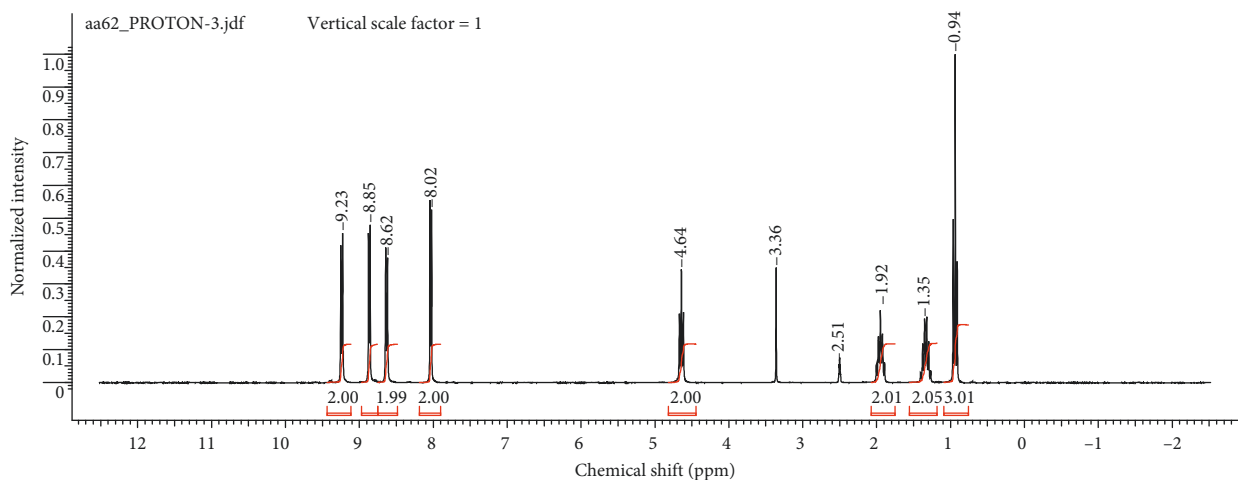
coupled with three fluorine atoms of the exchanged anion ($(CF_3SO_2)_2N^-$).

The coordination of the cation of the ionic liquid to $Co(II)$ resulted a hexacationic but lipophilic salt. The formation of the target compound was confirmed by CHNS elemental analysis and $Co(II)$ and halide estimation experiment results. Element found(calculated): C, 36.33(36.54); H, 2.98(3.24); N, 7.54(7.99), S, 11.88(12.18); Co, 2.68(2.80); Cl, 2.89(3.38).

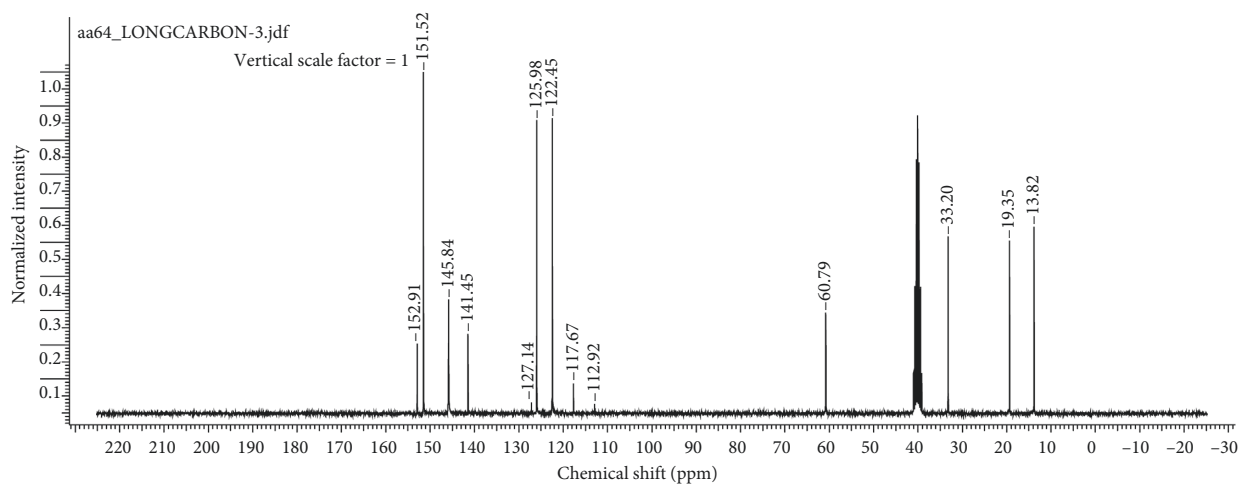
Furthermore, 1H , and ^{13}C NMR (Figures 1(c) and 1(d)) confirmed the coordination of the cation of the ligand. In the 1H NMR spectrum, the number of signals in the aromatic region is reduced due to the influence of the paramagnetic $Co(II)$ on certain protons in the aromatic portion of the ligand [26]. The ESI MS spectrum recorded dissolved in methanol signaled molecular ion peak for the cation

($m/z = 943.22/6 = 157.23$) (Figure 2(c)) which shows the coordination of four N-butyl-4,4'-bipyridinium and one methanol molecule to $Co(II)$. This is in a very good agreement with the observation that the complex demonstrated pink and blue colors in solution and dried, respectively.

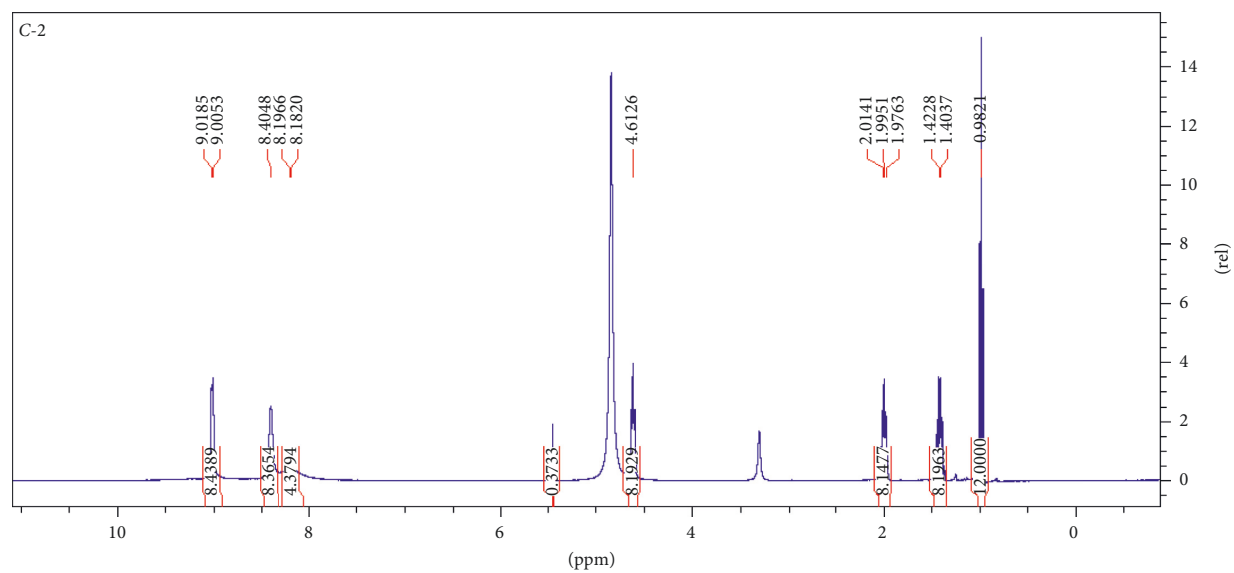
The complex demonstrated significantly lower molar conductivity value in ethanol ($124.33 S \cdot mol^{-1} \cdot cm^2$) than expected from 1:6 cation to anion ratio. The diminished conductivity is attributed to increase in the drifting (counterdirectional) speed. This is due to the strong solute (complex) and solvent (ethanol) interaction with the solvent cavity surrounding the cation and the anion. This could be anticipated due to the lipophilicity of the alkyl chain in the cation. Furthermore, the large molar masses of the cation and the anion retard speed of their motion. Moreover, the



(a)



(b)



(c)

FIGURE 1: Continued.

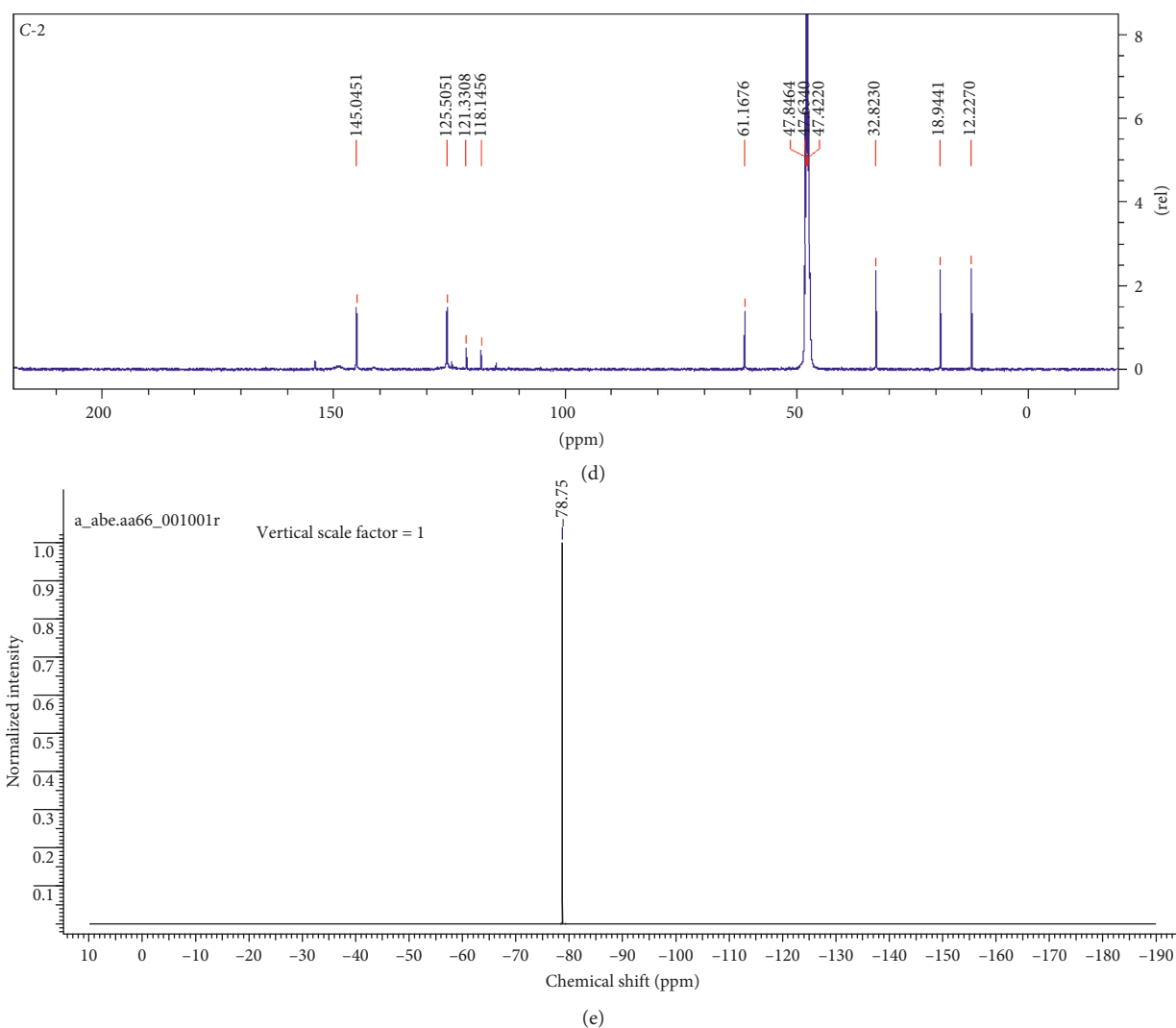


FIGURE 1: (a) ^1H NMR of the ionic liquid; (b) ^{13}C NMR of the ionic liquid; (c) ^1H NMR of the complex; (d) ^{13}C NMR of the complex; (e) ^{19}F NMR of the ligand.

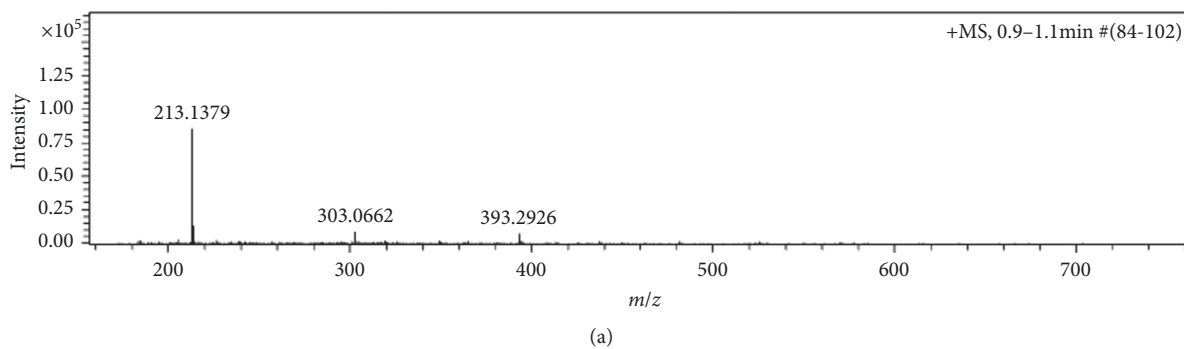


FIGURE 2: Continued.

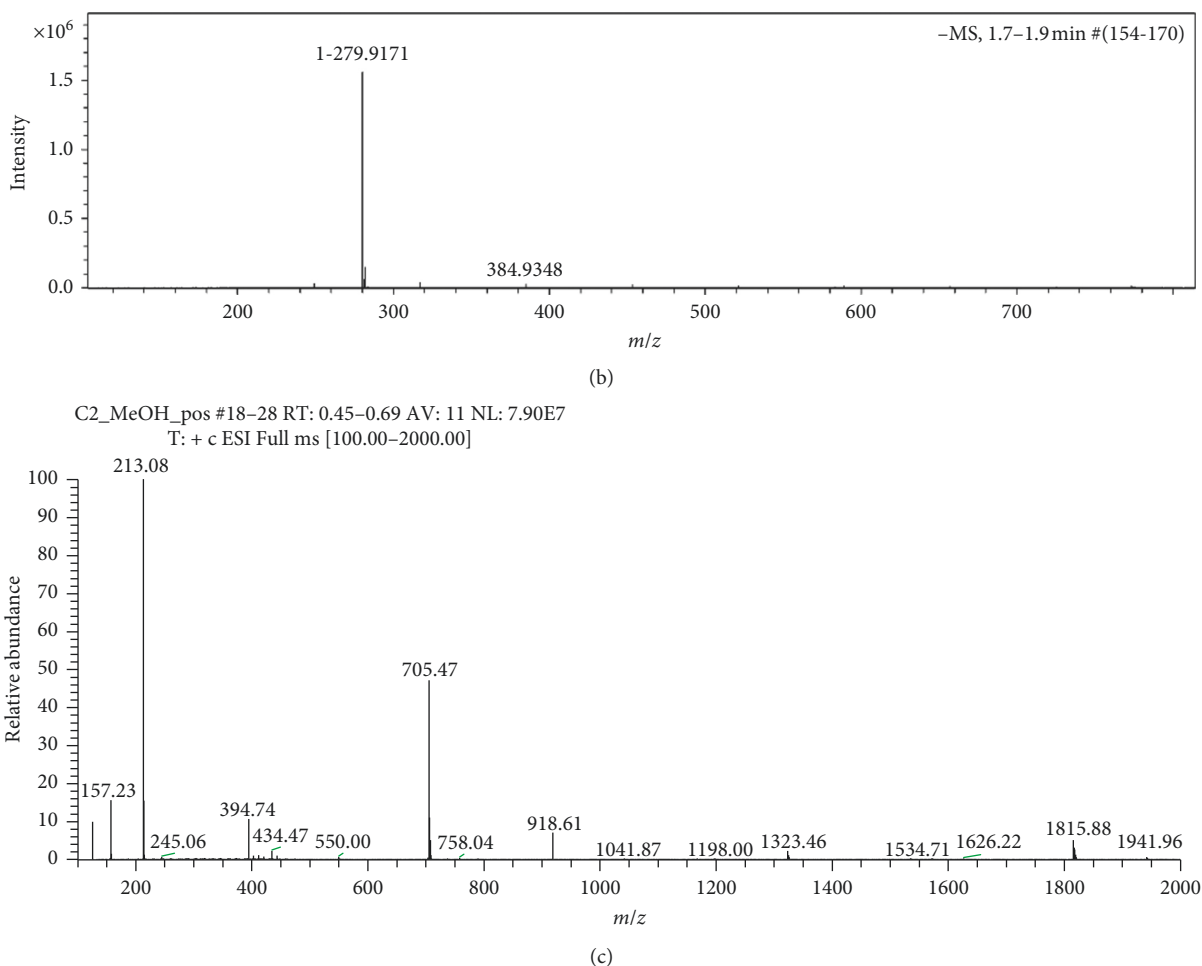


FIGURE 2: ESI MS of (a) the cation of the ionic liquid, (b) anion of the ionic liquid, and (c) cation of the complex.

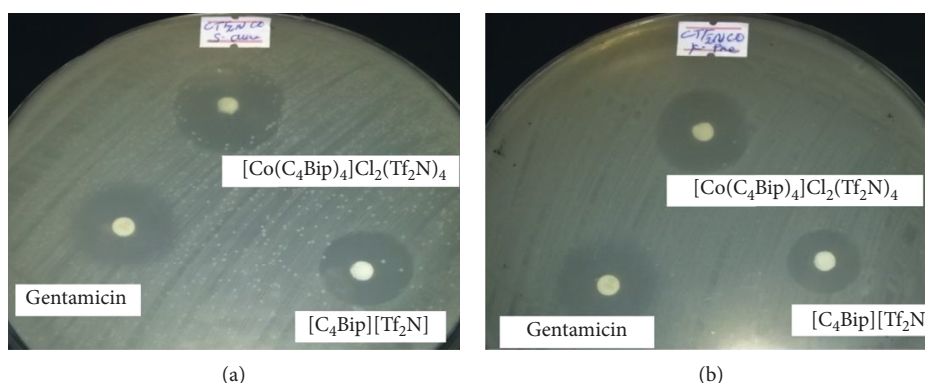


FIGURE 3: Inhibition observed by the ionic liquid and its complex as well as the reference. (a) Gram-negative bacteria *K. pneumoniae*. (b) Gram-positive bacteria *S. aureus*.

large sizes of the cation and the anion increase the frictional force as they move in opposite directions to their corresponding electrodes [27, 28].

The biological activity test shows that the ionic liquid and its Co(II) complex are biologically active against both the tested strains (Figure 3). The coordination of the ionic liquid

to the metal enhanced its activity against both strains. This could be anticipated as a result of the formation of rigid configuration of the ligand following the coordination. Compared with the reference compound gentamicin, the present complex is more active by 6.2% and 10% against *K. pneumoniae* and *S. aureus*, respectively (Table 1).

TABLE 1: Inhibition zones of the ionic liquid, the complex, and the reference.

Compound	Inhibition zone (mm)	
	Gram-negative bacteria <i>K. pneumoniae</i>	Gram-positive bacteria <i>S. aureus</i>
[C ₄ Bip][Tf ₂ N]	21.00 ± 0.03	27.00 ± 0.33
[Co(C ₄ Bip) ₄]Cl ₂ (Tf ₂ N) ₄	31.86 ± 0.24	33.00 ± 0.23
Gentamicin	30.00 ± 0.32	30.00 ± 0.34

4. Conclusions

The studies on the elemental analysis and ESI MS among other methods indicate the formation of a hexapositively charged hydrophobic complex by coordination of four cations of the ionic liquid with Co(II). The electrical conductance study in ethanol indicated the low electrolytic nature of the complex regardless of the large number of ions as a consequence of strong solvent-complex interactions, strong cation-anion friction, and significantly large mass of the cation and anion. The investigations on antimicrobial activity indicate the increased activity of the ionic liquid while coordinated to Co(II) as a consequence of improvement of the penetration of the complex into the lipid membrane and interference in the normal activity of the bacteria. The improved activity of the complex against both Gram-negative and Gram-positive bacteria indicates its wide range activity.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

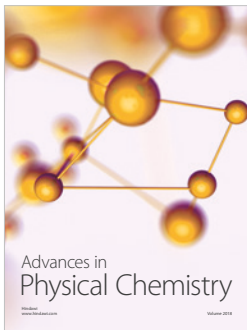
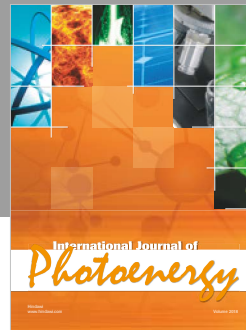
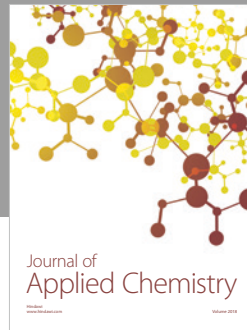
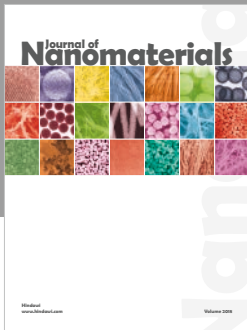
Acknowledgments

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