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 ([C4Bip][Tf2N]). It has been demonstrated by the isolation and characterization of tetakis-(*N*-butyl-4,4′-bipyridinium)cobalt(II)dichloride-tetrakis-(bis(trifluoromethylsulfonyl)amide, ([C4Bip]4Co)[Cl2(Tf2N)4]). The ligand and complex are characterized spectroscopically (*H, 13C, and 19F 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 environmentally 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′-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 13C NMR, using a Bruker AM-270 (270 MHz) and Bruker 400 MHz spectrometers, and 19F NMR using a Bruker AV-400 (376.5 MHz) spectrometer were employed to confirm 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 AgNO3 solution was added for the confirmation of the structures and check the purity of the synthesized ligand salt and complex. ESIMS was used to determine the synthesis of the intended structure (Figure 2(a)).

2.1. Synthesis. N-Butyl-4,4′-bipyridinium bromide [C4Bip]Br and N-butyl-4,4-bipyridinium bis(trifluoromethylsulfonyl)amide [C4Bip][Tf2N] were prepared following literature report [25] (Scheme 1).

2.2. N-Butyl-4,4′-bipyridinium Bromide [C4Bip]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 stirred for 1 h at 35°C. A light pink colored homogeneous solution was obtained. They were recrystallized from methanol to remove any unreacted 

2.3. N-Butyl-4,4′-bipyridinium Bis(trifluoromethylsulfonyl)Amide [C4Bip][Tf2N]. To a methanolic solution of CoCl2 (0.025 g, 0.925 mmol) being stirred magnetically in a water bath at room temperature, a methanolic solution of N-butyl-4,4′-bipyridinium bis(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 CoCl2 (yield: 0.374 g, 92.3%). The synthesis path is indicated in Scheme 1.

2.4. Tetrakis-(N-butyl-4,4′-bipyridinium)cobalt(II) Dichloride Tetrakis-(bis(trifluoromethylsulfonyl) Amide [Co(C4Bip)4] Cl2(Tf2N)4. To a methanolic solution of CoCl2 (0.025 g, 1.925 mmol) being stirred magnetically in a water bath at room temperature, a methanolic solution of N-butyl-4,4′-bipyridinium bis(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 CoCl2 (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 Co(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, 13C, and 19F NMR. The 1H, 13C, and 19F 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 13C 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 δ = −78.75 ppm in the 19F NMR (Figure 1(e)) and molecular negative ion peak (m/z = 279.9171) in the ESI MS MS of (CF3SO2)2N (Figure 2(b)). This evidence was compounded with the appearance of quartet peaks in the range δ = 112.92–127.14 ppm of 13C NMR (Figure 1(b)). The latter is the characteristic of carbon...
coupled with three fluorine atoms of the exchanged anion \((\text{CF}_3\text{SO}_2\text{N}^-)\).

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, \(^1\text{H}\) and \(^13\text{C}\) NMR (Figures 1(c) and 1(d)) confirmed the coordination of the cation of the ligand. In the \(^1\text{H}\) 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·mol\(^{-1}\)·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

**Scheme 1: Synthesis strategy of the complex.**
Figure 1: Continued.
Figure 1: (a) $^1$H NMR of the ionic liquid; (b) $^{13}$C NMR of the ionic liquid; (c) $^1$H NMR of the complex; (d) $^{13}$C NMR of the complex; (e) $^{19}$F NMR of the ligand.

Figure 2: Continued.
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).
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.

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[20] A. Benedetto and P. Ballone, "Room-temperature ionic liquids and biomembranes: setting the stage for applications in table 1: inhibition zones of the ionic liquid, the complex, and the reference.

| Compound                  | Gram-negative bacteria | Gram-positive bacteria |
|---------------------------|------------------------|------------------------|
| [C4Bip][Tf2N]            | 21.00 ± 0.03           | 27.00 ± 0.33           |
| [Co(C4Bip)4]Cl2(Tf2N)4   | 31.86 ± 0.24           | 33.00 ± 0.23           |
| Gentamicin                | 30.00 ± 0.32           | 30.00 ± 0.34           |

\[\text{Inhibition zone (mm)}\]
pharmacology, biomedicine, and bionanotechnology,” *Langmuir*, vol. 34, no. 33, pp. 9579–9597, 2018.

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