Synthesis, Molecular Modeling, and Biological Activity of Zinc(II) Salts with 1,4-Bis(benzimidazol-2-yl)benzene

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Zinc(II) halides and perchlorate react with 1,4-bis(benzimidazol-2-yl)benzene (L) in 1:2 molar ratio in n-butanol/2-methoxy ethanol (10 mL) at refluxing temperature to produce white/pale yellow-colored complexes of the formulae [ZnCl₂L]H₂O, [ZnBr₂L]₃H₂O, and [Zn(OClO₃)₂L]H₂OCH₂CH₂CH₂CH₃. Zinc(II) iodide also reacts with L in 1:2 molar ratio in n-butanol (HOCH₂CH₂CH₂CH₃) to yield white-colored complex of the formula [ZnL₂(OCH₂CH₂CH₂CH₃)]₂. The complexes were characterized by elemental analysis, molar conductance measurements, thermal analysis, and IR, ¹H-, ¹³C-NMR spectral studies. The complexes showed significant anthelmintic activity. The minimum energy configuration has been obtained for the zinc complexes using molecular modeling Pro Plus; a tool developed by ChemSW, inc, USA.

1. Introduction

Transition metal complexes containing bis-benzimidazolyl derivatives have been extensively studied. Several of these benzimidazolyl derivatives could modify their reactivity towards metal ions [1–6]. The zinc(II) is responsible for the function of carboxy peptidase A and carbonic anhydrase in biological systems [7–9]. Further, a number of Zn(II) complexes with variety of ligand show antimicrobial, anticarcinogenic, veterinary, anthelmintic, and poliovirus inhibitor activities [10–13]. Thus, the coordination behaviour of benzimidazoles with zinc is of considerable importance. In this context, I report here the synthesis and characterization of zinc(II) complexes containing 1,4-bis(benzimidazol-2-yl)benzene and their anthelmintic activity.

1.1. Reagents. The hydrated zinc(II) chloride was used as supplied (BDH). Terephthalic acid and o-phenylenediamine were from Merck Chemicals. The solvents used were from Merck Chemicals and they were purified according to literature methods [14]. Hydrated zinc(II) bromide, zinc(II) iodide, and zinc(II) perchlorate salts were prepared by dissolving the metal in hydrobromic acid, hydroiodic, acid and perchloric acid, respectively, followed by filtration of obtained precipitate and careful evaporation nearly to dryness under reduced pressure.

Drugs: Albendazole (BANDY, Mankind Pharma Ltd., New Delhi), Piperazine citrate, Tween 80.

1.2. Measurements. C, H, and N analyses were carried out on a Carlo Erba Microanalysers. IR spectra (in nujol) were recorded on a Nicolet 4000D spectrophotometer. Molar conductivity measurements were made with 10⁻³ M solution in dimethylformamide (DMF) using a digital (SYSTRONICS) conductivity meter-304 with a conventional dip-type conductivity cell with a cell constant 1.00 cm⁻¹. NMR spectra were recorded (in DMSO-d₆) on a Bruker WH-270 or AMX-400 MHz spectrometer using TMS as the internal standard. The thermograms were recorded on a Shimadzu Thermal Analyzer DT30 at a heating rate of 5°C/minute.

1.3. Preparation of the Ligand(1,4-Bis(benzimidazol-2-yl)benzene). The ligand was prepared according to the literature method [15]. Terephthalic acid (10 mmole) was stirred with o-phenylenediamine (20 mmole) in syrupy phosphoric acid (20 mL) at 240°C for 4 h. The coloured melt was poured into cold water (500 mL) with stirring to obtain a blue-green-coloured precipitate. The precipitate
was neutralized with 10% aqueous sodium carbonate solution. The resulting solid was recovered by filtration and recrystallized from ethanol to obtain a pale-pink compound (Figure 1). (yield 50%).

1.4. Preparation of the Complexes

1.4.1. [ZnCl₂L]nH₂O (X = Cl, n = 1; X = Br, n = 3). To a solution of zinc(II) halide (1 mmol) dissolved in 2-methoxyethanol/n-butanol (10 mL), the ligand (2 mmol) in the same solvent (15 mL) was added and the mixture was refluxed for 6–8 h, followed by concentration of the mixture under reduced pressure, during which time a buff/white/pale-yellow solid separated. This was filtered, washed with petroleum benzene 40–60°C (20 mL), and dried in a vacuum (yield 65%).

1.4.2. [ZnL(OCH₂CH₂CH₂CH₃)₂]J. To a solution of hydrated zinc(II) iodide (1 mmol) in n-butanol (20 mL), the ligand (2 mmol) in n-butanol (20 mL) was added. The resulting mixture was refluxed for 4–6 h. The solution was concentrated under reduced pressure when a white-coloured solid separated. The solid was filtered, washed with petroleum benzene 40–60°C (20 mL), and dried in a vacuum (yield 60–70%).

1.4.3. [Zn(OClO₃)₂L]HOCH₂CH₂CH₂CH₃. Zinc(II) perchlorate (1 mmol) was dissolved in n-butanol (5 mL), then the ligand (2 mmol) in n-butanol (10 mL) was added. The resulting mixture was refluxed for 6 h when a pale-yellow solid separated. This solid was filtered, washed with petroleum benzene 40–60°C (20 mL), and dried in a vacuum (yield 60%).

1.5. Procedure for Anthelmintic Activity. The anthelmintic assay was carried out as for the method of Ajaiyeoba et al. [16]. Indian adult earthworms Pheretima posthuma. The worms were procured from local supplier at Shimoga at the time of carrying out the experiment. The worms were washed with normal saline to remove all fecal matter used for the anthelmintic study. The earthworms of 4–6 cm in length and 0.3–0.4 cm in width were used for all experimental protocol due to its anatomical and physiological resemblance with intestinal roundworms parasite of human beings. The cleaned and uniform-size worms were kept in 6% dextrose solution for acclimating. The worms with normal motility were selected for the activity. In a separate Petri dish a, 2 mL of each test compound (5 mg/mL) in 0.1% Tween-20 suspension were placed and the volume was made up to 25 mL with an aqueous solution of dextrose (6%). The albendazole solution was served as standard. In each petri dish, one earthworm was placed. The time taken by the worm for paralysis was noted and the paralysis of worm was tested by placing the worm in water maintained at 50°C. Nonmotility at 50°C was taken as the death of the worm and correspondingly the time taken for the death was recorded.

Synthesized complexes were dissolved separately in minimum amount of Tween 80 and then volume was adjusted to 25 mL with dextrose solution. All solutions were freshly prepared before starting the experiment. Four groups of six earthworms each were released into 25 mL of desired formulation as follows:

1. vehicle: 5% Tween 80 in dextrose solution,
2. albendazole,
3. piperazine citrate,
4. ligand (L),
5. [ZnCl₂L]H₂O,
6. [ZnBr₂L]3H₂O,
7. [ZnL₂(OCH₂CH₂CH₂CH₃)₂],
8. [Zn(OClO₃)₂L]HOCH₂CH₂CH₂CH₃.

2. Results and Discussion

The physical properties and analytical data of the complexes are listed in Table 1. The complexes are insoluble in common organic solvents but are soluble in DMF and DMSO and show low conductivity in DMF at room temperature (25°C). This may arise from the replacement of the halide by DMF in solution and the existence an equilibrium of the type below [17]:

\[
\text{ZnX}_2\text{L} + \text{DMF} \leftrightarrow \text{[ZnX(DMF) L]}^+ + \text{X}^-.
\]
The IR spectra (in nujol mull) of the complexes are similar to the spectra of the uncoordinated N-heterocycle except for minor shifts in the positions of some of the bands and some changes in their intensities due to coordination. The complexes displayed νN-H band in the range 3150–3180 cm⁻¹ and this increased by 10–30 cm⁻¹ as compared to that of the uncoordinated ligand. The νC=N and νC=C vibrations are very close to each other and occur around 1616 cm⁻¹ as weak bands in the spectra of uncoordinated heterocycle and have been observed to shift by about 10–15 cm⁻¹ on complexation. The shift in the position of νC=N and νC=C is suggestive of coordination of the N-heterocycle via the tertiary nitrogen of the imidazole moiety [18, 19]. The νO-H of water of hydration [20] is observed around 3400 cm⁻¹. A strong band at 1574 cm⁻¹ and a band around 1550 cm⁻¹ are assigned to N-H in-plane bending vibrations of ligand and the complexes, respectively. The νC-N and δN-H vibrations are probably very close to one another and occur at 1320 cm⁻¹. The band due to p-disubstituted benzene ring vibrations occurs around 1300, 1250, and 760 cm⁻¹. The bands due to benzimidazole ring vibrations are located around 1280, 1010, and 960 cm⁻¹. The assignments are tentative and are based on the literature reports on related compounds [18, 19]. However, in the infrared spectrum of [Zn(OClO₃)₂L]HO(CH₂)₃CH₃ complex, in addition to the ligand bands, the peaks around 1100 and 622 cm⁻¹ of ν₃ and ν₄ of perchlorate are also observed. The former band is split indicating the presence of at least one perchlorate coordinated to the metal ion [21].

The ¹H NMR spectra of the complexes recorded in DMSO-d₆ exhibit resonances due to coordinated N-heterocycle. The spectral data of the complexes along with the assignments are compiled in Table 2. The spectra of the complexes are almost similar to those of the ligand, except for a slight shift in the positions of the signals. The X-ray crystal structure study of the ligand has been established by Bei and coworkers [15] that it has centrosymmetry. The molecule is twisted in such a way that the part of the molecule is in the plane opposite to the plane of the other part. The N–H resonance signal occurs at about 10–15 cm⁻¹ on complexation.
In addition to the ligand resonance signals, the peaks of n-butanol are also observed. The resonance signal found at 13.8 ppm indicates the presence of –CH₃ group. The carbon atoms of the two –CH₂ groups of n-butanol resonate at 18.6 and 34.6 ppm. The carbon of –CH₂–O— is observed at 60.3 ppm. Both positive and negative coordination-induced shifts are observed in the spectra of the complexes due to the ligand to metal σ-donation and metal-to-ligand π-donation, respectively [26].

Thermogravimetric analysis data of complex 
[ZnL₂(OCH₂CH₂CH₃)₂] has shown that there is a loss of a part of the solvent molecule (CH₃CH₂CH₃–) (0.58%, theoretical value 4.4% and found 5.1%) around 419°C. The weight loss due to 1.42% solvent molecule (OCH₂– and OCH₂–CH₂–CH₃) and two molecules of N-heterocycle takes place in the temperature around 600°C, which corresponds to a theoretical loss of 92.1% (found 93.4%). The final step of the decomposition corresponds to the formation of ZnO [27,28]:

\[
\begin{align*}
\text{ZnL}_2(\text{OCH}_2\text{CH}_2\text{CH}_3)_2 & \xrightarrow{419^\circ C} [\text{ZnL}_2(\text{OCH}_2\text{CH}_2\text{CH}_3)_2] + \text{OCH}_3 \\
\text{ZnO} - (\text{OCH}_2\text{CH}_2\text{CH}_3)_2 & \xrightarrow{598^\circ C} \text{ZnO} - (\text{OCH}_2\text{CH}_2\text{CH}_3)_2 - \text{OCH}_3 - 2\text{L}
\end{align*}
\]

(2)

Molecular modeling studies were carried out with an interactive graphics molecular program [29]. Energy minimization was repeated several times to obtain the global minimum. The Leonard-Jones equation was applied on M–N bond to obtain a configuration with minimum repulsion and hence minimum steric strain. A representative example of the structure of the complex [ZnCl₂L]H₂O, with minimum energy configuration, is shown in molecular model I (Figure 2). After global minimum configuration is attained, the total energy of the molecule in kJ/mol, percentage strain on the metal atom, and selected bond lengths, bond angles have been computed. The lowest energy of the complex is indicative of more stability; the values are given in Tables 4 and 5.

Based on the above discussion, the chloro-, bromo-, and perchlorate-complexes are proposed to possess tetrahedral
Table 5: Molecular modeling data.

| Compound   | Bond length (Å) | Bond angle (degrees) |
|------------|-----------------|----------------------|
| A          | —               | —                    |
| 1Zn-2N     | 1.76            | 2Zn-6N               | 1.79 |
| 1Zn-1Cl    | 2.10            | 2Zn-4Cl              | 2.10 |
| 1Zn-3Cl    | 1.82            | 3Zn-9N               | 1.76 |
| 1Zn-2Cl    | 2.10            | 3Zn-5Cl              | 2.10 |
| 2Zn-4N     | 1.77            | 3Zn-10                | 1.82 |
| 2Zn-3Cl    | 2.10            | 3Zn-6Cl              | 2.10 |
| B          |                 |                      |      |
| 1Zn-2N     | 1.76            | 2N-1Zn-1Cl           | 108.96 |
| 1Zn-1Cl    | 2.10            | 3N-1Zn-1Cl           | 108.96 |
| 1Zn-3Cl    | 1.82            | 4N-2Zn-6Cl           | 110.85 |
| 1Zn-2Cl    | 2.10            | 5N-2Zn-3Cl           | 110.64 |
| 2Zn-4N     | 1.77            | 6N-2Zn-4Cl           | 110.64 |
| 2Zn-3Cl    | 2.10            | 10N-3Zn-9N           | 109.90 |
| C          |                 |                      |      |
| 1Zn-2N     | 1.76            | 2N-1Zn-1Br           | 109.04 |
| 1Zn-1Br    | 2.28            | 3N-1Zn-2Br           | 109.24 |
| 1Zn-3N     | 1.82            | 4N-2Zn-3Br           | 110.71 |
| 1Zn-2Br    | 2.27            | 5N-2Zn-4Br           | 111.23 |
| 1Zn-2O     | 1.78            | 6N-2Zn-5Br           | 111.23 |
| D          |                 |                      |      |
| Zn-1N      | 1.75            | 1N-Zn-2N             | 109.45 |
| Zn-1O      | 1.77            | 1N-Zn-1O             | 108.16 |
| E          |                 |                      |      |
| Zn-N       | 1.79            | N-Zn-1O              | 98.379 |
| Zn-1O      | 1.76            | N-Zn-2O              | 95.25 |

Table 6: Showing anthelmintic activity of synthesized complex compounds with standard.

| Sl. no. | Group       | Paralysis (in min) | Death (in min) |
|---------|-------------|--------------------|----------------|
| 1       | Control (Tween80) | 221.17 ± 0.48     | 283.67 ± 1.05 |
| 2       | Albenzazole  | 74.83 ± 0.60      | 105.67 ± 0.67 |
| 3       | Piperazine citrate | 72.83 ± 0.87     | 108.83 ± 0.60 |
| 4       | Ligand (L)  | 78.36 ± 0.15      | 113.12 ± 0.45 |
| 5       | [ZnCl₂L]H₂O | 51.00 ± 1.18      | 96.83 ± 0.48  |
| 6       | [ZnBr₂L]H₂O | 73.67 ± 1.02      | 89.00 ± 0.58  |
| 7       | [ZnL₂(OCH₂CH₂CH₂CH₃)₂] | 46.00 ± 0.86 | 66.50 ± 0.62 |
| 8       | [Zn(OClO₃)L]L-HOC₄H₉ | 91.00 ± 0.97 | 136.50 ± 0.76 |

3. Anthelmintic Activities of Synthesized Complex

The results revealed that synthesized complexes have significant anthelmintic activity at 5 mg/mL concentrations. The results are comparable with standard drugs albendazole and piperazine citrate at the same concentration. Table 6 reveals that almost all complexes showed a significant activity against the parasites. In the case of the perchlorate complex, at least one perchlorate monodentately coordinated to the metal ion as supported by IR spectrum. The molecular modeling suggests that the N-heterocycles act as bridging ligand and, therefore, have a polymeric structure. In the case of [ZnL₂(OCH₂CH₂CH₂CH₃)₂] complex, ¹H and ¹³C NMR spectral studies and the thermogravimetric data show the presence of two solvent molecules, that is, n-butanol, which are coordinated to the metal ion through oxygen atom, and the complex is also proposed to have tetrahedral geometry around the metal ion.

![Figure 3: Anthelmintic activity.](image-url)
activity compared to the standard drug, as well as the ligand; and out of four synthesized complexes, [Zn(OClO$_2$)$_2$ L]HOCH$_2$CH$_2$CH$_2$CH$_3$ complex showed less anthelmintic activity (Figure 3).

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