Research Article

Synthesis, Spectroscopic, and Antimicrobial Studies on Bivalent Zinc and Mercury Complexes of 2-Formylpyridine Thiosemicarbazone

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A series of metal complexes of Zn(II) and Hg(II) having the general composition [M(L)2]X2 (where L = 2-formylpyridine thiosemicarbazone; M = Zn(II) and Hg(II); X = Cl−, NO3−, and 1/2SO42−) have been prepared and characterized by elemental chemical analysis, molar conductance, and spectral (IR and mass) studies. The IR spectral data suggests the involvement of sulphur and azomethane nitrogen in coordination to the central metal ion. On the basis of spectral studies, a tetrahedral geometry has been assigned for Zn(II) and Hg(II) complexes. The free ligand and its metal complexes have been tested in vitro against a number of microorganisms in order to assess their antimicrobial properties.

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1. Introduction

Thiosemicarbazones are very versatile ligands. They can coordinate to metals as neutral molecules or, after deprotonation, as anionic ligands, and can adopt a variety of different coordination modes [1]. The mono-thiosemicarbazones usually behave as tridentate ligands while the bis-thiosemicarbazones normally bind to the metal center through the two S atoms, the two azomethine nitrogen, and the pyridine nitrogen [2]. Interest in metal complexes with thiosemicarbazones and semicarbazone ligands has been stimulated because biological activities are often enhanced on complexation. Thiosemicarbazones and their metal complexes have received considerable attention because of their antibacterial, antifungal, antitumor, antiamoebic, antimalarial, antiviral, radioprotective, trypanocidal, and anti-inflammatory activities [3–14].

In view of the above applications, the present work relates to the synthesis, spectroscopic, and antimicrobial studies on Zn(II) and Hg(II) complexes of 2-formylpyridine thiosemicarbazone. The ligand used in the study is depicted in Figure 1.

2. Experimental

2.1. Materials. All the chemicals used were of Analys grade and procured from Sigma-Aldrich and Fluka. Metal salts were purchased from E. Merck and used as received.

2.2. Synthesis of Ligand (L). Hot ethanolic solution of thiosemicarbazide (4.55 g, 0.05 mol) and 2-formylpyridine (4.75 mL, 0.05 mol) were mixed slowly with constant stirring. This mixture was refluxed at 70–80°C for 2 hours. On cooling, a cream colored compound was precipitated out. It was filtered, washed with cold EtOH, and dried under vacuum over P4O10 (yield (65%), mp 210°C). Elemental chemical analysis data is shown in Table 1.

2.3. Synthesis of Complexes. Hot ethanolic solution (20 mL) of ligand (0.02 mol) and hot ethanolic solution (20 mL)
Figure 1: Synthesis and structure of ligand.

Table 1: Analytical data for the ligand and its Zn(II) and Hg(II) complexes.

| Compounds          | Molecular formulae | Atomic mass found (calcd) | Yield (%) | Color       | Mp (°C) | Analysis found (calcd) | Molar conductance (Ω⁻¹cm²mol⁻¹) |
|--------------------|--------------------|---------------------------|-----------|-------------|---------|------------------------|--------------------------------|
| Ligand (L)         | C₂H₆N₄S           | 179(180)                  | 65        | Shiny Cream | 210     | 46.67 4.45 31.11 —     | —                               |
|                    |                    |                           | (4.97)    |             |         | (46.62) (4.49) (31.20) |                                |
| [Zn(L)₂]Cl₂       | ZnC₁₄H₁₆N₈S₂Cl₂   | 496(495)                  | 61        | Off white   | 285     | 33.95 3.26 22.59 13.15 | 122                             |
|                    |                    |                           | (3.01)    |             |         | (33.93) (3.23) (22.62) (13.13) |                                |
| [Zn(L)₂](NO₃)₂    | ZnC₁₄H₁₆N₁₀S₂O₆  | 551(549)                  | 59        | Milky       | 212     | 30.58 2.96 20.43 11.85 | 128                             |
|                    |                    |                           | (3.23)    |             |         | (30.60) (2.91) (20.40) (11.83) |                                |
| [Zn(L)₂](SO₄)     | ZnC₁₄H₁₆N₈S₃O₄  | 520(521)                  | 55        | Yellow      | >350    | 32.29 3.09 21.43 12.44 | 125                             |
|                    |                    |                           | (2.86)    |             |         | (32.24) (3.07) (21.49) (12.47) |                                |
| [Hg(L)₂]Cl₂       | HgC₁₄H₁₆N₈S₂Cl₂   | 633(631)                  | 62        | Off white   | 225     | 26.67 2.57 17.78 31.89 | 133                             |
|                    |                    |                           | (3.91)    |             |         | (26.62) (2.53) (17.74) (31.85) |                                |
| [Hg(L)₂](NO₃)₂    | HgC₁₄H₁₆N₁₀S₂O₆  | 687(685)                  | 60        | Dark brown  | 125     | 24.58 2.36 20.40 29.31 | 140                             |
|                    |                    |                           | (4.11)    |             |         | (24.52) (2.33) (20.43) (29.34) |                                |
| [Hg(L)₂](SO₄)     | HgC₁₄H₁₆N₈S₃O₄  | 655(657)                  | 60        | Brown       | 180     | 25.53 2.40 17.09 30.55 | 138                             |
|                    |                    |                           | (3.94)    |             |         | (25.57) (2.43) (17.04) (30.59) |                                |

2.4. Analysis. The C, H, and N were analyzed on Carlo-Erba 1106 elemental analyzer. The nitrogen content of the complexes was determined using Kjeldahl’s method. Zinc and mercury metal ions were determined complexometrically. Molar conductance was measured on the ELICO (CM82T) conductivity bridge. Electronic impact mass spectrum was recorded on JEOL, JMS-DX-303 mass spectrometer. IR spectra (KBr) were recorded on FTIR spectrum BX-II spectrophotometer. The molecular weights of the complexes were determined cryoscopically in benzene.

2.5. Antimicrobial Screening. In vitro antimicrobial screening was performed by the agar disc diffusion method [16, 17]. All the test organisms were obtained from Microbial Type Culture Collection and Gene Bank (MTCC), Institute of Microbial Technology, Chandigarh, India. Nutrient agar growth media was prepared according to the instructions of MTCC. 25 mL nutrient agar media was poured in each petriplate of 90 mm diameter. The inoculum was spread on the top of solidified media. Sterile discs of Whatmann no. 1 filter paper having a diameter of 6 mm, impregnated with the test compounds, were placed at four equidistant places on the inoculated petriplates. The zone of inhibition was calculated in millimeters.

2.5.1. Antibacterial Screening. The antibacterial activity of the ligand and its metal complexes were tested against gram-positive (Staphylococcus aureus and Staphylococcus epidermides) and gram-negative (Escherichia coli and Pseudomonas aeruginosa) pathogenic bacteria at a concentration of 100 μg/disc⁻¹. Nutrient agar media was prepared by using peptone, beef extract, yeast extract, NaCl, agar-agar, and distilled water. Bacterial cultures were adjusted to 0.5 McFarland turbidity standard and inoculated onto the nutrient agar plates [18]. The discs were carefully transferred onto the seeded agar plates. Filter paper disc treated with DMSO served as control and, Amikacin (30 μg/disc⁻¹) was used as a standard drug. All determinations were made in duplicate for each of the compounds. An average of two independent readings for each compound was recorded. The petriplates were incubated at 37°C for 24 hours. The zone of inhibition was calculated.

2.5.2. Antifungal Screening. The antifungal activity of the ligand and its metal complexes were tested against two
pathogenic fungi, Candida albicans and Aspergillus niger at a concentration of 200 μg/disc⁻¹ for each. Nystatin was used as standard fungicide, and DMSO served as a means of control. For Candida albicans, nutrient agar media was prepared using yeast extract, peptone, dextrose, agar-agar, and distilled water. Inoculum suspension in normal saline was prepared from fresh, mature (3 to 5 days old) cultures grown on nutrient agar slants. Using spectrophotometry at 530 nm, turbidity was measured and adjusted to match a 0.5 McFarland density standard resulting in an inoculum containing 1 × 10⁶ to 5 × 10⁶ fungal cells/mL [19]. This suspension was used to directly inoculate agar plates.

For Aspergillus niger, nutrient agar media was prepared using czapek concentrate (NaNO₃, KCl, MgSO₄·7H₂O, FeSO₄·7H₂O, and distilled water), K₂HPO₄, yeast extract, sucrose, agar-agar, and distilled water. Seven days old colonies were covered with approximately 1 mL of sterile 0.85% saline, and the suspensions were made by gently probing the colonies. The resulting mixture of conidia and hyphal fragments was withdrawn and transferred to sterile tube. After heavy particles were allowed to settle for 3 to 5 minutes, the upper homogenous suspensions were collected. The densities of the conidial suspensions were read and adjusted to an optical density (OD) that ranged from 0.09 to 0.11 (80% to 82% transmittance) at 530 nm [20]. The sterile discs impregnated with the test compounds were placed on the already seeded plates at 30°C for 48 hours. A clearing zone around the disc indicated the inhibition activity of the test compounds on the pathogenic fungi.

3. Results and Discussion

The complexes were synthesized by reacting ligand with the metal ions in 2 : 1 molar ratio in an ethanolic medium. The ligand that behaves as bidentate coordinates through the Nₐzomethane and Nₚyridine chelating centers (Figure 2). Elemental analysis of complexes corresponds to the composition as shown in Table 1. All the complexes are found to be soluble in DMSO and DMF, sparingly soluble in water and ethanol, and insoluble in acetone. The molar conductance measurements of the complexes in DMF lies in the range of 122–140 Ω⁻¹ cm² mol⁻¹, indicating their 1 : 2 electrolytic behavior. Thus, the complexes may be formulated as [M(L)₂]X₂, (where M = Zn(II) and Hg(II); L = 2-formylpyridine thiosemicarbazone; X = Cl⁻, NO₃⁻ and 1/2SO₄²⁻).

4. Mass Spectrum

The electronic impact mass spectrum of the ligand (Figure 3) shows the final peak at 179 amu [(C₇H₈N₄S), calculated atomic mass 180 amu], and other peaks like 44, 60, 78, 88, 91, 119, and 135 amu may correspond to various fragments. The weak peak described at 135 amu is assigned to the fragment [C₆H₆N₃]+, corresponding to the loss of CS group. A very weak peak at 119 amu is assigned to the fragment [C₆H₆N₃]+, corresponding to the loss of CSNH₂ group. The most intense peak at 91 corresponds to the fragment [C₆H₆N₃]+, corresponding to the loss of CSNH₂ group. Other peaks at 88, 78, 60, and 44 correspond to the fragments [CH₃N₃S]+, [C₅H₄N]+, [CSNH₂]+, and [CS]+, respectively.

Complex [Zn(L)₂]Cl₂ shows a single peak at 496 amu, which coincides with that of molecular ion. Loss of two chloride ions is in agreement with a peak at 425 amu. Loss of one of the ligands is in agreement with a peak at 315 amu. A single peak at 179 amu coincides with that of 2-formylypyridine thiosemicarbazone (Figure 4). Complex
Table 2: Important infrared spectral bands (cm$^{-1}$) and their assignments, where s = strong; ms = medium strong; m = medium; mw = medium weak; w = weak.

| Compounds                        | $\nu$(N–H) | $\nu$(N=N) | Assignments                           | $\nu$(C=N)$_{azomethane}$ | $\nu$(C=N)$_{pyridine}$ | $\nu$(M–N) |
|----------------------------------|------------|------------|---------------------------------------|---------------------------|------------------------|------------|
| C$_7$H$_8$N$_4$S ligand (L)      | 3267 s     | 1107 s     | 1611 s                                | 557 m                     | —                      | —          |
| [Zn(L)$_2$]Cl$_2$                | 3275 s     | 1183 s     | 1589 s                                | 664 m                     | 474 m                  | 478 m      |
| [Zn(L)$_2$](NO$_3$)$_2$          | 3275 m     | 1177 s     | 1588 m                                | 661 m                     | 478 m                  | 478 m      |
| [Zn(L)$_2$](SO$_4$)              | 3286 m     | 1167 ms    | 1560 m                                | 673 m                     | 486 mw                 | 486 mw     |
| [Hg(L)$_2$]Cl$_2$                | 3292 ms    | 1155 m     | 1594 s                                | 626 m                     | 460 w                  | 460 w      |
| [Hg(L)$_2$](NO$_3$)$_2$          | 3295 s     | 1171 m     | 1551 m                                | 621 m                     | 459 m                  | 459 m      |
| [Hg(L)$_2$](SO$_4$)              | 3273 s     | 1163 m     | 1599 ms                               | 621 m                     | 453 w                  | 453 w      |

Table 3: Antibacterial screening data of the ligand and its Zn(II) and Hg(II) complexes.

| Compounds                        | (Conc.) $\mu$g/disc | Diameter of zone of inhibition (mm) |
|----------------------------------|---------------------|-------------------------------------|
|                                  |                     | Staphylococcus aureus | Staphylococcus epidermidis | Escherichia coli | Pseudomonas aeruginosa |
| Ligand (C$_7$H$_8$N$_4$S)        | 100                 | 20                     | 16                      | 18               | 08                    |
| [Zn(L)$_2$]Cl$_2$                | 100                 | 10                     | 09                      | 09               | 10                    |
| [Zn(L)$_2$](NO$_3$)$_2$          | 100                 | 12                     | 10                      | 08               | 08                    |
| [Zn(L)$_2$]SO$_4$                | 100                 | 08                     | 09                      | 07               | 07                    |
| [Hg(L)$_2$]Cl$_2$                | 100                 | 24                     | 20                      | 22               | 16                    |
| [Hg(L)$_2$](NO$_3$)$_2$          | 100                 | 25                     | 18                      | 21               | 12                    |
| [Hg(L)$_2$]SO$_4$                | 100                 | 20                     | 17                      | 19               | 10                    |
| Amikacin                         | 30                  | 26                     | 22                      | 21               | 20                    |

[Zn(L)$_2$](NO$_3$)$_2$ shows one peak at 551 amu, which coincides with that of molecular ion. Loss of one of the ligands is in agreement with a peak at 370 amu. [Zn(L)$_2$](SO$_4$)$_2$, [Hg(L)$_2$]Cl$_2$, [Hg(L)$_2$](NO$_3$)$_2$, and [Hg(L)$_2$](SO$_4$) show peaks at 520, 633, 687, and 655 amu, respectively, which are in agreement with their molecular formulae.

5. Infrared Spectrum

The assignments of the significant IR spectral bands of ligand and its metal complexes are presented in Table 2. The highest frequency band of the 2-formylpyridine thiosemicarbazone at 3429 cm$^{-1}$ can be assigned to asymmetric $\nu$(N–H) vibration of the terminal NH$_2$ group. The other bands at 3267 and 3164 cm$^{-1}$ may be due to the symmetric $\nu$(N–H) vibrations of the imino and amino groups. A band at 1611 cm$^{-1}$ in the IR spectra of the ligand is due to $\nu$(C=N)$_{azomethane}$ group. Coordination of azomethine nitrogen in complexes is suggested by the shift of $\nu$(C=N)$_{azomethane}$ band to lower frequencies along with the occurrence of $\nu$(N=N) band at higher frequency in the IR spectra of complexes compared to the ligand. Coordination of imine nitrogen is also consistent with the presence of a band at 453–486 cm$^{-1}$, assignable to $\nu$(M–N). Another band at 557 cm$^{-1}$ in the free ligand is due to $\nu$(C=N)$_{pyridine}$ group and is also shifted toward higher frequency. This indicates that the nitrogen atom of the pyridine group is also involved in complex formation. The thioamide $\nu$(C=S) band at 776 cm$^{-1}$ of free ligand is not shifted on complexation which indicates the noninvolvement of sulfur in coordination [21]. The absence of large systematic shift of $\nu_{as}$(NH$_2$) and $\nu_{sym}$(NH$_2$) modes to lower frequencies indicates no interaction between the terminal amino nitrogen and the metal ions. In each complex, two 2-formylpyridine thiosemicarbazone ligands coordinate to the central metal ion through two pyridine N atoms and two azomethine N atoms. Thus, it is concluded that the ligand acts as a bidentate chelating agent.

6. Anions

The infrared spectra of the nitrate complexes show sharp and strong band at 1384 cm$^{-1}$, characteristic for uncoordinated nitrate group [22]. IR bands in the region of 1408–1426 and 615–622 cm$^{-1}$, characteristic of uncoordinated sulfate group, are seen in the infrared spectra of sulfate complexes [23].

7. Antimicrobial Studies

Zinc Complexes. Results of bactericidal screening show that the free ligand (L) was much more active than its zinc complexes, while the antifungal results show that all the zinc complexes are more active than the free ligand. The variation in the effectiveness of different compounds against different organisms depends either on the impermeability of the cells of the microbes or the difference in ribosomes of microbial cells [24].
Mercury(II) Complexes. The antimicrobial screening data shows that the ligand exhibits antimicrobial properties, and it is important to note that the Hg(II) metal chelates exhibit more inhibitory effect than the parent ligand. From Table 3, it is clear that the zone of inhibition is much larger for metal chelates against gram-positive (Staphylococcus aureus and Staphylococcus epidermidis) and gram-negative (Escherichia coli and Pseudomonas aeruginosa) pathogenic bacteria. The increased activity of metal chelates can be explained on the basis of chelation theory. It is known that the chelation tends to make the ligand act as a more powerful and potent bactericidal agent, thus killing more of the bacteria than the ligand. It is observed that, in a complex, the positive charge of the metal is partially shared with the donor atoms present in the ligand, and there may be π-electron delocalization over the whole chelating [25]. This increases the lipophilic character of the metal chelate and favors its permeation through the lipid layer of the bacterial membranes. There are also other factors which increase the activity, namely solubility, conductivity, and bond length between the metal and the ligand.

The result of fungicidal screening (Table 4) shows that Hg(II) complexes were more active than the free ligand against pathogenic fungi, Candida albicans and Aspergillus niger. The mode of action may involve the formation of a hydrogen bond through the azomethane nitrogen atom with the active centers of the cell constituents, resulting in interference with the normal cell process [24].

| Compounds                  | Conc. (μg/disc) | Candida albicans | Aspergillus niger |
|----------------------------|-----------------|------------------|------------------|
| Ligand (C₇H₆N₅S)          | 200             | 14               | —                |
| [Zn(L)₂]Cl₂               | 200             | 15               | 14               |
| [Zn(L)₂](NO₃)₂            | 200             | 16               | 12               |
| [Zn(L)₂](SO₄)₂            | 200             | 14               | 07               |
| [Hg(L)₂]Cl₂               | 200             | 20               | 22               |
| [Hg(L)₂](NO₃)₂            | 200             | 16               | 16               |
| [Hg(L)₂](SO₄)₂            | 200             | 12               | 08               |
| Nystatin                   | 200             | 26               | 18               |

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