Synthesis of Anthranilic Acid and Phthalic Anhydride Ligand and their Metal Complexes

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Abstract
Anthranilic acid and phthalic anhydride have the ability to make ligand complexes with metal ions, which were found to be important for various applications. In the present study, the attempts were carried to form complexes of anthranilic acid and phthalic anhydride ligand with lead acetate (Pb(CH3COO)2), cobalt chloride (CoCl2.6H2O), cadmium sulfate (CdSO4.H2O), copper chloride (CuCl2.2H2O), and tin chloride of well-defined stoichiometry in the range of pH 6 and 8 in variable ratios. The IR spectra of complexes were interpreted and compared with data in the literature. Furthermore, the resultant complexes were evaluated for anti-bacterial potential.

Keywords: Anthranilic acid; Phthalic Anhydride; DMSO; Methanol; Chloroform; NaOH

Introduction
The compounds containing the complex ion or complex molecule in which central metal atom or ion is surrounded by a number of oppositely charged ions or molecules are known as co-ordination compounds [1], complex compound or simply complex. Coordination basically refers to the "coordinate covalent bonds" (dipolar bonds) between the ligands and the central atom in 1914, when first coordination complex, hexol was resolved by Werner [2].

Among the ligands, anthranilic acid (C7H7NO2) is one of the best compounds used by Carl Julius Fritzche (1808-1871) in the laboratory in St. Petersburg by degrading ancient dye indigo [3]. It is a white solid amino acid in pure form whereas commercially available in yellow form. Its molecule consists of a benzene ring with two adjacent functional groups, a carboxylic acid and an amine [3]. Several investigators worked on the synthesis of anthranilic acid dyes in the various conditions which have shown significant biological activity especially against bacteria S. aureus and E. coli and [4]. The mixed ligand complexes of Co (II), Ni (II), Cu (II) and Zn (II) with anthranilic acid and tributylphosphine have shown profound activity against Staphylococcus, Klebsiella spp, and Bacillus [5]. Furthermore, the rhodium complexes with (N-phenyl) anthranilic acid ligands are used as catalysts for the hydrogenation [6]. Several other mixed ligands complexes with anthranilic acid were reported to have antifungal and antibacterial potential [7].

Phthalic anhydride (C4H2(CO)2O) is colorless solid and an important industrial chemical, especially for the large-scale production of plasticizers for plastics [8]. The phthalic anhydride ring opening reaction by alcohols when carried out in presence of different metal salts, results in the formation of metal carboxylate complexes [9]. The phthalic anhydride ring opening reaction used for chiral separation of optically active alcohols and amines [10], however in the presence of amino acids such as glycine, the reactions of phthalic anhydrides help in preparing N-phthaloylglycinate complexes of transition metals [11]. The metal complexes of amino acids with phthalic anhydride revealed higher antimicrobial activity P. aerugenosa, E. coli, S. aureus and C. albicans than their respective ligands [12].

In the present study, we synthesized the complexes of anthranilic acid and phthalic anhydride ligands with cadmium (Cd), copper (Cu), of cobalt (Co), lead (Pb) and tin (Sn), however special emphasis has been given to the first ever complexes of Co and lead Pb. For the structural elucidation of these complexes IR spectral analysis was used. The antibacterial potential of the complexes was assessed against Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Methicillin-Resistant Staphylococcus Aureus (MRSA).

Material and Methods
All chemicals and the reagents used in our study were reagent grade (Table 1). The solvents were redistilled by standard techniques before use.

| S.NO. | Chemical Name | Chemical Formula | Mol. weight |
|-------|---------------|------------------|-------------|
| 1.    | Lead acetate  | Pb(CH3COO)2      | 361.33      |
| 2.    | Cobalt chloride | CoCl2.6H2O     | 237.93      |
| 3.    | Cadmium sulfate | CdSO4.H2O  | 226.490     |
| 4.    | Copper chloride | CuCl2.2H2O  | 170.48      |
| 5.    | Tin chloride  | SnO2.2H2O        | 225.63      |

Solvent
1. Distal Water  
2. Methanol  
3. DMSO

Chemicals
1. Anthranilic acid C7H7NO2  
2. Phthalic anhydride C4H2(CO)2O  
3. Sodium hydroxide NaOH

Table 1: The list of chemicals, reagents and solvents used in the study.

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use. All the glass wares were carefully washed with distilled water and methanol and then dried in the oven at 100°C before the use.

Experimental

Synthesis of ligand: Anthranilic acid (1.1g) was taken in erlenmeyer flask 25 cm³ with phthalic anhydride (1 g) and heated in paraffin oil at 130°C-150°C. Then poured into a beaker containing distilled water, allowed to cool, filtered and dried it in oven at 60°C. Recrystallization was carried out using ethanol as solvent to yield 1.2 g of product [13].

Preparation of Metallic Solution: Metals solution of Lead acetate (Pb(CH₃COO)₂), Cobalt chloride (CoCl₂.6H₂O), Copper chloride (CuCl₂.2H₂O), Cadmium sulfate (CdSO₄·H₂O), and Tin chloride (SnCl₂.2H₂O), by weighing accurately 2-3 g and 10 cm³ methanol was added and then stirred.

Complexation of ligand with metal: The formation of complex of ligand with essential and trace elements involve the reaction of ligand with metal halide in methanol 20 cm³. The complex formation involved stirring the reaction mixture containing ligand and metal salts for 30-40 minutes at room temperature. The reaction mixture was filtered, washed with water and methanol and dried at room temperature to yield the product. The general structure of these complexes is shown in the Figure 1.

Synthesis of ligand-cadmium complex: Ligand (1.5 g) was dissolved in DMSO (10 ml) and cadmium sulphate solution (4.3 g dissolved in 10 ml of DMSO) was added slowly to the solution. The mixture was stirred for 30 minute and the pH was adjusted at 8.0 by 0.5 M NaOH. The reaction mixture was then filtered, recrystallized to yield the product (0.4 g), the percent yield was found to be 14.13% (Table 2).

Synthesis of ligand-tin complex: Ligand (1.5 g) was dissolved in DMSO (10 ml) and Tin chloride solution (0.95 g dissolved in 20 ml of DMSO) was added slowly to the solution. The mixture was stirred for 30 minute and the pH was adjusted at 8.0 by 0.5 M NaOH. The reaction mixture was then filtered, recrystallized to yield the product (0.5 g), the percent yield was found to be 18.51% (Table 2).

Antimicrobial activity

The antibacterial sensitivity was performed using modified agar well diffusion method to test the antibacterial potential of the compounds. The Mueller-Hinton Agar (MHA) was used as medium. The cultures were taken in triplicates at incubation temperature of 37°C for 24 to 72 hours. The broth culture (0.6 ml) of the test organism was placed in a sterile petri-dish and 20 ml of the sterile molten MHA was added to each petri-dish. Holes were bored in to the medium using 0.2 ml of the compound. The reference drug, streptomycin was used as standard antimicrobial agent in concentration of 2 mg/ml. Inoculation was done for 1 hour to make possible the diffusion of the antimicrobial agent into the medium. Incubation was done at 37°C for 24 h and the diameters of the zone of inhibition of microbial growth were measured in the plate in mm [15,16].

Results and Discussion

The IR spectra of ligands and ligand complexes with Co, Pb, Cd, Cu, Sn are demonstrated in Table 3. The band of carboxylic (COOH) appeared at 3119cm⁻¹ in the spectrum of ligands however it was observed in the range of 3444cm⁻¹, 3455cm⁻¹, 3469cm⁻¹, 3456cm⁻¹ in Lead (Pb), Cobalt (Co), Cadmium (Cd), Copper (Cu) and Tin (Sn) complexes respectively, which are in co-relation with previous studies [17]. The imide (CONH) band of the ligands appeared at 1723cm⁻¹ however the complexes show this band at around 1619-1620 cm⁻¹ range. This observation indicated that coordination of the
The presence of metal oxygen (M-O) stretching vibrations at carboxylic carbonyl group at 537-672 cm⁻¹, 522-639 cm⁻¹, 585-752 cm⁻¹, and 568 cm⁻¹ in Lead (Pb), Cobalt (Co), Cadmium (Cd), Copper (Cu), Tin (Sn) complexes respectively for the metal complexes which was absent in ligand. Thus it suggests that coordination complexes formed by the ligand are bi-dentate.

In the present study, the complexes of anthranilic acid and pthalic anhydride ligands have better anti-pathogenic effect compared to the rest of three metal complexes. The cobalt complex exhibited significance activity against the tested strain among the entire compounds.

Table 3: The values of the metal complexes collected from IR spectra.

| COMPOUND | (COOH) (cm⁻¹) | (CONH) (cm⁻¹) | (C-N) (cm⁻¹) | (C=C) (cm⁻¹) | (M-O) (cm⁻¹) | (OH) (cm⁻¹) |
|----------|---------------|---------------|--------------|--------------|--------------|-------------|
| [Ligand] | 3119          | 1723          | 1248         | 1469         | -            | -           |
| [Pb(Ligand)] | 3444          | 1619          | 1228         | 1403         | 537-672      | 3444        |
| [Co(Ligand)] | 3455          | 1620          | 1229         | 1469         | 522-639      | 3455        |
| [Cd(Ligand)] | 3469          | 1653          | 942          | 1487         | 585-752      | 3469        |
| [Cu(Ligand)] | 3456          | 1718          | 1169         | 1465         | 535-763      | 3456        |
| [Sn(Ligand)] | 3456          | 1655          | 1216          | 1354         | 568          | 3456        |

Where, the COOH, CONH, C-N, C=C, M-O and OH represent carboxylic carbonyl, imide carbonyl, carbon-nitrogen single bond, carbon-carbon double bond, metal-oxygen bond and hydroxyl group respectively.

Table 4: Antibacterial sensitivity of synthetic compounds where.

| Microorganism            | 1 | 2 | 3 | 4 | 5 | STD |
|--------------------------|---|---|---|---|---|-----|
| Bacillus subtilis        | - | - | 13| - | - | 20  |
| Staphylococcus aureus    | - | - | 10| 11| - | 22  |
| Pseudomonas aeruginosa   | - | - | 22| - | - | 22  |
| MRSA                     | - | - | 15| - | - | 20  |

Key: - = Not active; Well size: 4 mm

S. aureus, K. pneumonia, B. subtilis, MRSA: Methicillin-resistant Staphylococcus aureus.
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