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

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Abstract

Anthranilic acid and phthalic anhydrides have the ability make ligand complexes with the 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 ($Pb(CH_3COO)_2$), Cobalt chloride ($Cocl_2.6H_2O$), Cadmium sulfate ($CdSO_4 \cdot H_2O$), Copper chloride ($CuCl_2.2H_20$), 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 the 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 ($C_6H_4(NH_2)COOH$) is one of the best compound used by Carl Julius Fritzche (1808-1871) in the laboratory in St. Peterburg 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 anthranillic acid and tributylphosphine have shown profound activity against *Staphylococcus*, *Klebsiella SPP.* and *Bacillas* [5]. Furthermore, the rhodium complexes with (N-phenyl) anthranillic 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 ($C_6H_4(CO)_2O$) is colorless solid and an important industrial chemical, especially for the large-scale production of plasticizers for plastics [8]. The phthallic 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 phathalate esters are also produced via phthallic 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-phthaloylglycinato 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 pthalic 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

S.NO.	Chemical Name	Chemical Formula	Mol. weight
	Salts		
1.	Lead acetate	$Pb(CH_3COO)_2$	361.33
2.	Cobalt chloride	$CoCl_2.6H_2O$	237.93
3.	Cadmium sulfate	$CdSO_4 \cdot H_2O$	226.490
4.	Copper chloride	$CuCl_2.2H_20$	170.48
5.	Tin chloride	$Sncl_2.2H_2O$	225.63
	Solvent		
1.	Distal Water	H_2O	18
2.	Methanol	CH_3OH	32
3.	DMSO	C_2H_6OS	78
	Chemicals		
1.	Anthranilic acid	$C_7H_7NO_2$	137.14
2.	Pthalic anhydride	$C_8H_4O_3$	148.12
3.	Sodium hydroxide	NaOH	40

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

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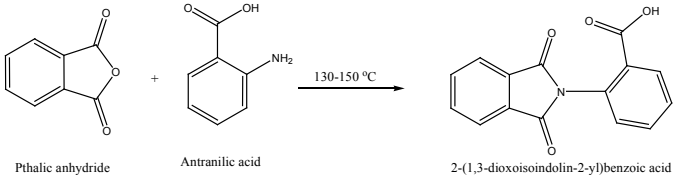
use. All the glass wares were carefully washed with distilled water and methanol and then dried in the oven at 100°C before the use.

Experimental

Synthesis of ligand: Anthranilic acid (1.1g) was taken in erlenmeyer flask 25 cm^3 with pthalic 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]. Same types of worked has also been reported in literature [14] using vanillin, 4-aminoantipyrine and 1-phenyl 2, 3 dimethyl-4-aminopyrozol-5-one.



Pthalic anhydride | Antranilic acid | 2-(1,3-dioxoisoindolin-2-yl)benzoic acid

Preparation of reagents

0.5 M NaOH is prepared by mixing 0.5 gm of NaOH in 25 cm^3 of water.

Preparation of Metallic Solution: Metals solution of Lead acetate ($Pb(CH_3COO)_2$), Cobalt chloride ($Cocl_2.6H_2O$), Cadmium sulfate ($CdSO_4.H_2O$), Copper chloride ($CuCl_2.2H_20$), and Tin chloride ($Sncl_2.2H_2O$), by weighing accurately 2-3 g and 10 cm^3 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 cm^3. 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-lead acetate complex: Ligand (1.5 g) was dissolved in DMSO (10 ml) and Lead acetate (2.12 g) dissolved in DMSO (10 ml) was added slowly to the solution. The mixture was stirred for 30 min while the pH was adjusted at 8.0 by 0.5 M NaOH solution. The reaction mixture was then filtered, recrystallized to yield the product (1.01 g), the percent yield was found to be 27.9% (Table 2).

Synthesis of ligand-cobalt complex: Ligand (1.5g) was dissolved in DMSO (10 ml) and the solution of cobalt chloride (1.33 g dissolved in 10 ml of DMSO) was added slowly to the solution. The mixture was stirred for 30 minute while the pH was adjusted at 8.0 by 0.5 M NaOH solution. 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-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 using 0.5 M NaOH solution. The reaction mixture was then filtered, recrystallized to yield the product (0.25 g) and the percent yield was found to be 4.31% (Table 2).

Synthesis of ligand- copper complex: The ligand solution was prepared by dissolving ligand (1.5 g) in 10 ml of DMSO and copper chloride solution (0.95g 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 (0.4 g), the percent yield was found to be 16.32% (Table 2).

Synthesis of ligand-tin complex: The ligand solution was prepared by dissolving ligand (1.5 g) in 10 ml of DMSO and Tin chloride solution (1.2 g dissolved in 10 ml DMSO) was added slowly to the solution. The mixture was stirred for 30 minute and 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}, 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

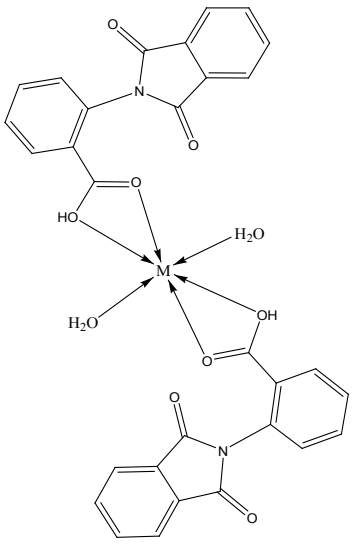


Figure 1: General structure of complexes.

S.No	Ligand	Metals	Ratio	DMSO (ml)	Reaction Time (Min.)	Product yield (%)
1	Anthranilic Acid + Pthalic Anhydrides	$Pb(CH_3COO)_2$	1.5:2.12	20	30-45	27.9
2	Anthranilic Acid + Pthalic Anhydrides	$CoCl_2.6H_20$	1.5:1.33	20	30-45	14.13
3	Anthranilic Acid + Pthalic Anhydrides	$CdSO_4 \cdot H_2O$	1.5:4.3	20	30-45	40.31
4	Anthranilic Acid + Pthalic Anhydrides	$CuCl_2.2H_20$	1.5:0.95	20	30-45	16.32
5	Anthranilic Acid + Pthalic Anhydrides	$Sncl_2.2H_2O$	1.5:1.2	20	30-45	18.51

Table 2: The ratio of reactants and percent yield in each reaction.

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

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

Table 4: Antibacterial sensitivity of synthetic compounds where.

ligand occurs through the oxygen from the carboxylic carbonyl group rather than imide groups as the shift was not significant in case of imide linkage [18].

The presence of metal oxygen (M-O) stretching vibrations at carboxylic carbonyl group at 537-672cm^{-1}, 522-639cm^{-1}, 585-752cm^{-1}, 535-763cm^{-1}, 535-763cm^{-1}, 568cm^{-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. The anthranilic acid and pthalic anhydride complexes have diverse application in daily life and some of them have been found useful for human life while others are harmful. Some of their application reported from literature such as functionalization of Polyanthranilic Acid (PAA), a self-doped conducting polymer with Co (II) metal complex has been reported and used in the development of azidothymidine drug sensor [19]. The complexes synthesized in our study might have potential and should be studied in the light of these reports. Complexes of lead have been found to be Carcinogenic and have been reported in literature [20]. Dollwet and Sorenson reported the synthesis and applications of copper complexes, and found to be effective for sterilization of chest wounds and drinking water [21]. The use of tin as modifier for transition metal complexes has been extensively studied, as hydrogenation and aromatization catalysts in the process of petroleum reforming [22,23].

The synthetic compounds were further evaluated for their antibacterial properties against selected bacterial strain (*Bacillus subtilis, Staphylococcus aureus, Pseudomonas aemginosa, Methicillin-resistant Staphylococcus aureus*. The antibacterial potential of compounds is shown in Table 4. The promising effects was observed by compound 4 against *Staphylococcus aureus* with zone of inhibition 11 mm, while compound 3 showed excellent activities against *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aemginosa,* with zone of inhibition ranging from 10 to 22 mm at tested concentration of (2 mg/ml). The compound were also screening against resistance pathogen (*Methicillin-resistant Staphylococcus aureus)* only compound 3 exhibited significance activity against the tested strain among the entire compounds.

Conclusion

In the present study, the complexes of anthranilic acid and pthalic anhydride ligands with cadmium (Cd), copper (Cu), of cobalt (Co), lead (Pb) and Tin (Sn) were synthesized and screened for anti-pathogenic effect. We concluded that the complex of cobalt (Co) anthranilic acid and pthalic anhydride ligands have better anti-pathogenic effect compared to the rest of three metal complexes. The cobalt complex demonstrated better activity against *Pseudomonas aeruginosa* than rest of tested bacterial strains. The use of such complexes might be better for treatment of bacterial infection and should be investigated further.

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