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Studies on oxadiazole–salicylic acid combined molecule as a ligand and its metal chelation

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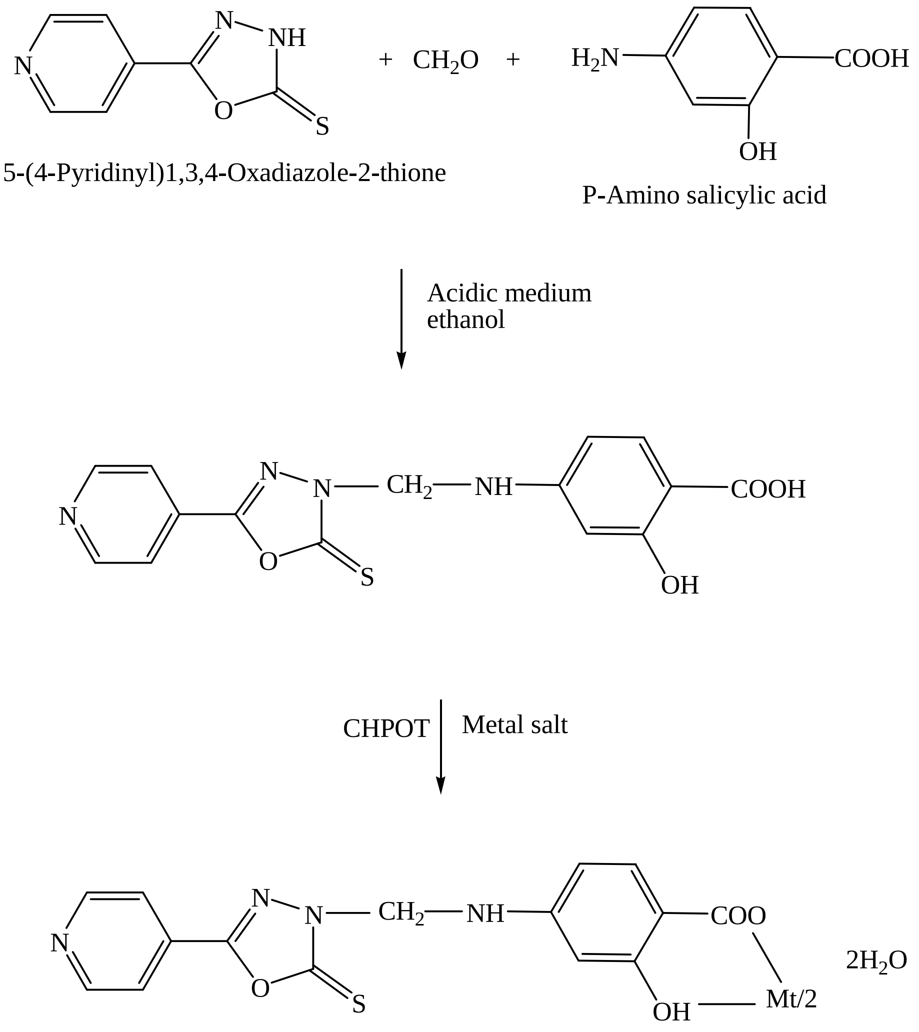
ABSTRACT

Mannich reaction of-5(4-pyridinyl)-1, 3,4-oxadiazole with 4-aminosalicylic acid and formaldehyde in ethanol afford 3-(4-carboxy-3-hydroxyphenyl aminomethyl)-5-(4-pyridinyl)-1,3,4-oxadizole-2-thione(CHPOT) The various metal complexes viz Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+}, Fe^{3+} *and* $UO_2{}^{2+}$ *of CHPOT have been prepared. The CHPOT and its metal complexes were characterized by elemental analysis, spectral features, magnetic moment and antimicrobial activity.*

Key words: 1, 3,4- Oxadiazole, p-Amino salicylic acid (PAS), metal complexes, IR & NMR spectroscopy, magnetic moment, antibacterial activity.

INTRODUCTION

Oxadiazole derivatives are found as important heterocyclic compounds. They found in number of pharmaceutical applications [1-4]. Their 2-thione derivatives are also find as pharmaceutical applications such as antibacterial, antiflammatory, stimulants , pesticidal etc.[4-9]. Having drug moeity i.e. isoniazide for the 5-(4-pyridinyl)-1,3,4- oxadiazole –2-thione is very good pharmaceutical agent [7-9]. If the drug type molecule like p-amino salicylic acid introduced in the molecule of this oxadiazole the end molecule may play good antimicrobial agent. Hence it was thought to study oxadiazole-p-amino salicylic acid combined CHPOT. Thus the present paper comprises the synthesis, characterization, chelating properties and microbial activity of CHPOT molecule. The reaction route is as shown in scheme.



CHPOT- Metal complexes

$Mt = Cu^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+}, Co^{2+}, Fe^{3+}, UO_2^{2+}$

MATERIALS AND METHODS

Materials
5-(4- pyridinyl)1,3,4, Oxadiazole-2- thione (POT) was prepared by method reported in literature.[10]. P –Aminosalicylicacid (PAS) (i.e. 4-Aminosalicylic acid) was obtained from local dealer. All other chemicals used were of analytical grade.

Synthesis of 3-(4-carboxy-3 hydroxyphenyl aminomethyl)-5-(4-pyridynil)-1,3,4-oxadiazole-2-thione:

Formation of CHPOT.
A mixture of 5-(4-pyridinyl)-1, 3,4,-Oxadizole-2-thione(POT) (0.02mole), formaldehyde (0.02 mole), and 4- Amino salicylic acid (PAS) (0.02mole) in ethanol (70ml) was refluxed for 4hr. Subsequently ethanol was distilled off and pasty mass obtained. It was triturated with petroleum ether (40-60c). The solid designated as CHPOT was isolated and dried in air. Yield was 70%. Its m.p. was $149.50^{0}C$ (uncorrected).

Elemental Analysis

$C_{20}H_{16}N_4O_3$ (360):

	C%	H%	N%
Calculated	52.32	3.48	16.27
Found	52.2	3.4	16.2

Acid Value:

Theoretical: 164 mg KOH/1g. Sample
Found : 160 mg KOH/1g. Sample

IR Features:

1480-1520 cm^{-1}	1,3,4, Oxadiazole
3030,1500,1600 cm^{-1}	Aromatic
1680 cm^{-1}	CO of COOH
3200-3600 cm^{-1}	OH
3400 cm^{-1}	Sec.NH
2850-2920 cm^{-1}	CH_2

NMR :

	7.2 –7.6 ppm	Multiplate aromatic
(DMSO)	2.56 ppm (1H)	Singlet CH_2
	12.2 ppm (1H)	Singlet (COOH)
	3.9 ppm (1H)	Singlet (OH)
	9.1ppm (1H)	Singlet (NH)

Synthesis of metal complexes of CHPOT

Formation of CHPOT-metal complexes.

The Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+} $UO_2{}^{2+}$, , and Fe^{3+} metal ion complexes of CHPOT have been prepared in similar manner. The procedure is as follow:

To a solution of CHPOT (0.1mole) in ethanol-acetone (1:1) mixture (150ml), 0.1N KOH solution was added drop wise with stirring. The sticky precipitates were obtained at neutral P^H. These were dissolved by addition of water up to clear solution. It was diluted to 250ml. by water and was known as stock solution. 25ml of the stock solution (which contains 0.01 mole(CHPOT) was added drop wise to the solution of metal salt (0.005mole for divalent metal ions and 0.0033 mole for Fe^{3+} ion) in water at room temperature. Sodium acetate or ammonia was added up to complete precipitation. The precipitates were digested on water bath at 80^0 C for 2 hrs. The digested precipitates of complex were filtered washed with water and air-dried. It was amorphous powder. Yield was almost quantitative. The details are given in Table-1.

Measurement:

The elemental analysis for C, H, and N were carried out on Thermofinigen Flash 1101 elemental analyzer. IR spectra of CHPOT and its metal complexes were scanned on a Nicolet 760 FTIR spectrophotometer in KBr.The metal content of the metal complexes were performed by decomposing a weighed amount of each metal complex followed by EDTA titration as reported in literature [11]. Magnetic susceptibility measurement of the entire metal complex was carried out at room temperature by the Gouy method. Mercury tetrathiocynatocobaltate(II). Hg [Co (NCS) $_4$] was used as a calibrant. The diffused reflectance spectra of solid metal complex were recorded on Backman DK Spectrophotometer with solid reflectance attachments, MgO was employed as the reflectance compound.

Anti-fungal activity:

The fungicidal activity of all compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms listed in Table-3 were used. The anti-fungal activity of all the samples was measured by cup plate method [12]. Each of the plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200gms, dextrose 20gms, agar 20gms and water suspended (1000ppm) in a PDA medium and autoclaved at 120`c for 15 min. at 15 atm pressure. These medium were poured into sterile petri plate and the organisms were inoculated after cooling the petri plates. The percentage inhibition for fungi was calculated after 5 days using the formula given below.

$$\text{Percentage of Inhibition} = \frac{100(X-Y)}{X}$$

Where X: Area of colony in control plate
Y: Area of colony in test plate

The fungicidal activity all compounds is shown in Table –3.

RESULTS AND DISCUSSION

The parent ligand CHPOT was an amorphous yellow powder, soluble in various solvents like dioxane, DMSO and DMF. The results of elemental analysis of the ligand reported in Table–I are consistent with the predicted structure as shown in Scheme-1. The ligand was synthesized as shown in the scheme-1. Examination of IR spectrum (not shown) of CHPOT reveals that a broad band of phenolic hydroxyl stretching is observed at 3200-3600 cm^{-1} as well as additional absorption bands at 3030, 1500 and 1600 are characteristics of the salicylic acid[13,14]. The strong band at 1680 for C=O and band at 3400 for sec. NH. The NMR data (shown in experimental part) also comfirm the structure of CHPOT. The metal complexes of CHPOT with the metal ions Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, Fe^{3+}, Zn^{2+}, UO_2^{2+} vary in colors. On the basis of the proposed structure as shown in scheme-1, the molecular formula of the CHPOT ligand is $C_{20}H_{16}N_4O_3$. Which upon complexation coordinates with one central CHPOT atom at four coordination sites and with two water molecules. Therefore the general molecular formula of the resulting metal complex $[C_{15}H_{11}N_4O_3S_2]$ M.2H$_2$O for divalent metal ions. This has been confirmed by results of elemental analysis of all the seven metal complexes and their parent ligand. The data of elemental analysis reported in Table-1 are in arrangement with the calculated values of C, H, and N based on the above mentioned molecular formula of parent ligand as well as metal complexes.

Inspection of the IR Spectra (not shown) of metal complexes reveals that all the spectra are identical in all respects. The comparison of IR spectrum of the parent ligand CHPOT with that of its each metal complex has revealed certain characteristics differences. One of the significant difference to be expected between the IR spectrum of the parent ligand and its metal complexes is the presence of more broadened bands in the region of 3200-3600 cm^{-1} for the metal complexes as the oxygen of the O-H group of the ligand forms a coordination bond with the metal ions. [13-15]. This is explained by the fact that water molecules might have strongly absorbed to the metal complexes sample during their formation. Another noticeable is that the band due to the COO anion at 1600 cm^{-1} in the IR spectrum of each metal complex. The band at 1400 cm^{-1} in the IR spectrum of HL assigned to in plane of OH determation [13-15] is shifted towards higher frequency at the spectra of the metal complexes due to the formation of metal oxygen bonds. This has been further confirmed by a week band at 1105 cm^{-1} corresponding to C-O-M stretching [12]. Thus all of these characteristics features of the IR studies suggested the structure of the metal complexes as shown in scheme.

Examination of data of the metal content in each compound revealed a 1:2 metal: liagnd (M: L) stoichiometry in all of the complexes of divalent metal ions and 1:3 metal: ligand stoichiometry for Fe^{3+} ions.

Magnetic moment ($^{\mu}{}_{eff}$) each of the metal complex is given in Table-2. Examination of these data reveals that all complexes other than that of Zn^{2+} and $UO_2{}^{2+}$ are para-magnetic while those of Zn^{2+} and $UO_2{}^{2+}$ are diamagnetic. The diffuse electronic spectrum of the [Cu $HL(H_2O)_2$] metal complexes shows broad bands at 15873 and 24691 cm^{-1} due to the ^2T $^2T_{2g}$ transition and charge transfer, respectively suggesting a distorted octahedral structure [16-18] for the [Cu $HL(H_2O)_2$] complex. Which is further confirmed by the higher value of $^{\mu}{}_{eff}$ of the [$CuHL(H_2O)_2$] complex. The [NiHL $(H_2O)_2$] and [Cu $HL(H_2O)_2$] complexes gave two absorption bands respectively at 15603,22998 and 15384,22727 cm^{-1} corresponding to $^4T_{1g}$ $^2T_{1g}$ and $^4T_{1g}$ (p) transitions. Thus absorption bands of the diffuse, reflectance spectra and the value of the magnetic moments ($^{\mu}{}_{eff}$) indicate and octahedral configuration for the [NiHL $(H_2O)_2$] and [Cu $HL(H_2O)_2$] complexes. The spectra of [Mn HL $(H_2O)_2$] shows weak bands at 15384,17653, and 22955 cm^{-1} assigned to the transitions $^6A_{1g}$ $^4T_{1g}$ (4G), $^6A_{1g}$ $^4T_{2g}$ (4G) and $^6A_{1g}$ (F) $^4T_{1g}$ respectively suggesting an octahedral structure for the [Mn HL $(H_2O)_2$] complex. The spectrum of Fe^{3+} complex has not been adequately characterized. The spectrum comprises the band ground 1900 cm^{-1} and other weak band ground 2300 cm^{-1}. The latter has not very long tail. These may have the transitions ^6A_g $^4T_2$ (4G) and $^6A_1$ $^4T_1$ (4G). The high intensities of the bands suggests that they might be charge transfer in origin- $^{\mu}{}_{eff}$ is found to be lower than normal range. In the absence of low temperature moments it is difficult to give any significance. As the spectrum of the [Zn $HL(H_2O)_2$] polymer is not well resolved, it is not interpreted but it is $^{\mu}{}_{eff}$ value shows that it is diamagnetic as expected.

Table 1. Analytical andspectral data of CHPOT ligand and its metal chelates

Molecular Formula	Mol.Wt	Yield (%)	Elemental Analysis							
			% C		% H		%N		%M	
			Cald.	Found	Cald.	Found	Cald	Found	Cald	found
$C_{15}H_{12}N_4O_4.S$	344	62	52.32	52.2	3.48	3.4	16.27	16.2		
$C_{30}H_{26}N_8O_{10}.S_2Cu$	785.54	58	45.82	45.7	3.3	3.2	14.25	14.2	8.08	8.0
$C_{30}H_{26}N_{8\ 10}.S_2Mn$	776.94	60	46.33	46.2	3.34	3.3	14.41	14.3	7.07	7.0
$C_{30}H_{26}N_{8\ 10}.S_2Co$	780.93	53	46.09	45.9	3.32	3.3	14.34	14.3	7.54	7.4
$C_{30}H_{26}N_8O_{10}.S_2Zn$	787.39	59	45.72	45.6	3.3	3.2	14.22	14.2	8.30	8.2
$C_{30}H_{26}N_8O_{10}.S_2Ni$	780.71	62	46.11	46.0	3.33	3.2	14.34	14.2	7.52	7.3
$C_{45}H_{39}N_{12}O_{15}S_3Fe$	1138.84	50	47.41	47.3	3.42	3.3	14.75	14.6	4.9	4.8
$C_{30}H_{26}N_8O_{10}.S_2UO_2$	992.73	54	36.30	36.2	2.64	2.5	11.29	11.2	23.98	23.0

The antifungal activity of all the samples measured for various plant pathogens. Inspection of the result shown in Tabel-2 indicates that all compounds are good toxic for fungi. Out of all the compounds copper complex is more toxic than others. These compounds almost inhibit the fungi about 70%. Hence produced metal complexes can be employed as garden fungicides. Further work in direction is in progress.

Table 2 : Reflectance Spectral Data of ML_1, Chelates (cm^{-1})

Metal chelates	Absorption band(Cm^{-1})	Transitions	Magnetic moment(BM)
Cu- $(CHPOT)_2 .2H_2O$	23,370	C.T	1.95
	15,655	${}^{2}{}_{B1g} \rightarrow {}^{2}{}_{A1g}$	
Ni- $(CHPOT)_2 .2H_2O$	24,478	${}^{3}{}_{A2g} \rightarrow {}^{3}{}_{T1g}(p)$	3.85
	15,607	${}^{3}{}_{A1g} \rightarrow {}^{3}{}_{T1g}(f)$	
Co- $(CHPOT)_2 .2H_2O$	24,660	${}^{6}{}_{A1g}(f) \rightarrow {}^{4}{}_{T2g}(f)$	3.87
	18,867	${}^{6}{}_{A1g}(f) \rightarrow {}^{4}{}_{T2g}$	
	8,928	${}^{6}{}_{A1g}(f) \rightarrow {}^{4}{}_{T2g}(p)$	
Mn-$(CHPOT)_2 .2H_2O$	24,045	${}^{6}{}_{A1g} \rightarrow {}^{4}{}_{A1g}(4fg)$	5.5
	18,657	${}^{6}{}_{A1g} \rightarrow {}^{4}{}_{T2g}(4g)$	
	16,222	${}^{6}{}_{A1g} \rightarrow {}^{4}{}_{T1g}(4g)$	
Zn-$(CHPOT)_2 .2H_2O$	-	--	
Fe-$(CHPOT)_2 .2H_2O$	22,750	${}^{6}{}_{A1g} \rightarrow {}^{4}{}_{T2g}(4g)$	5.8
	18,245	${}^{6}{}_{A1g} \rightarrow {}^{4}{}_{T1g}(4g)$	

Zn-$(CHPOT)_2 .2H_2O$ is diamagnetic in nature

Table-3 Antifungal activity of Ligand CHPOT and its Metal complexes

Sample	Zone of inhibition of fungas at 1000 ppm(%$^{)}$					
	Botrydepladia thiobromine	*Nigrospora Sp.*	*Rhizopus Nigricans*	*Aeperginus niger*	*Amdida Albicans*	*Amdida Kruseigos candida glabrata405*
CHPOT	56	60	71	72	68	60
CHPOT-Mn^{2+}	70	70	75	60	55	68
CHPOTCo^{2+}	72	80	80	64	68	75
CHPOTNi^{2+}	72	75	72	76	69	68
CHPOTCu^{2+}	60	78	80	83	80	76
CHPOT-Fe^{3+}	76	68	65	78	77	75
CHPOTZn^{2+}	64	72	63	76	73	80

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