Syntheses, Characterization and Biological Studies of Some Metal (II) Complexes With 4-(*P*-Chlorophenyl)-2-Phenyl-5-Thiazoleacetic Acid

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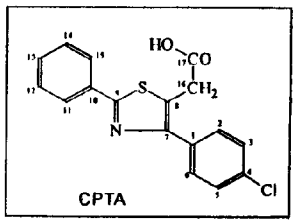
Summary: Some new metal complexes of 4-(p-chlorophenyl)-2-phenyl-5-thiazoleacetate (CPTA) with Co(II), Ni(II), Cu(II), Cd(II), Pb(II) and Zn(II) have been synthesized and characterized by elemental analysis, magnetic susceptibility, ^{1}H NMR and infrared spectroscopy. Their biological studies have been performed against different bacteria and fungi.

Introduction

In medicinal chemistry, metal complexes as pharmaceuticals have received limited attention compared with organic compounds [1]. Interaction between metals and medicines have been becoming important subjects recently, because activities of some drugs having high affinities to metals were influenced by the interactions with metals [2]. Throughout history, both ancient and modern, metals and metal compounds have been used in medicine to treat a variety of ailments [3-6]. In the last century, metal complexes were used to treat diseases ranging from syphilis (organoarsenic compounds) to cancer (platinum anti-tumor drugs) to arthritis (gold compounds) [3].

In an accessible literature no work has been done on the synthesis and characterization of the metal complexes of 4-(p-chlorophenyl)-2-phenyl-5-thiazoleacetic acid (CPTA). The ligand CPTA is an orally active anti-inflammatory drug, and has structure characterized by phenyl, chlorophenyl, thiazol and acetate groups and have potential for coordination to metal ions. Hence, an attempt have been made to synthesize and characterize certain metal complexes like (1) Co(II), (2) Ni(II), (3) Cu(II), (4) Cd(II), (5) Pb(II) and (6) Zn(II) with CPTA.



CPTA

Results and Discussion

Table-1 shows the physical data of the complexes. These were prepared in high yields, having sharp melting points and are soluble in chloroform, ethyl acetate and butyl acetate.

Table-2 shows the different IR vibrational frequencies of complexes and acid. The formation of complex was confirmed by the absence of ν_{OH} broad band in the region 2980-2700cm^{-1}. The IR spectra of the free acid show also two bands at 1691 and 1396 cm^{-1} corresponding to the asymmetric and symmetric COO stretching vibrations, respectively. Both bands exhibited marked changes on complexation indicating that carboxylate group of the acid is involved in the complex formation. The bands in region of 480-450 cm^{-1} and 380-310 cm^{-1} indicate the M-O and M-S bond, respectively [7].

Magnetic susceptibility measurements play important role in characterization of complexes. The magnetic moments indicate that metal complexes are of high spin type thus confirming the octahedral geometry for Co complex with H_2O molecules in *trans* position [8] while tetrahedral geometry for Ni and Cu complexes. The other complexes were diamagnetic. Thus magnetic and IR studies suggested that the ligand is acting as bidentate through oxygen and sulfur atom.

The ^{1}H NMR data for the ligand and diamagnetic metal complexes are given in Table-3. The expected resonances were assigned by their multiplicity and intensity patterns. The integration of

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Table 1:- Analytical, Physical and Magnetic Data

Complex	Color	M.P. °C	Yield %	Elemental Composition		μ_{eff}	Metal %
				%C cal./found	%H cal./found	B.M.	Cal./ Found
(I) $Co(CPTA)_2.2H_2O$	Light Brown	109-111	87.0	54.33/54.02	3.46/3.12	5.21	7.85/ 7.72
(II) $Ni(CPTA)_2$	Green	105-107	92.0	57.06/57.00	3.08/3.06	3.80	8.25/ 8.12
(III) $Cu(CPTA)_2$	Green	35-37	78.0	56.75/55.97	3.05/3.10	1.64	8.76/ 8.69
(IV) $Cd(CPTA)_2$	White	258-260	74.0	53.13/53.20	2.86/2.80	-	14.58/ 14.12
(V) $Pb(CPTA)_2$	White	235d	76.0	47.28/47.10	2.55/2.58	-	23.98/ 23.76
(VI) $Zn(CPTA)_2$	White	262d	68.0	56.49/56.47	3.05/3.09	-	9.04/ 8.95

Table 2:- Important Assignments of Characteristic IR vibrations (cm^{-1})

Complex	V(COO)		M - O	M – S
	$V_{Asym}(COO)$	$V_{sym}(COO)$		
Acid	1691	1396	-	-
I	1648	1365	474	355
II	1661	1368	470	315
III	1685	1360	451	310
IV	1592	1385	470	360
V	1651	1365	478	380
VI	1670	1379	465	340

Table 3:- ^1H NMR Data

Compound	δppm (Assignment)
CPTA	1.9 s (CH_2); 7.31 d (2H, 2/6); 7.27 d (2H, 3/5); 7.64 d (2H, 11/15); 7.47 m (2H, 12/14); 7.37 m (1H, 13); 11.2 s (OH)
IV	2.1 s (CH_2); 7.30 d (2H, 2/6); 7.28 d (2H, 3/5); 7.60 d (2H, 11/15); 7.47 m (2H, 12/14); 7.37 m (1H, 13);
V	2.3 s (CH_2); 7.29 d (2H, 2/6); 7.28 d (2H, 3/5); 7.61 d (2H, 11/15); 7.47 m (2H, 12/14); 7.37 m (1H, 13);
VI	2.1s (CH_2); 7.30 d (2H, 2/6); 7.27 d (2H, 3/5); 7.61 d (2H, 11/15); 7.47 m (2H, 12/14); 7.37 m (1H, 13);

s, singlet; d, doublet; m, multiplet

^1H NMR spectra are in good agreement with the expected number of protons in the complexes.

Biological activity for acid and metal complexes were carried out against various bacteria and fungi by the 'agar well diffusion' method [9] and the results are given in Tables-4 and 5.

The results indicate that nickel, cadmium and lead complexes show better activity against tested bacteria whereas all complexes found more active against *Escherichia coli*. Non of the complexes showed any activity against *Pseudomonas aeruginosa*. The order of antibacterial activity is IV > II = V > III = VI > I, i.e., $Cd(CPTA)_2$ is most active and $Co(CPTA)_2 2H_2O$ least.

The antifungal activities show that zinc, lead and cadmium carboxylates are rather highly active against all the tested fungi. This is interesting to note that ligand itself is inactive against *Nigrospora oryzae* but metal carboxylates are highly active against the same fungus which might be due to carboxylate group bonded to metal which could act as better carrier in these compounds. The order of antifungal activity is IV > V > VI > I > II, i.e., Cd(CPTA)2 has higher activity in the series.

Experimental

The CPTA was obtained through the courtesy of Wyeth Pharmaceuticals Co. and recrystallized from benzene before use. The metal salts were of analytical grade and used without further purification. Solvents were purified before use by standard methods [10].

Melting points of the complexes were recorded in a capillary tube using Electro thermal melting point apparatus model MP-D, Mitamura Riken Kogyo (Japan) and are uncorrected. Elemental analyses were carried out on CHN Elemental Analyzer Model 240 B, Perkin Elmer Norwalk Connicitas, USA. Metals were estimated by Atomic Absorption Spectrophotometer model SAFAS MONOCO France [11]. The magnetic susceptibility measurements of the complexes were determined on Vibrating Sample Magnetometer (Japan).

Table 4:- Antibacterial Activity

Bacterium	Zone[a]	Std.[b]	Std.[c]	Acid	I	II	III	IV	V	VI
Corynebacterium diphtheriae	1	13	12	-	-	8	-	7	-	7
	2	-	-	6	-	9	-	8	6	8
Staphylococcus pryogenes	1	17	18	-	-	6	-	-	6	-
	2	-	-	6	-	7	-	6	7	-
Staphylococcus aureus	1	18	19	-	-	9	-	6	-	-
	2	-	-	6	6	10	6	7	-	-
Proteus mirabilis	1	18	17	-	-	-	-	-	-	-
	2	-	-	6	-	-	-	6	-	-
Escherichia coli	1	18	19	6	6	6	6	6	8	7
	2	-	-	7	7	7	7	7	9	8
Shigella boydii	1	16	17	-	-	-	-	6	6	6
	2	-	-	6	-	-	6	7	7	7
Pseudomonas aeruginosa	1	-	-	-	-	-	-	-	-	-
	2	-	-	-	-	-	-	-	-	-

[a] Zone, 1 = Zone of Inhibition in mm, in 100 μg /100 μl
2 = Zone of Inhibition in mm, in 200 μg /100μl
[b] Standard = 10 μg Ampicillin [c] Standard = 10 μg Tobramycine

Table 5:- Antifungal Activity [a]

Fungus	Acid	1	2	4	5	6
Allescheria boydu	+++	-	-	+++	+++	-
Aspergillus niger	-	-	-	++	-	+
Candida albicans	+	+++	-	+++	+++	+++
Curvularia lunata	+++	++	+	++	+++	++
Drechslera rostrata	+++	++	+++	+++	+++	++
Nigrospora oryzal	-	+	+++	+++	++	++
Microsporum canis	+++	+++	+++	+++	+++	+++
Pleurotus ostreatus	+++	+++	+++	+++	+++	+++
Stachybotrys atra	++	+	+++	+++	++	++
Trichophyton mentagrephyte	+++	+++	-	+++	+++	+++

[a] 200 μg/ml, + = low activity, ++ = good activity, +++ = high activity, - = no activity.
Standard = Miconazole and Ketoconazole

The antimicrobial activities were determined by agar well diffusion' method. The culture of bacteria was uniformly inoculated on the agar plates to obtain a confluent lawn. The sterile 6mm discs, having known concentration of compounds, were placed on the medium aseptically. The plates were incubated for 24 hours at 37 ^{0}C. After this period the zone of inhibition was measured in mm.

Antifungal behaviour was determined by agar tube diffusion method. Test tubes containing sterile Sabour and dextrose agar were inoculated with the test compounds at different concentrations and kept at standard position at room temperature to solidification. Test fungal cultures were inoculated on the slant, and growth inhibition was observed after an incubation period of seven days.

Syntheses

The hydroxides of the metals, prepared by reacting 2.0 mole of NaOH with 1.0 mole of chloride or nitrate of respective metal in aqueous medium, was allowed to react with 0.2 mole of CPTA in 100 mL of ethanol. The mixture was stirred and refluxed for 1-2 hours. The insoluble material was filtered off and solvent was removed under reduced pressure. The resulting solid was recrystallized in isopropanol/methanol (1:1) mixture and dried in vacuum.

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