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Synthesis and biological activity of acetylacetone thiosemicarbazone and their metallic complexes

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ABSTRACT
In present work, Ligand acetylacetone thiosemicarbazone and their 11 complexes of the type ML_2X_2, ML_2X', where M = Cu(II), Cd(II), Co(II), Zn(II), Hg(II); L = acetylacetone thiosemicarbazone; X = Cl, NO_3 or CH_3COO; X′ = SO_4 have been synthesized and characterized with the help of molar conductance, magnetic susceptibility measurements, infra-red and ultra-violet spectroscopy. The spectral data revealed that the thiosemicarbazone act as bidentate ligand, making use of thionic sulphur and the azomethine nitrogen atom for co-ordination to the central metal atom. All the compounds have been screened for their antibacterial activity against Gram positive bacteria *Staphylococcus aureus*, *Staphylococcus epidermidis* and Gram negative bacteria *Escherichia coli and Pseudomonas aeruginosa*. Some of complexes exhibited appreciable activity.

Key Words: Thiosemicarbazone, thiosemicarbazone complexes, metallic complexes, characterization, antibacterial activity and spectral studies.

INTRODUCTION

Thiosemicarbazones are of considerable interest because of their chemistry and potentially beneficial biological activity, such as antibacterial, antifungal, antiviral, antiamoebic, antimalarial and antitumor activity (Klayman *et al.*, 1979; Scovill *et al.*, 1984; Klayman *et al.*, 1984; Liberta *et al.*, 1992; West et at., 1993; Liu *et al.*, 1995; Sharma *et al.*, 2005; Rebolleo *et al.*, 2005). The biological activities of thiosemicarbazones are considered to be due to their ability to form chelates with metals. Biological activities of metal complexes differ from those of either ligands or the metal ions, and increase and/or decreased biological activities are reported for several transition metal complexes. Thiosemicarbazone are versatile compounds; two structural isomers (E-, Z – form) are possible and they can co-ordinate to the metal either as a neutral ligand or as a deprotonated ligand through the NS atoms (West *et al.*, 1996; Kasuga *et al.*, 2003).

In this work, ligands acetylacetone thiosemicarbazone and their eleven metallic complexes were prepared and characterized by molar conductance, magnetic susceptibility measurements, ultra-violet and infra-red spectroscopy. Their antibacterial activities were evaluated by measuring the zone of inhibition using disc diffusion method against Gram positive bacteria *Staphylococcus aureus*, *Staphylococcus epidermidis* and Gram negative bacteria *Escherichia coli* and *Pseudomonas aureginosa*.

EXPERIMENTAL

Material and measurements

All the chemicals and solvents of Sigma-Aldrich/CDH/Rankem/Merck were AR grade and used without any further purification. All the reaction were monitored by TLC using methanol:chloroform (9:1) as solvent system. TLC plates were prepared by spreading method and are dried in air and activated by heating in hot air oven at 110°C for 20 minutes. Iodine chamber was used for visualization of TLC spots. Melting point of all synthesized compounds was determined in open glass capillaries. Magnetic susceptibility measure-

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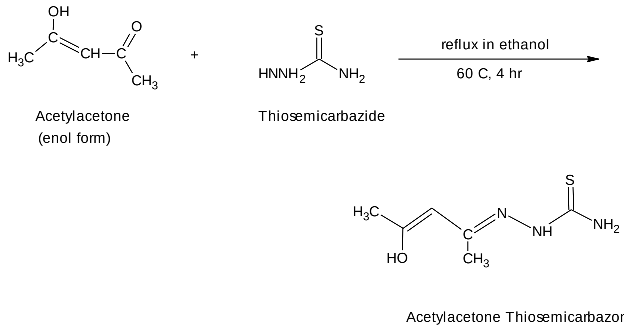

Figure 1: Synthesis of ligand(L); Acetylacetone Thiosemicarbazone ($C_6H_{12}N_3OS$).

ments were carried out in the polycrystalline state on a Vibrating Sample magnetometer. IR spectra were recorded by making KBr pellets on Jasco fourier transform IR spectrophotometer (FT/IR-4100). UV spectra were recorded by making methanol solution on Systronic pc based double beam spectrophotometer 2202. All the synthesized compounds were screened for their antibacterial activity using agar diffusion method.

Thiosemicarbazide (0.01mol, 0.91g) was dissolved in ethanol (approx. 60ml) by refluxing at 50°C in 250 ml Rbf. In the refluxing solution, the acetylacetone (0.01mol, 1.02ml) solution in ethanol (approx. 30ml) was added. The reaction mixture was refluxed for four hours at 60°C. The volume of reaction mixture was reduced and then cooled on ice water. The crystals of acetylacetone thiosemicarbazone were precipitate out. The crystals were recrystallized by ethanol. Yield: 1.62g (90%); m.p.: 119°C; TLC: R_f: 0.94 ($CHCl_3$:CH_3OH, 9:1, v/v).

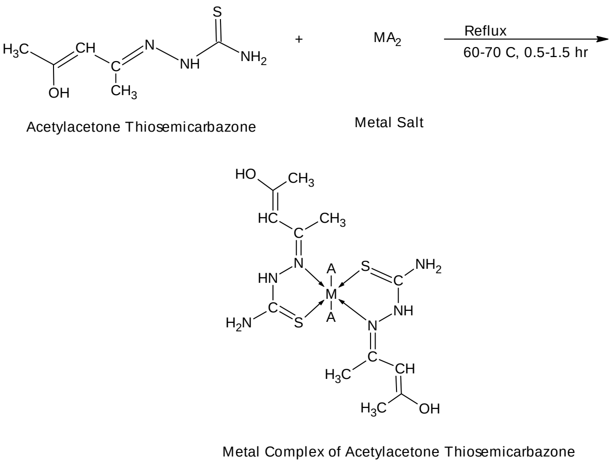

Figure 2: Synthesis of metal complexes of Acetylacetone Thiosemicarbazone.

Ethanol solution of metal salts was refluxed with ethanol solution of acetylacetone thiosemicarbazone in 1:2 ratio for 0.5-1.0 hr. Volume of the resulting clear solution was reduced to 10ml by a rotary vacuum evaporator and the solution was left overnight. The resulting crystalline compounds were filtered under suction, washed with ethanol and ether, and dried in vacuum.

RESULTS AND DISCUSSION

Physical Properties

Complexes reported in the present investigation have the general composition ML_2X_2 and ML_2X', where M = Cu(II), Cd(II), Co(II), Zn(II), Hg(II); L = acetylacetone thiosemicarbazone; X = Cl or NO_3 or CH_3COO; X′ = SO_4. These are crystalline compounds. The complexes of copper(II) are green,

Table 1: Analytical data of compounds.

Comp. no.	Comp.	% Yield	m.p.	Conductance $\Omega^{-}cm^2mol^{-1}$	μ*eff* B.M.	Soluble in
Comp. 1	L	90	119	-	-	Ethanol, Chloro- form
Comp. 2	$[CuL_2Cl_2]$	42	209	8.8	1.76	DMSO, DMF
Comp. 3	$[CuL_2(NO_3)_2]$	32	250	10.6	1.80	DMSO, DMF
Comp. 4	$[CuL_2 SO_4]$	37	205	9.6	1.91	DMSO, DMF
Comp. 5	$[CdL_2 SO_4]$	73	220	9.2	3.6	DMSO, DMF
Comp. 6	$[CoL_2Cl_2]$	28	238	10.5	4.9	DMSO, DMF
Comp. 7	$[CoL_2(No_3)_2]$	30	203	9.8	4.8	DMSO, DMF
Comp. 8	$[ZnL_2Cl_2]$	37	218	11.2	-	DMSO, DMF
Comp. 9	$[ZnL_2(No_3)_2]$	29	242	10.4	-	DMSO, DMF
Comp. 10	$[ZnL_2SO_4]$	60	230	9.3	-	DMSO, DMF
Comp. 11	$[ZnL_2(CH_3COO)_2]$	24	210	8.9	-	DMSO, DMF
Comp. 12	$[HgL_2SO_4]$	28	243	11.2	2.3	DMSO, DMF

Table 2: Infra-red (cm^{-1}) and ultra-violet (λ_{max} in nm) spectrum data of compounds.

Comp.	υ(C=N)	υ(C=S)	λ_{max}
Comp.1	1620	800	272
Comp.2	1593	751	245
Comp.3	1595	744	248
Comp.4	1572	699	232
Comp.5	1575	739	259
Comp.6	1595	719	260
Comp.7	1598	720	238
Comp.8	1597	749	268
Comp.9	1595	743	265
Comp.10	1586	740	269
Comp.11	1578	746	286
Comp.24	1553	738	241

cadmium(II) are cream, cobalt(II) are dark orange, zinc(II) are white, and mercury(II) are black. All the complexes have low molar conductance values in acetone medium indicating their non-electrolytic nature. All the complexes have μ*eff* values in the range of 1.82 to 4.9 B.M indicating presumably a spin-free octahedral or distorted octahedral configuration of these compounds (Table 1).

Infra-Red Spectra

IR spectra of compounds provide evidence regarding the bonding sites in the complexes. Acetylacetone thiosemicarbazone shows a broad band around 3450 cm-1 indicating that there is free OH group involved in some type of hydrogen bonding and the ligand is a monothiosemicarbazone. In complexes υ(OH) is observed around 3450cm-1, indicating that the OH group has not taken part in coordination. υ(C=S) in the ligand is observed at 800 cm-1 but in the complexes, it is found in the 720-750 cm-1 region suggesting the bonding through sulphur of the thiocarbonyl group. υ(C=N) with some amount of contribution of δ(NH2) is found at 1620 cm-1 and a lowering in frequency of this band on complexes formation supports the coordination through the terminal hydrazine nitrogen (Table 2).

Table 3: Antibacterial activity of compounds (comp. 1 to 12) and standard.

Comp.	Conc. of comp. per disc	Gram Positive Bacteria		Gram Negative Bacteria	
		S. aureus	*S. epidermidis*	*E. coli*	*P. auriginosa*
		Zone of inhibition in mm (mean of three replicates)			
Comp. 1	30μg	-	-	-	-
	200μg	4	3	3	-
Comp. 2	30μg	6	8	9	5
	200μg	14	12	13	9
Comp. 3	30μg	6	9	5	8
	200μg	13	11	10	15
Comp. 4	30μg	3	3	4	4
	200μg	10	9	9	10
Comp. 5	30μg	6	6	5	6
	200μg	13	11	13	14
Comp. 6	30μg	3	-	-	2
	200μg	10	7	6	6
Comp. 7	30μg	3	-	-	3
	200μg	9	7	7	8
Comp. 8	30μg	6	5	7	7
	200μg	12	10	16	13
Comp. 9	30μg	5	4	5	4
	200μg	10	9	8	10
Comp. 10	30μg	4	3	2	3
	200μg	8	9	7	6
Comp. 11	30μg	5	4	8	4
	200μg	6	7	11	10
Comp. 12	30μg	10	11	8	8
	200μg	19	16	14	16
Amikacin	30μg	20	21	21	24

Ultra-Violet spectra

UV spectra of ligand and complexes were recorded in methanol. In UV spectra ligand shows λ_{max} at 272 nm with a shoulder band. It indicates that in methanol solution the ligand exist in thiol form. After complexation, λ_{max} shifted to lower frequency/higher frequency depending upon the centre metal atom. The increase in intensity is attributed to extended conjugation in the ligand moiety after complexation (Table 2).

Biological activity

The synthesized compounds were tested for their antibacterial activity by measuring the inhibition area on agar plates (diffusimetric method) with Gram positive bacteria *Staphylococcus aureus* MTCC 737, *Staphylococcus epidermidis* MTCC 3615 and Gram negative bacteria *Escherichia coli* MTCC 1687, and *Pseudomonas aureginosa* MTCC 1687. The results of antibacterial activity of complexes together with the result of free butanone thiosemicarbazone as comparison are listed in table 3, as estimated by zone of inhibition (mm).

The results show that free thiosemicarbazone (comp. 1) does not have effective antimicrobial activity against selected test organisms, while complexes (comp. 2 to 12) have effective antimicrobial activity. The comp. 12 showes good activity against the entire test organism. The comp. 2, 3, 5 and 8 posses moderate activity while remaining compounds show poor activity against test organisms.

CONCLUSION

The ligand, acetylacetone thiosemicarbazone and their metallic complexes were synthesized and characterized by the infra-red and ultra-violet spectroscopic method. It is examined that in these comoplexes the ligand has NS donor bidentate nature. The biological behavior revealed that ligand shows a weak activity against the test bacterial strains. The chelation induced significant changes in the biological activity of the ligand. Complexes (comp. 12) show good activity against the selected test organisms.

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