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Synthesis, ,Thermal and Biological Evaluation of Six Co-Ordinate Complex And Heterocyclic Base Adducts of Co (II) Derived From N(4) Thiosemicarbazone

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ABSTRACT

Complex and adducts of cobalt (II) have been synthesized by the reaction of copper (II) chloride with 5-chloro-2-hydroxy acetophenone N(4) phenyl thiosemicarbazone in presence of heterocyclic base like pyridine (py), α/β/γ-picoline. Thiosemcarbazone has been characterized by 13C, 1H NMR,ESI-MS as well as IR, electronic spectra. Octahedral geometry for the six coordinate complex and adducts has been predicted from magnetic and spectroscopic data. The thiosemicarbazone and its Co (II) complexes have been found antifungal,antibacterial and show growth inhibitory activity against Pseudomonas Putida, Escherichia coli, Asper gillus Nigar and Candida Albicans.

KEYWORDS Thiosemicarbazone,N(4) phenyl thiosemicarbazone, Bioactive metal complexes, CoCl2.6H2O.

Introduction

Thiosemicarbazones are good ligands with beneficial biological activity.their biological activity is related to their ability to coordinate to metal centres.Thiosemicarbazone derivatives possess additional functional groups which can coordinate to metal ion.This suggests the biological activity may also depend on the non coordinating groups.

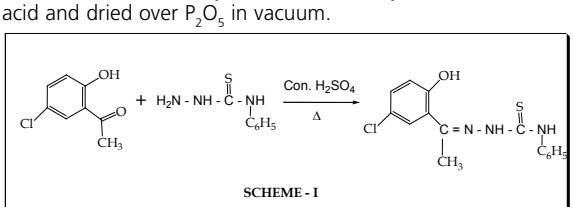
Thiosemiarbazones and their metal complexes because of their versatile biological activity and prospective use of drugs [1] have been explored for 50 years [2,3].Thiosecarbazones have been extensively studied due to their biological properties ranging from antifungal [4],antibacterial [5],antimalarial [6],antiviral [7].The abiity of thiosemicarbzone to chelate with metals in biological system is due to their ctivity.Upon co-ordination, the lipophilicity,which controls the entry rte,is modified nd side effects may be decreased [8]. Metal complexes formed by salicylaldehyde thiosemicarbazone ($ONSH_2$). This ligand loses a proton from the phenolic group and acts as a singly charged tridentate ligand, coordinating through oxygen, the imino-nitrogen and thione sulphur atom. It acts as a doubly negatively charged tridentate by losing proton from mercapto group. The Co (III) complexes $[Co(ONSH)_2]$ Cl and $[Co(ONSH)(ONS)].H_2O$ have been repoted [9]. Co (II) forms complexes of composition $Co(HL)_2$ and Co_2L_3. 5-methyl-β-N(2-hydroxy phenyl) methylenedi-thiosemicarbazate ($ONSH_2$), its 5-chloro, 5-nitro and 3-methoxy derivatives, acetylacetone schiff bases and 2-hydroxy-4-methyl-5,6-dizo-7-thiono-8-thianona-2,4-diene act as doubly negatively charged ONS tridentate ligands by the loss of two protons. Thiosemicarbazones are used for making electrodes [10].

In present work we report the synthesis, spectral characterisation and biological studies of six coordinate complex and adducts of Co (II) with 5-chloro 2-hydroxy acetophenone *N*(4) phenyl thisemicarbazone.

Experimental

Materials and instrumentation

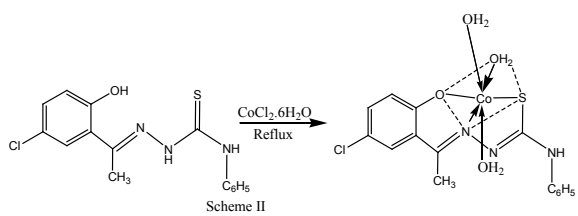
The *N*(4) thiosemicarbazone was synthesized by refluxing 5-chloro 2-hydroxy acetophenone and *N*(4) phenyl thiosemicarbazide in ethanol in the mole ratio 1:1 for 4 hours for two hours. The product obtained was filtered , washed with cold ethanol and then diethyl ether. It was recrystalised from acetic acid and dried over P_2O_5 in vacuum.



SCHEME - I

Synthesis of complex

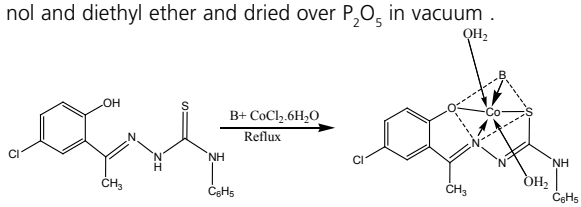
Co (II) salt was dissolved in absolute ethanol.The ethanolic solution of thiosemicarbazone in slight excess over the metal: ligand ratio of 1:1 was added to it dropwise and with constant stirring.The rection mixture was refluxed for an hour,after addition of one gram of sodium acetate.The brown product was filtered and washed with a small portion of hot water,cold ethanol and then diethyl ether.The product was then dried over P_2O_5 in vacuum.



Scheme II

Synthesis of adducts

The complex Co.L.B (B-heterocyclic base like pyridine, , α-picoline, β-picoline,γ-picoline) was synthesized by adding slowly ehanolic solutions of $CoCl_2.6H_2O$,heterocyclic base to the hot ethanolic solution of thiosemicarbazone in the ratio 1:1:1 and refluxing reaction mixture for 7 hours. The adduct obtained was filtered and washed with hot water, cold ethanol and diethyl ether and dried over P_2O_5 in vacuum .



Scheme III

(Where B = pyridine,α/β/-γ-picoline)

Physical measurements

Magnetic measurements were carried out by Faraday method. High purity $[Co(SCN)_4]$ was used as standard. Diamagnetic corrections were made by Pascal's constants. IR spectra were recorded in the range 4000-200 cm^{-1}. NMR spectra were recorded in the mixture of $CDCl_3$ and DMSO-d_6 (1:1 v/v) with a Bruker AC-300F 300MHz spectrometer. Conductivity measurements were carried out on Conductivity Bridge, Systonics conductivity meter-304. UV-Visible spectra were measured on Jasco UV-visible double beam spectrophotometer.Metal in the complex and adducts was estimated by E.D.T.A using xylenol orange as an indicator.

Table 1 Physical measurements

Compounds	Colour	Empirical Formula	Molar conductance $Ohm^{-1}cm^{-2}mole^{-1}$	Magnetic Moment B.M.
L	Yellow	$C_{15}H_{14}N_3ClOS$	-	-
Co-L.$(H_2O)_3$	Brown	$C_{15}H_{18}N_3O_4ClSCo$	45.8	4.50
Co-L.Py.$(H_2O)_2$	Brown	$C_{20}H_{21}N_4O_3ClSCo$	95.7	4.52
Co- α-Pico. $(H_2O)_2$	Brown	$C_{21}H_{23}N_4O_3ClSCo$	70.9	4.57
Co-L β-Pico. $(H_2O)_2$	Brown	$C_{21}H_{23}N_4O_3ClSCo$	60.5	4.62
Co.L.γPico. $(H_2O)_2$	Brown	$C_{21}H_{23}N_4O_3ClSCo$	40.5	4.58

Infrared Spectroscopic data (cm^{-1})
IR-spectral data
1**. L**: ν (- OH) 3300; ν (C = N) 1640; ν (- C – S) 794 (s), 1360 (m); ν (N – N) 1055; ν (^{2}N-H) 3225; ν (C – O) 1290.

2 [CoL$(H_2O)_3$]: ν (C = N) 1608; ν (C = N-N=C) 1540, ν (C-S) 695, 1290,ν (N-N) 1119, ν (M - N) 455, ν (M-O) 525, ν (M-S) 320, ν (C - O) 1230, ν(H_2O) 3540,3560.

3 [CoLpy$(H_2O)_2$]: ν (C = N) 1590; ν (C = N-N=C) 1525, ν (C-S) 725, 1315; ν (N-N) 1119, ν (M - N) Base 275, ν (M - N) 469, ν (M - O) 529, ν (M-S) 310, ν (C - O) 1230, Band due to HB 1270, ν(H_2O) 3545,3565.

4 [CoLα-pico**$(H_2O)_2$]:** ν (C = N) 1595; ν (C = N-N=C) 1510, ν (C-S) 760, 1282, ν (N-N) 1120, ν (M - N) Base 278, ν (M - N) 450, ν (M - O) 525, ν (M-S) 325, ν (C - O) 1238, Band due to HB 1401, ν(H_2O) 3555,3570.

5 [CoLβ-pico**$(H_2O)_2$]:** ν (C = N) 1603; ν (C = N-N=C) 1515, ν (C-S) 722, 1288; ν (N-N) 1120, ν (M - N) Base 230, ν (M - N) 455, ν (M - O) 528, ν (M-S) 315, ν (C - O) 1240, Band due to HB 1485, ν(H_2O) 3560,3572.

6. [CoLγ**-pico$(H_2O)_2$]:** ν (C = N) 1598; ν (C = N-N=C) 1535, ν (C-S) 740, 1312,ν (N-N) 1125, ν (M - N) Base 230, ν (M - N) 440, ν (M - O) 535, ν (M-S) 330, ν (C - O) 1235, Bands due to HB 1445, ν(H_2O) 3570,3588.

TGA analysis data:
The TGA curves of complexes were recorded between the temperatures 30 °C to 800 °C

1. **Co.L.$(H_2O)_3$**: First step, 114 °C, Mass loss 8.36 % second step, 138.29 °C, Mass loss, 12.54 % Third Step 240.43 °C, Mass loss, 28.02 % Fourth Step, 365.14 °C, Mass loss 55.5 %, Residue 800 °C, % of CoO, 17.92 (17.40).

2. **CoL.py.$(H_2O)_2$**: First step, 115 °C, Mass loss 7.32 % second step,140.40 °C, Mass loss, 15.70 % Third Step 248 °C, Mass loss, 25.02 % Fourth Step, 360.29 °C, Mass loss, 55.01 %, Residue, 790.57 °C, % of CoO, 15.83 (15.23).

3. **CoL.**α**-pico.$(H_2O)_2$** : First step, 115.29 °C, Mass loss 7.12 % second step, 140.50 °C, Mass loss, 19.00 % Third Step 225.45 °C, Mass loss, 26.02 % Fourth Step, 361.14 °C, Mass loss 56.5 %, Residue 800 °C, % of CoO, 14.14 (14.81).

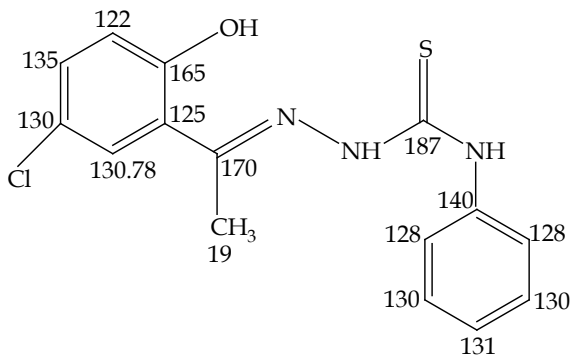
4. **CoL.**β**-pico.$(H_2O)_2$** : First step, 115.28 °C, Mass loss 7.15 % second step, 142.14 °C, Mass loss, 17.52 % Third Step 237 °C, Mass loss, 27.02 % Fourth Step, 366.29 °C, Mass loss, 65.01 %, Residue, 778.57 °C, % of CoO, 14.17 (14.81).

^{1}H-NMR

Signals at 11.6, 3.30 ppm are assigned to – OH, - CH_3 protons respectively.

L does not show any peak corresponds to S-H proton, indicating it exists in thioketo form. Absence of ^{2}NH proton signal suggests enolisation of ^{2}NH – C = S group to ^{2}N=C-SH. Little low field position of ^{4}NH (7.9 ppm) could be attributable to the deshielding caused by – N = C〈 of the system N=CSH = NH. Aromatic protons show multiples at 6.9, 7.20 , 7.60,7.65,7.77,7.30,6.20,7.29 ppm range.

^{13}C-NMR (DMSO-D_6): δppm 122 (C=C), 135 (C=C), 130 (C=C-Cl), 130.78 (C=C), 125(C=C),165 (C=C-OH),170 (C=N),19 (=C-CH_3),187 (C=S),140 (NH-C=C),128 (C=C),130 (C=C),131 (C=C),130 (C=C),128 (C=C).



(Calcd) found ESI-MS m/z, ion M$^+$: $C_9H_{10}ClN_3OS$ (319.77) 319.92,$C_{15}H_{18}N_3O_4ClSCo$ (430.75) 430.11, $C_{20}H_{21}N_4O_3ClSCo$ (491.83) 491.10, $C_{21}H_{23}N_4O_3ClSCo$ (505.86) 505.12, $C_{21}H_{23}N_4O_3ClSCo$ (505.86) 505.19, $C_{21}H_{23}N_4O_3ClSCo$ (505.86) 505.87.

Table.2 Analytical data

Compounds	Elemental Analysis Found (Calculated) %				
	Metal%	%C	%H	%N	%S
L	-	56.07 (56.34)	4.81 (4.41)	13.62 (13.14)	10.91 (10.03)
Co-L.$(H_2O)_3$	13.12 (13.68)	41.03 (41.82)	4.82 (4.27)	9.08 (9.76)	7.65 (7.44)
Co-L.Py.$(H_2O)_2$	11.72 (11.98)	48.12 (48.84)	4.76 (4.30)	11.82 (11.39)	6.81 (6.52)
Co-L.α-Pico.$(H_2O)_2$	11.20 (11.65)	49.12 (49.86)	4.96 (4.58)	11.94 (11.08)	6.72 (6.34)
Co-L. β-Pico. $(H_2O)_2$	11.35 (11.65)	49.52 (49.86)	4.05 (4.58)	11.72 (11.08)	6.06 (6.34)
Co.L.γ-Pico.$(H_2O)_2$	11.77 (11.65)	49.15 (49.86)	4.09 (4.58)	11.88 (11.08)	6.77 (6.34)

Table 3 .Electronic spectral data (cm^{-1})

Compound	Mode	d-d	L→M	n→π*	π→π*
L	DMF	-	-	25971 28571	40865
Co-L.$(H_2O)_3$	DMF	17820	27055 25641	30860 35465	44889
Co-L.Py.$(H_2O)_2$	DMF	17594	27027 25641	31156 34400	44444
Co-L.α-Pico.$(H_2O)_2$	DMF	17544	25641 22989	30580 25650	42553
Co-L.β-Pico.$(H_2O)_2$	DMF	17634	25907 23585	33110 31260	43478
Co.L.γ-Pico.$(H_2O)_2$	DMF	17391	25500 22727	33650 31055	41667

5. **CoL. γ-pico.$(H_2O)_2$**: First step, 115 °C, Mass loss 7.19 % second step, 150.29 °C, Mass loss, 18.00 % Third Step 232.43 °C, Mass loss, 28.02 % Fourth Step, 370.14 °C, Mass loss 60.5 %, Residue 800 °C, % of CoO, 14.35 (14.81).

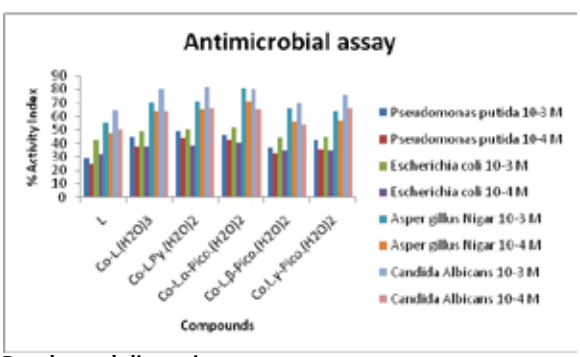
Biological activity (Agar well diffusion method)
Table.4 % Activity index of L , Co (II) complexes and standered

Compound % Activity Index	Pseudomonas putida		Escherichia coli		Asper gillus Nigar		Candida Albicans	
	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M
L	29.41	25.00	42.30	32.26	55.56	47.36	64.71	50.00
Co-L.$(H_2O)_3$	45.13	37.90	49.02	37.70	70.20	64.20	80.30	64.00
Co-L.Py.$(H_2O)_2$	49.04	43.45	50.00	38.71	71.20	65.18	81.34	66.10
Co-L.α-Pico.$(H_2O)_2$	46.07	42.68	51.50	40.39	80.80	70.90	80.10	65.10
Co-L.β-Pico.$(H_2O)_2$	37.25	32.34	44.16	34.40	65.60	55.90	69.90	54.01
Co.L.γ-Pico.$(H_2O)_2$	42.20	35.12	45.16	34.42	64.15	56.63	75.44	66.00
Standered	100	100	100	100	100	100	100	100

(Std-Bicip)
% activity index was calculated by the formula

$$\% \text{ Activity Index} = \frac{\text{Zone of inhibition of test compound}}{\text{Zone of inhibition of standard (diameter)}} x100$$

Fig.1 % Activity Index Bar Graph



Results and discussion

The colours, elemental analysis, stoichiometries of ligand and its complexes are presented in Table 1. Elemental analysis data are consistent with 1:1 ratio of metal ion, thiosemicarbazone for complex and 1:1:1 ratio for metal, thiosemicarbazone and heterocyclic base for all adducts. The complex and all adducts are insoluble in most of the common polar and non polar solvents. They are soluble in DMF in which conductivity measurements were made (30^0C), showing all complexes to be non electrolyte [11]. Mass spectral data confirmed the structure of the thiosemicarbazone as indicated by molecular ion peak (M + 1) corresponding to their molecular weights.The magnetic susceptibility of complex and adducts carried out at room temperature (27^0C) fall in the range of 4.50-4.62 B.M (Table 1). The high spin octahedral complexes show magnetic moment in the range 4.50-4.62 B.M. respectively [12].

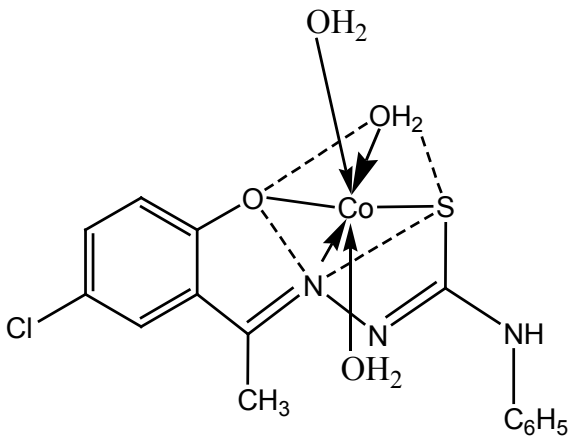
The Co (II) complexes are usually obtained in tetrahedral and octahedral environments and less frequently in planer environment.The ground term of Co (II) is ^4T_1g or ^4Eg in octahedral coordination depending on whether the complex is high spin or low spin. The electronic spectrum of complex and adducts shows three bands due to spin allowed transitions in the range 22,000-28,000 cm^{-1} and 17,000-18,000 cm^{-1} which correspond to ^4T_1g (F) → ^4T_2g (F) (ν_1), ^4T_1g(F) → ^4A_2g (F) (ν_2) and ^4T_1g(F) → ^4T_1g (P) (ν_3) respectively expected for d^7 system in octahedral field. The absorption bands at 22,000 – 28,000 cm^{-1} range are assigned to the L → M transitions respectively. The appearance of these bands suggested octahedral geometry around Co (II) [13].

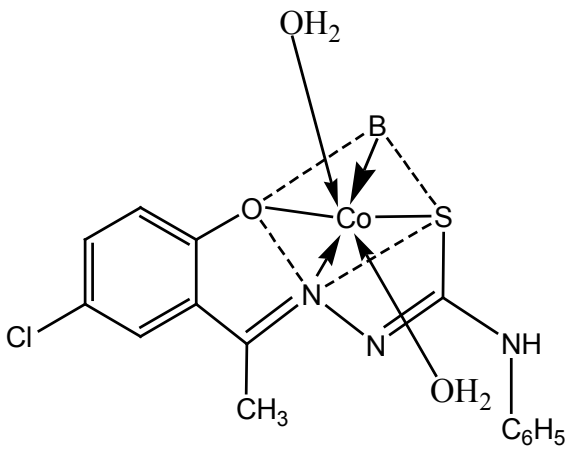
The most important bands in the infrared spectra of Co (II) complexes is useful to detect the bonding sites of all ligand molecules interacted with the metal. The coordination of azomethine nitrogen shifted ν (^{7}C = ^{1}N) to lower wave numbers. The band shifted from 1640 cm^{-1} in uncomplexed thiosemicarbazon spectra to about 1590-1608 cm^{-1} in the spectra of complexes. The shifting of ν (NN) to higher wave numbers in the spectra of complexes confirms the coordination of azomethine nitrogen. The new band appeared at 440 - 470 cm^{-1} confirms the coordination of azomethine nitrogen [14]. The loss of $^{-2}$NH proton on coordination via thiolate sulphur decreases the ν (C = S) bands found at 794, 1360 cm^{-1} in L . The presence of new band at 310 - 330 cm^{-1} is assignable to ν (CoS) [14, 15]. New band at 525 - 535 is assignable to ν (CoO) [16]. The coordination of N atom (s) of heterocyclic base is confirmed by ν (CoN) band in 230-280 cm^{-1} range. The bands due to ν (H_2O) re also observed.The bands of coordinated heterocyclic bases observed in IR spectra of all complexes.

The coordinated water molecules were eliminated from their complexes at relatively higher temperature than lattice water molecules.The coordinated water molecules in complex and adducts were removed in one step. The two water molecules were removed at a temperature less than 120 °C The TGA data of complex and adducts indicated that the decomposition proceeded in several steps. There are three steps after the removal of three water molecules in complex and two molecues in adducts. First at a temperature iess than 142 °C, second less than 250 °C and third less than 360 °C. The decomposition was complete and CoO formed at a temperature > 750 °C.

The antibacterial activity was determined using the agar well diffusion method. The activity was determined by measuring the diameter of the inhibition zone (in mm). Biological activity was measured in two different molar concentrations (10^{-3}M, 10^{-4} M). The chelate Cu.L.bipy showed maximum activity against bacterial and fungal species than free ligand. The results of antibacterial and antifungal studies are given in Table 4. Out of these six compounds tested, Co.L.py.$(H_2O)_2$ was found more active against four cultures. The thiosemicarbazone was found less active than its complex and adducts. Thus increase in coordination number in complexes increases microbial activity. Thus it is evaluated that the coordination of metal ion to ligand is responsible for high biological activity.It has been observed that the % activity index decreases on dilution ie it is more in concentrated solution.

Expected structures





(B = pyridine, α-picoline, β–picoline,γ-picoline)

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