

## Studies on synthesis, characterisation, molecular modeling and antimicrobial activity of some metal chelates of pyrazolone based ligands

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Some novel complexes of the ligands N-(3-methyl 1-thiocarbamyl-5-oxo-2-pyrazolin-4-ylene)-N'-(4'-antipyrine) hydrazine (HATP) and N-(3-methyl-1-thiocarbamyl-5-oxo-2-pyrazolin-4-ylene)-N'-(4'-benzothiazole) hydrazine (HBTP) with Mn(III), Cr(III), Fe(III), Co(III), Zn(II) and Cd(II) have been prepared and characterised by elemental analysis, molar conductance values, magnetic susceptibility measurements and various spectral studies. The chemical studies and spectral data indicate that HATP and HBTP are in the hydrazone form. All complexes are six coordinates with  $O_h$  or  $D_{4h}$  symmetry. Fe(III), Mn(III) and Cr(III) complexes are of high spin while Co(III), Zn(II) and Cd(II) chelates are diamagnetic. Molecular mechanics calculations also confirm the complexation behaviour of the ligands. HATP is neutral tetradentate towards Zn(II) and Cd(II) whereas tridentate with Co(III) and Mn(III) having compositions  $[M(HATP)X_2]$  and  $[M(HATP)X_3]$  for  $M=Zn(II)$  and Cd(II) and  $M=Mn(III)$  and Co(III) and  $X=Cl, OAc$  and  $NO_3$ . HBTP is neutral tridentate towards all the metals with composition  $[M(HBTP)(H_2O)X_2]$  and  $[M_1(HBTP)X_3]$  where  $M=Cd(II)$  and  $Zn(II)$ ,  $M_1=Fe(III)$  and  $Cr(III)$  and  $X=Cl, OAc$  and  $NO_3$ . Ligands and complexes have been screened for their antibacterial activity against gram-positive and gram-negative bacteria.

Pyrazolone derivatives have been extensively investigated on their wide range of promising pharmacological activities<sup>1,2</sup>. Hydrazones of pyrazolone derivatives are of current interest due to their high coordinating ability and applications in synthetic and analytical chemistry.<sup>3,4</sup> Further, azo-hydrazone tautomerism of aryl azo derivatives of  $\beta$ -dicarbonyls, naphthols and 2-pyrazolin-5-ones has evoked considerable interest and controversy in the past.<sup>5-7</sup> In addition to the medicinal applications of hydrazones, they have been investigated as donors because of their varied ligational behaviour towards different metal ions and manifestations of novel structural features in the metal complexes<sup>8</sup>. In view of this, the synthesis, characterisation and antibacterial assay of a few complexes of HATP and HBTP with Mn(III), Cr(III), Co(III), Zn(II) and Cd(II) metal ions have been carried out.

### Materials and Methods

Thiosemicarbazide (Loba), 4-amino antipyrine (Fluka) and 2-aminobenzo thiazole (Loba) are used as supplied and all other chemicals and metal salts used were of AR grade.

### Synthesis of HATP

3-methyl 1-thiocarbamyl 2-pyrazolin-5-one (MTP) has been prepared by reported method<sup>9</sup>. 4-Amino antipyrine (10 g, 0.05 mol) was diazotised and the diazonium salt solution was added slowly with stirring to an ice-cold alkaline solution of MTP (7.85 g, 0.05 mol). This mixture was kept in an ice bath for 30 min with occasional stirring. Bright red crystals of HATP separated were suction filtered, washed with pet. ether and then recrystallised from ethanol. The purity was checked by TLC and elemental analysis. (M.P.-210°C, yield 80%).

### Synthesis of HBTP

The diazotised 2-amino benzothiazol (16 g, 0.05 mol) was coupled with MTP (7.85 g, 0.05 mol)<sup>10</sup>. Yellowish brown crystals of HBTP separated were suction filtered, washed with pet. ether and then recrystallised from ethanol. The purity was checked by TLC and elemental analysis. (M.P.-195°C, yield 70%).

### Synthesis of complexes

Complexes were prepared by a general method by refluxing aqueous ethanolic solutions of metal salts (0.05 mol) and ligands (0.06 mol) in ethanol for

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one h. On cooling, the solid complexes separated were filtered and washed with ethanol to remove excess ligand and then with benzene. It was then dried over  $P_4O_{10}$ .

Metal contents were estimated by usual procedure after digesting the complexes with con.  $H_2SO_4$  and the results were further confirmed by Atomic Absorption Spectroscopy. Chloride and bromide in the complexes were estimated by Volhards method and perchlorate was determined by Kurtz method<sup>11,12</sup>. Nitrogen content was determined indirectly by elemental analysis using Elemental analyser Heraeus Carlo-Erba-1108, at RSIC, CDRI, Lucknow. Magnetic moments of all the complexes were determined in Gouy Balance calibrated using  $[HgCo(NCS)_4]$  at room temperature. Molar conductivities of the complexes were measured using Elico-Digital Conductivity meter. Analytical data, yield, decomposition temperature and magnetic moment and molar conductivity values of the complexes are represented in Table I. UV-Vis absorption spectra of

the ligands and complexes were recorded in methanol on Shimadzu- 25 UV-Vis Spectrometer in the range 800-200 nm. IR spectra of the ligands and complexes were recorded on Perkin-Elmer IR Spectrometer using KBr pellet method. NMR spectra were recorded on JEOLGSX 400 NMR spectrometer at RSIC, IIT, Chennai. Mass spectra of the ligands were recorded using HEWLETT PACKARD HP 5995 mass spectrophotometer. Thermogravimetric analysis of a few complexes were carried out on Mettler TA 4000 Thermal Analyser in air at the rate of  $10^\circ C/min$ .

#### Molecular modelling studies

In our experiment, molecular mechanics calculations were done with HyperChem Release 5.1 Professional version an interactive graphics program that allows rapid structure building, geometry optimisation and molecular display<sup>13</sup>. Molecular modelling software HyperChem has the ability to handle transition metals. Energy minimisation was repeated several times to find global minimum.

Table I—Characterisation data of the complexes

Complex	Colour	Yield %	Decom Temp	Molar conduct $ohm^{-1}cm^2 mol^{-1}$	Metal found (Calc) %	$\mu_{eff}$ (BM)
$[Zn(HATP)Cl_2]$	Yellow	71	320	1.40	12.88(12.80)	—
$[Mn(HATP)Cl_3]$	Brown	69	315	1.80	10.29(10.30)	4.91
$[Co(HATP)Cl_3]$	Black	65	350	1.40	10.25(10.30)	—
$[Cd(HATP)Cl_2]$	Brown	60	325	2.20	20.27(20.25)	—
$[Zn(HATP)(NO_3)_2]$	Yellow	65	385	1.90	11.67(11.65)	—
$[Mn(HATP)(NO_3)_3]$	Brown	68	410	1.48	8.90(8.95)	4.88
$[Co(HATP)(NO_3)_3]$	Black	70	370	2.37	9.71(9.78)	—
$[Cd(HATP)(NO_3)_2]$	Brown	65	340	1.70	18.5(18.49)	—
$[Zn(HATP)(OAc)_2]$	Yellow	70	365	2.30	11.71(11.70)	—
$[Mn(HATP)(OAc)_3]$	Brown	72	330	1.92	8.93(8.97)	4.90
$[Co(HATP)(OAc)_3]$	Black	60	345	1.28	8.59(8.50)	—
$[Cd(HATP)(OAc)_2]$	Brown	65	350	1.48	18.68(18.70)	—
$[Zn(HBTP)(H_2O)Cl_2]$	Yellow	75	370	1.78	14.02(14.0)	—
$[Fe(HBTP)Cl_3]$	Black	75	330	1.40	11.70(11.50)	5.9
$[Cr(HBTP)Cl_3]$	Darkgreen	60	320	2.54	10.9(10.85)	3.89
$[Cd(HBTP)(H_2O)Cl_2]$	Brown	64	310	1.95	19.40(19.38)	—
$[Zn(HBTP)(H_2O)(OAc)_2]$	Yellow	65	365	2.12	13.36(13.35)	—
$[Fe(HBTP)(OAc)_3]$	Black	72	420	3.65	10.18(10.20)	5.89
$[Cr(HBTP)(OAc)_3]$	Darkgreen	61	415	1.48	9.56(9.55)	3.82
$[Cd(HBTP)(H_2O)(OAc)_2]$	Brown	60	390	2.37	22.34(22.40)	—
$[Zn(HBTP)(H_2O)(NO_3)_2]$	Yellow	65	385	2.30	12.88(12.85)	—
$[Fe(HBTP)(NO_3)_3]$	Black	72	400	1.98	9.89(9.92)	5.91
$[Cr(HBTP)(NO_3)_3]$	Darkgreen	62	390	1.85	8.68(8.66)	3.88
$[Cd(HBTP)(H_2O)(NO_3)_2]$	Brown	60	385	2.25	21.90(21.89)	—

### Antimicrobial Screening

The bacterial activity of HATP and HBTP and a few of their complexes investigated were tested against Gram-positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae* by disc diffusion method using agar nutrient as medium and gentamycin as control<sup>14</sup>. DMSO was used as solvent for making test solutions of all the compounds studied. The paper disc (6 mm) containing the compound (100 µg/disc) was placed on the surface of the nutrient agar plate previously spread with 0.1 ml of sterilised culture of microorganism. After incubating this at 37°C for 36 h, the diameter of inhibition zone around the paper disc was measured. These values are reported in Table 2.

### Results and Discussion

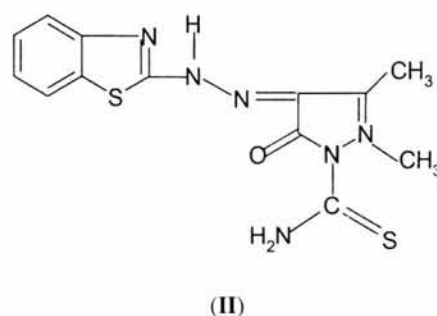
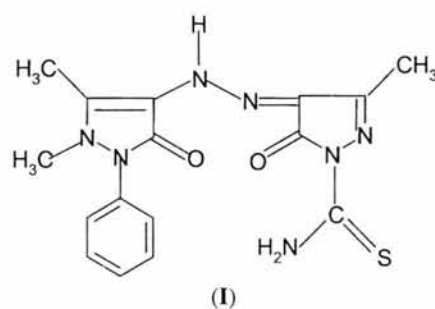
The complexes synthesized were coloured, non-hygroscopic, stable solids, all of them decomposing above 280°C and soluble in DMSO. The molar conductivity values obtained in DMSO show that they are non-electrolytes.

<sup>1</sup>H NMR spectra of ligands are recorded in DMSO -*d*<sub>6</sub> and the peaks observed at 7.3-7.7 δ and 7-7.9 δ are assigned to aromatic protons of the ligands. HATP showed low field signal for the hydrazone proton at 13.3 δ<sup>15</sup>. This low field shift may be due to intramolecular hydrogen bonding. The hydrazone proton of HBTP appears at 8.7δ. The signals at 2.1δ (6H), 2.5 δ (3H) and 2.9 δ (2H) may be due to two identical C-CH<sub>3</sub>, N-CH<sub>3</sub> and NH<sub>2</sub> protons respectively.

IR spectra of the free ligands show a band around 1660 cm<sup>-1</sup> which may be assigned to ν C=O of thiocarbamylpyrazolone part<sup>16</sup>. The band at 1640 cm<sup>-1</sup> in the spectra of HATP is due to ν C=O of antipyrine<sup>17</sup>. The bands at 1620 cm<sup>-1</sup> and 1590 cm<sup>-1</sup> can be C=N modes of HATP and HBTP respectively<sup>18</sup>. A weak broad band around 3100 cm<sup>-1</sup> can be assigned to the stretching frequency of intramolecularly hydrogen bonded NH in HATP and the band at 3170 cm<sup>-1</sup> in the spectrum of HBTP can be assigned due to the N-H of the hydrazone part<sup>19</sup>. The stretching frequencies of NH<sub>2</sub> and C=N appeared around 3360 and 1110 cm<sup>-1</sup> respectively<sup>20</sup>. The -N=C-S ring stretching frequency in HBTP is observed at 2010 cm<sup>-1</sup> (ref. 21). NMR and IR spectra of ligands reveal that coupling of 4-diazoantipyrine

Table 2—Antibacterial activities of the ligands and complexes (Zone formation in mm)

Compound	Pseudo- monas	S. aureus	E. coli	Klebsiella
Control	20	22	15	18
HATP	18	10	10	—
[Zn(HATP)Cl <sub>2</sub> ]	20	12	13	8
[Mn(HATP)Cl <sub>3</sub> ]	20	11	12	10
[Cd(HATP)Cl <sub>2</sub> ]	21	15	14	12
[Co(HATP)(NO <sub>3</sub> ) <sub>3</sub> ]	20	12	11	8
HBTP	—	18	—	16
[Cr(HBTP)Cl <sub>3</sub> ]	8	20	8	18
[Cd(HBTP)(H <sub>2</sub> O)(NO <sub>3</sub> ) <sub>2</sub> ]	10	22	10	20



and 2-diazobenzothiazole with 3-methyl 1-thiocarbamyl-2-pyrazolin-5-one at its 4<sup>th</sup> position has resulted in the production of a hydrazone, via rearrangement<sup>22,23</sup> (I & II).

In the IR spectra of HATP complexes of Co(III) and Mn(III), the stretching frequencies of C=O and C=N bonds are found lowered by 40-60 cm<sup>-1</sup> showing that both carbonyl oxygen atoms and azomethine nitrogen atom are coordinated to the metal ions. Therefore, in these complexes, HATP acts as neutral tridentate ligand coordinating with its two carbonyl oxygen atoms and azomethine nitrogen atom. In addition to the above changes, Zn(II) and Cd(II) complexes of HATP show shift in the ν N-H mode of NH<sub>2</sub> group to 3300 from 3360 cm<sup>-1</sup>, revealing the

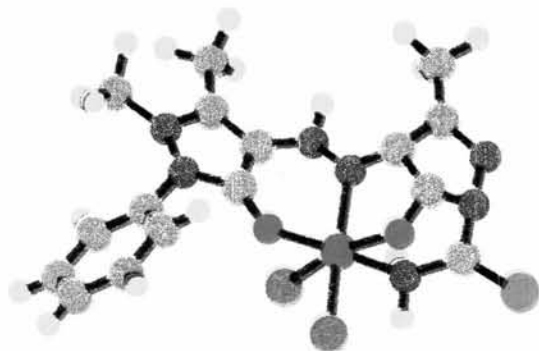


Fig 1(a)—Energy minimised configuration of  $[\text{Zn}(\text{HATP})\text{Cl}_2]$ . [Colour code: Yellow, H; Red, O; Dark blue, N; Light Blue, C; Magenta, Zn; Green, Cl; Orange, S]



Fig 1(b)—Energy minimised configuration of  $[\text{Cr}(\text{HBTP})\text{Cl}_3]$ . [Colour code as in Fig. 1a; Dark green, Cr; Light green, Cl].

coordination of nitrogen atom of  $\text{NH}_2$  group. Therefore, the ligand HATP acts as tetradentate of  $\text{N}_2\text{O}_2$  type in  $\text{Zn}(\text{II})$  and  $\text{Cd}(\text{II})$  complexes.

The negative shift in the frequencies of  $\nu\text{C}=\text{O}$  and  $\nu\text{C}=\text{N}$  and  $\nu\text{N}-\text{H}$  of  $\text{NH}_2$  found in the spectra of all the complexes of HBTP reveals the coordination through carbonyl oxygen, azomethine nitrogen and amino nitrogen atoms so that HBTP acts as ONN donor. The bands around  $3300\text{--}3500\text{ cm}^{-1}$  and  $800\text{--}830\text{ cm}^{-1}$ , found only in the spectra of  $\text{Zn}(\text{II})$  and  $\text{Cd}(\text{II})$  complexes of HBTP indicate the presence of coordinated water molecule, which was confirmed by TG analysis and Karl-Fisher method<sup>11,24</sup>. The presence of additional non-ligand bands in the spectra of all the complexes around  $530\text{--}570\text{ cm}^{-1}$  and  $450\text{--}420\text{ cm}^{-1}$  are assignable to M-N and M-O stretching frequencies<sup>25</sup>.

Thermal studies of metal complexes were carried out under static air condition. The thermogram of HBTP complexes of  $\text{Zn}(\text{II})$  and  $\text{Cd}(\text{II})$  complexes indicate two clear cut stages, first corresponding to the dehydration of the coordinated water molecule and second to the decomposition process<sup>24</sup>.  $\text{Mn}(\text{III})$ ,  $\text{Co}(\text{III})$  and  $\text{Cr}(\text{III})$  complexes show only a single stage decomposition and that is not of dehydration.

The room temperature magnetic moment values found for these complexes are in agreement with high spin  $O_h$  or  $D_{4h}$  symmetry for  $\text{Mn}(\text{III})$ ,  $\text{Cr}(\text{III})$  and  $\text{Fe}(\text{III})$  complexes.  $\text{Co}(\text{III})$  complexes are diamagnetic.

The electronic spectra of  $\text{Mn}(\text{III})$  complexes show bands around  $14880$ ,  $16830$  and  $18350\text{ cm}^{-1}$  assignable to  ${}^5B_{1g} \rightarrow {}^5A_{1g}$ ,  ${}^5B_{1g} \rightarrow {}^5B_{2g}$  and  ${}^5B_{1g} \rightarrow {}^5E_g$  transitions<sup>24</sup>. In  $\text{Co}(\text{III})$  complexes two bands are observed at  $18215\text{ cm}^{-1}$  and  $21825\text{ cm}^{-1}$  corresponding to  ${}^1A_{1g} \rightarrow {}^1T_{1g}$  and  ${}^1A_{1g} \rightarrow {}^1T_{2g}$  transitions<sup>25</sup>.  $\text{Cr}(\text{III})$

complexes exhibit bands at  $18000\text{ cm}^{-1}$  and  $20000\text{ cm}^{-1}$  which may be attributed to the transitions arising from  ${}^4A_{2g} \rightarrow {}^4T_{2g}$  and  ${}^4A_{2g} \rightarrow {}^4T_{1g}$  (F). The  ${}^4A_{2g} \rightarrow {}^4T_{2g}$  (P) is most probably obscured by charge transfer band around  $26000\text{ cm}^{-1}$ . The  $\text{Fe}(\text{III})$  complexes show a shoulder at  $17150\text{ cm}^{-1}$  and a band at  $12658\text{ cm}^{-1}$ . They are considered as due to  ${}^6A_{1g} \rightarrow {}^4T_{2g}$  and  ${}^6A_{1g} \rightarrow {}^4T_{1g}$  transitions respectively<sup>24</sup>. These transitions favour an  $O_h$  symmetry for the  $\text{Fe}(\text{III})$  complexes.

From molecular mechanics calculations, it was found that the minimised energy for all the complexes of HATP and HBTP ( $23\text{--}30$  and  $28\text{--}35\text{ kcal}$ ) are lower than those of the pure ligands HATP and HBTP ( $41.8642$  and  $43.678\text{ kcal}$ ). Thus high heats of complexation observed for these complexes explain their stability. The energy minimized configurations of  $[\text{Zn}(\text{HATP})\text{Cl}_2]$  and  $[\text{Cr}(\text{HBTP})\text{Cl}_3]$  complexes are given in Figs 1a and 1b.

The comparison of diameters of the inhibition zones of the compounds investigated and listed in Table 2 shows that  $\text{Cd}(\text{II})$  complexes exhibit highest antibacterial activity against Gram-positive and Gram-negative bacteria studied, as they have largest diameters of inhibition zones, and  $\text{Cd}(\text{II})$  complexes are found more active against *Pseudomonas* and *Klebsiella* than even the control gentamycin at the same concentration and identical conditions. The complexes are more antibacterial than the respective ligands against all the bacteria studied.

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