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Studies on Synthesis, Characterization and Antimicrobial Activity of Some Oxocation Chelates of Pyrazolone Based Ligands

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Some novel complexes of the ligands, 1-thiocarbamyl-3-methyl-4-(4′-amino antipyrine hydrazono)-2-pyrazolin-5-one (HAATP) and 1-thiocarbamyl-3-methyl-4-(2′-amino phenol hydrazono)-2-pyrazolin-5-one (H_2OATP) with VO(II), UO_2(II) and MoO_2(II) have been prepared and characterized by elemental analysis, molar conductance and magnetic susceptibility measurements and various spectral studies. The ligands and their vanadyl complexes were screened for their antibacterial and antifungal activities.

Key Words: Pyrazolin-5-ones, Oxocation complexes, Antimicrobial activity.

INTRODUCTION

The chemistry and wide range of pharmaceutical properties of 2-pyrazolin-5-one derivatives have been extensively investigated[1]. Hydrazones of pyrazolone derivatives are of particular interest due to their high coordinating ability and application in synthetic and analytical chemistry[2, 3]. 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[4]. In view of this the synthesis, characterization and antimicrobial assay of the complexes of HAATP and H_2OATP with VO(II), UO_2(II) and MoO_2(II) have been investigated and reported.

EXPERIMENTAL

All chemicals used in the synthesis of the compounds were of AR grade while solvents were distilled prior to their use.

Synthesis of HAATP and H_2OATP: 3-Methyl-1-thiocarbamyl-2-pyrazolin-5-one (MTP) was prepared by the reported method [5]. 4-Amino antipyrine (0.05 mol) was diazotized and coupled with MTP (0.05 mol) to get HAATP which was recrystallised as bright red crystals from ethanol. Its purity was tested by TLC (m.p. 210°C, yield 80%).

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Ortho-aminophenol (0.05 mol) was diazotized and coupled with MTP (0.05 mol) to get H_2OATP which was recrystallized as brown crystals from ethanol. Its purity was checked by TLC (m.p. 215°C., yield 75%).

Synthesis of complexes: The complexes were prepared by general method. An aqueous ethanolic solution of the corresponding metal salt (0.05 mol) was refluxed with ligand (0.05 mol) for 2 h. The solid complex separated was filtered, washed with ethanol and finally with benzene and dried over P_4O_{10}.

Vanadium was estimated as V_2O_5 and uranium as U_3O_8 by pyrolysis. Molybdenum was estimated gravimetrically as oxinate. Chloride in the complexes was estimated by Volhard's method. Nitrogen content was determined indirectly by elemental analysis. Magnetic moments of the complexes were determined in Gouy balance using $[HgCo(NCS)_4]$ at room temperature. Molar conductivity values of the complexes were measured using Elico digital conductivity meter. Analytical data of the complexes are presented in Table-1. UV-Vis absorption spectra of the compounds were recorded in methanol on Schimadzu-25 UV-Vis spectrophotometer in the range 800–200 nm. IR spectra of the compounds were recorded on Perkin Elmer IR spectrometer using KBr pellet method. NMR spectra were recorded on Jeol GSX 400 NMR spectrometer at RSIC, IIT, Chennai. Mass spectra of the ligands were recorded using Hewlett-Packard HP 5995 mass spectrometer. The room temperature X-band ESR spectra of the vanadyl complexes were recorded on a Bruker ESP spectrometer using powder samples at microwave frequency of 9.4–9.465 GHz at a field set of 3200G using DPPH as the reference. TG analyses of the vanadyl complexes were carried out on Mettler TA 4000 thermal analyser in air at the rate of 10°C/min.

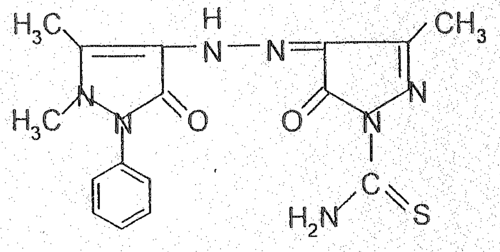
Antimicrobial Screening: The ligands and their vanadyl complexes were screened for their antibacterial activity against *S. aureus* (SA), *E. coli* (EC), *B. licheniformis* (BL), *B. brevis* (BB), *B. Subtilis* (BS) and *K. aeruginosa* (KA) by disc diffusion method[6]. Antifungal activity was tested by incorporating the test solution (1 mg/mL) in Sabouraud dextrose agar media against human pathogens: *Pencillium* species (PS) and *Candida albicans* (CA), plant pathogens *Rhizopus* species (RS) *Phytophthora infestans* (PI) and *Aspergillus niger* (AN) and an industrially important strain *Saccharomyces* species (SS). The antimicrobial studies were done at Department of Biotechnology, Kariavattom, Trivandrum.

RESULTS AND DISCUSSION

Molar conductance values in nitrobenzeue (1×10^{-3} M) show the non-electrolytic nature of all the complexes except for the Mo complex of HAATP which is 1 : 1 electrolyte (Table-1).

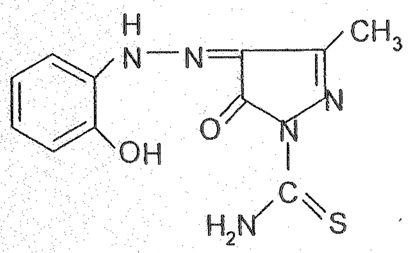
The spectral characterization of the ligand HAATP was in accordance with that reported earlier[4]. ^1H NMR spectra of the ligands in $CDCl_3$ exhibited peaks at 7.3–7.7 δ which are assigned to the aromatic protons. Both the ligands exhibited a low field signal for the hydrogen proton around 14.1 δ.[4] This low field shift may be due to intramodular hydrogen bonding. The signals at 2.3 δ (6H), 2.8 δ (3H) and 3.1 δ (2H) are assigned to the $C—CH_3$, $N—CH_3$ and NH_2 protons respectively.

IR spectra of the ligands showed a band around 1660 cm^{-1} assigned to ν(C═O) of thiocarbamoyl pyrazolone[7]. The band at 1640 cm^{-1} of HAATP is due to the vibration of antipyrine ring[8]. A weak broad band around 3100 cm^{-1} may be assigned to the stretching frequency of intramolecularly hydrogen bonded NH in both the ligands. The stretching frequencies of NH_2 and (C═N) appeared around 3360 and 1620 cm^{-1} respectively. The ν(C═S) band appeared at 1100 cm^{-1}. H_2OATP exhibited a broad band at 3250 cm^{-1} due to ν(OH). The pressure of ν(C═N) in the spectra of the ligands clearly indicates that the coupling has taken place at the fourth position of the thiocarbamyl pyrazolone and has resulted in the production of a hydrazone *via* rearrangement[9] (Figs. 1 and 2).



HAATP

Fig. 1



H_2OATP

Fig. 2

In the IR spectra of the complexes of HAATP and H_2OATP, the stretching frequencies of (C═O) and (C═N) bonds are found lowered by 40–60 cm^{-1} showing the involvement of carbonyl oxygen and azomethine nitrogen in coordination to the metal ion. In the complexes of H_2OATP the absence of the band due to ν(OH) suggests the coordination of the deprotonated hydroxyl oxygen. These are further confirmed by the presence of additional bonds in the spectra of the complexes at around 550 and 520 cm^{-1} assignable to ν(M—N) and ν(M—O) stretching frequencies[10]. A strong broad band observed at 3460 in the uranyl complex of H_2OATP may be assigned to the stretching mode of coordinated water. This is further confirmed by elemental and TG analysis. In all the complexes the bands due to NH_2 and (C═S) remain unshifted suggesting the non-participation of these groups. Hence HAATP acts as a neutral tridentate ligand coordinating through its two carbonyl oxygens and azomethine nitrogen atom. H_2OATP acts as monobasic tridentate ligand coordinating through its deprotonated phenolic oxygen, carbonyl oxygen and azomethine nitrogen.

In the vanadyl complexes, strong bands characteristic of vanadyl oxygen are observed at 980 cm^{-1} and in uranyl complexes strong bands are observed around 880 and 920 cm^{-1} which are in agreement with the literature reports[11]. In the molybdenyl complexes, the bands at 910 and 930 cm^{-1} confirm the *cis* configuration of the molybdenyl oxygens[12].

The vanadyl chelate has a magnetic moment of 1.69 BM which is expected for a d^1 system[13]. This suggests that the complex is monomeric and involves no metal-metal interaction[14]. The uranyl and molybdenyl complexes are diamagnetic as expected.

Thermal studies of the vanadyl complex of HAATP were carried out under static air condition. This complex shows a single stage decomposition pattern being devoid of any water of coordination. Final mass loss corresponds to that of V_2O_5.

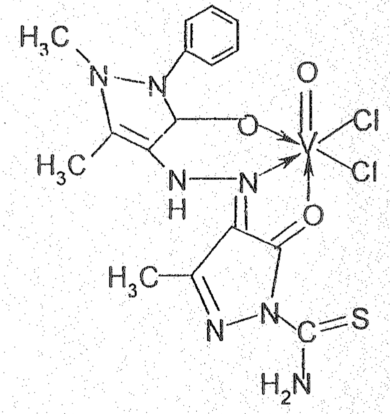
The ESR spectra of the vanadyl complexes of HAATP and H_2OATP exhibit an eight line pattern at room temperature (Table-1). The spectra obtained are typical of the spectra shown by magnetically dilute oxovanadium(IV) complexes[15]. For all the complexes, the trend $g_{\parallel} < g_{\perp} < g_e$ [2.0036] was observed and this indicates that the unpaired electron is in b_{2g} (d_{xy}) orbital localized on the metal, thus excluding any possibility of its direct interaction with the incoming ligand[16].

TABLE-1
CHARACTERIZATION DATA OF THE COMPLEXES

Complex	Colour	Yield (%)	Metal (%) Found (Calcd.)	Electrolytic nature	μ_{eff} (BM)	ESR parameters (gauss)		
						$g_{\parallel}$	$g_{\perp}$	g_{av}
$[VO(HAATP)Cl_2]$	Green	70	10.2 (10.0)	Non-electrolyte	1.69	1.96	2.00	1.98
$[VO(HOATP)Cl]$	Brown	65	13.2 (13.4)	Non-electrolyte	1.69	1.97	2.03	2.01
$[UO_2(HAATP)Cl_2]$	Brown	60	33.2 (33.4)	Non-electrolyte	Dia-magnetic	–	–	–
$[UO_2(HOATP)H_2O.Cl]$	Brown	60	39.4 (39.6)	Non-electrolyte	Dia-magnetic	–	–	–
$[MoO_2(HAATP)Cl]Cl$	Brown	40	16.6 (16.8)	1 : 1 electrolyte	Dia-magnetic	–	–	–
$[MoO_2(HOATP)Cl]$	Brown	40	21.5 (21.8)	1 : 1 electrolyte	Dia-magnetic	–	–	–

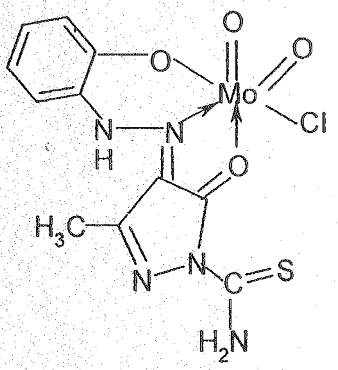
The electronic spectra of all the complexes show an intense broad absorption band in the region 26000–24000 cm^{-1} which may be attributed to the ligand → metal charge transfer transitions. In addition to this band, the vanadyl complexes exhibit bands at 13070, 16260 and 22220 cm^{-1} assignable to $^2B_2 \rightarrow {}^2E_1$, $^2B_2 \rightarrow {}^2B_1$ and $^2B_2 \rightarrow {}^2A_1$ respectively. The uranyl complexes show a band at 21050 cm^{-1} assignable to the charge transfer transition, coupled with $^1\Sigma_g^+ \rightarrow {}^3\pi_u$ of the dioxouranium ion[17]. The molybdenyl complexes show no absorption in the visible region as expected for a $4d^0$ system. From the above data tentative structures proposed for the complexes $[VO(HAATP)Cl_2]$ and $[MoO_2(HOATP)Cl]$ are given in Figs. 3 and 4.

Antimicrobial Activity: The ligands and their vanadyl complexes were screened for antibacterial activity and the inhibition zone diameters in mm are



[VO(HAATP)Cl$_2$]

Fig. 3



[MoO$_2$(HOATP)Cl]

Fig. 4

presented in Table-2. It was observed that the activity of the ligands was enhanced on complexation. Significant activity was observed against *B. licheniformis* and this was comparable with that of the standard piperacillin. all the compounds exhibited more activity than the standards tetracyclin and piperacillin towards *E. coli*.

TABLE-2
ANTIMICROBIAL ACTIVITY AT 30 μg/DISC ZONE INHIBITION DIAMETER IN mm

Compounds	Bacteria					
	Sa	*Ec*	*Bl*	*Bb*	*Bs*	*Ka*
HAATP	9	8	12	8	7	7
[VO(HAATP)Cl$_2$]	14	12	16	13	11	12
H_2OATP	7	7	8	8	7	7
[VO(HOATP)Cl]	10	9	10	10	8	10
Cephalexin	33	15	18	15	18	15
Tetracycline	24	7	20	24	21	20
Pipperacillin	16	7	16	25	25	16

The comparison of the fungitoxicity of the ligands and their vanadyl complexes (Table-3) shows that the compounds are active against *Rs*, *Ss* and *Ca*. *A. niger* is found to be very resistant to all the compounds except the standard miconozole. while fungus *Pi* was resistant to the ligands but the complexes exhibited moderate activity against it.

TABLE-3
ANTIFUNGAL ACTIVITY AT 1 mg/mL

Compounds	Fungi					
	Rs	*Ss*	*An*	*Pe*	*Ca*	*Pi*
HAATP	–	–	+	–	–	±
[VO(HAATP)Cl_2]	–	–	+	–	–	±
H_2OATP	–	–	+	–	–	±
[VO(HOATP)Cl]	–	–	+	–	–	±
Miconozole	–	–	–	–	–	–

+ not active; – active; ± moderately active

It may be concluded that these compounds pose to be good bactericidal and fungicidal agents.

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