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Synthesis, Characterization and Biocidal Activities of Mixed-Ligand Complexes of Dioxomolybdenum(VI) Derived from Sulpha Drugs and 4-Benzoyl-3-methyl-l-phenyl-2-pyrazoline-5-one

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Dioxomolybdenum(VI) complexes with Schiff bases derived from 4-benzoyl-3-methyl-l-phenyl-2-pyrazoline-5-one and sulpha drugs sulphamoxole and sulphaguanol. The ligands and their MoO_2^{2+} complexes have been characterized on the basis of elemental analysis, electronic. I.R., ^{1}H NMR spectral studies. On the basis of electronic spectral studies, octahedral geometry of all the complexes has been proposed. The *in vitro* antimicrobial activity of the investigated compounds was tested against the bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* and fungi *Candida albicans* and *Rhizopus stolonifer*. The data indicate that all the metal complexes have higher antimicrobial activity than the free ligands.

Key Words: Sulpha drugs, Sulphamoxole, Sulphaguanol, Molybdenum(VI).

INTRODUCTION

N-Phenyl-2,3-dimethyl-4-pyrazolin-5-one and its derivatives, are an active moiety in the class of non-steroidal, antiinflammatory agents used in the treatment of arthritis and other musculoskeletal and joint disorders.

The Schiff bases derived by the condensation of sulphonamides with pyrazolone derivatives are not only good complexing agent[1] but bacteriocides[2] as well. The pronounced biological activity of metal complexes of Schiff base derived from sulpha drugs[3] has led to considerable interest in their coordination chemistry. Metal complexes of Schiff base derived from sulpha drugs and other pyrazoline derivatives are effective antifouling agaents[4] antibacterial and antiviral agents. Such metal complexes are also used as bactericides[5], fungicides[6], acaricides[7] and industrial and agriculture biocides[8]. The potential for biological and physiological activity of molybdenum complexes have stimulated the discovery of variety of molybdenum complex in various oxidation states[9].

Present paper show the to synthesise and characterise some dioxomolybdenum(VI) complexes with Schiff bases derived from 4-benzoyl-3-methyl-l-phenyl-2-pyrazoline-5-one and sulphamoxole and sulphaguanol.

EXPERIMENTAL

Synthesis of Schiff base: An ethanolic solution of 4-benzoyl-3-methyl-l-phenyl-2-pyrazoline-5-one (BMPHP) (0.01 mol, 2.78 g) was added to the separate solution of sulphamoxole and sulphaguanol (0.01 mol, each) in 25 mL ethanol, along with few drops of HCl (2.5 mL, 3.10 g, 0.01 mol). The whole content was refluxed on water bath with stirring for 4-5 h and then filtered to remove insoluble sulpha drug if any. The filtrate so obtained was concentrated on water both and left over night at room temperature when yellow crystals of Schiff base separated out from their respective solution. The crystal thus obtained were washed with ethanol and dried in vacuum. The characterization data of Schiff bases are given in Table-1.

Preparation of MoO_2 (acac)$_2$: $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (30.0 g) was dissolved in water (100 mL) and acetylacetone (acacH: 40 mL) was added. The pH of the solution was adjusted to 3.5 using 10 % HNO_3 and a solid began to precipitate. After 1.5 h yellow $MoO_2(acac)_2$ (28 g)) was isolated by filtration, washed with water ethanol and ether and dried in vacuum.

Synthesis of dioxomolybdenum complexes: The respective Schiff base [(4'-benzoylidene-3'-methyl-1'-phenyl-2'-

TABLE-1
MICROANALYSIS OF LIGAND AND METAL COMPLEXES

Schiff base/metal complexes	Elemental analysis (%): Calcd. (Found)					Molar conductivity ($ohm^{-1}cm^2$ mol^{-1})	μ_{eff} (BM)
	C	H	N	S	Mo		
$C_{28}H_{25}N_2O_4S$	63.65 (63.75)	4.68 (4.74)	13.21 (13.28)	5.98 (6.07)	–	–	–
$C_{28}H_{25}N_7O_4S$	61.93 (62.02)	4.88 (4.97)	13.80 (13.91)	6.28 (6.36)	–	–	–
$C_{56}H_{54}N_4O_{16}S_2Mo_2$	46.80 (46.86)	3.66 (3.76)	13.56 (13.66)	4.39 (4.46)	13.26 (13.38)	10.0	1.84
$C_{56}H_{54}N_{14}O_{16}S_2Mo_2$	46.76 (46.86)	8.66 (13.66)	13.52 (13.66)	4.36 (4.46)	13.28 (13.38)	13.2	1.77

pyrazoline-5'-one)sulphamoxole] and (4'-benzoylidene-3'-methyl-1'-phenyl-2'-pyrazoline-5'-one) sulphaguanol (0.1 mol) was dissolved by heating in 25 mL ethanol. To this solution an ethanolic solution (10 mL) of *bis*(acetyl acetonato) dioxomolybdenum(VI) (0.01 mol) was added. The resulting solution was refluxed for 8-10 h and then concentrated to half of its volume. The resulting precipitate was filtered and washed several times with ethanol. The product was dried in vacuum.

Antimicrobial activity: The newly synthesized ligands and their metal complexes were screened *in vitro* for their antibacterial activity against bacteria: *S. aureus*, *E. coli*, *K. pneumoniae* and also fungi *C. albicans* and *R. stolonifer* by well diffusion method[10] using agar nutrient. Ampicillin and norfloxacin are used as control for bacteria and fungi, respectively. The suspension of each microorganism was added to a sterile agar medium, then poured into sterile petri plates and left to solidification the well was dug in the agar media using sterile metallic borer in each plate the test solution (3×10^{-3} M) was prepared by dissolving the compounds in DMSO and the well was filled with test solution using micropipette. The plates were incubated for 24 h in the case of bacteria and 70 h for fungi at 35 ºC. The extarcts were subjected to further assay with a series on the time basis (24, 48 and 72 h). During this period the test solution was diffused and affected the growth of the inoculated microorganisms activity was determined by the diameter of the zone showing complete inhibition (mm). Growth of the inhibition was compared with the control the zone of inhibition is given as the average of three independent determinations.

RESULTS AND DISCUSSION

Microanalysis: The analytical data of the complexes are given in Table-1. All the metal complexes were slightly soluble in methanol and ethanol but are freely soluble in dimethyl formamide and dimethyl sulfoxide.

Infrared spectral studies: The MoO_2^{2+} moiety form a *cis*-dioxo geometry, characterised by two infrared active modes of ν_{as}(O=Mo=O) and ν_s(O=Mo=O) in C_{2v}-symmetry, in the 915-890 and 945-940 cm^{-1} regions[11].

The IR-spectrum of ligands N-(3'-methyl-1'-phenyl-5'-pyrazolinidene)sulfamoxole and N-(3'-methyl-1'-phenyl-5'-pyrazolinidene)sulfaguanol show ν(C=O) cyclic in the region (1650-620 cm^{-1}) suggesting their existence in the keto-form in the solid state.

The $MoO_2(acac)_2$ reacts with each of the Schiff base ligands in ethanol to form stable dioxomolybdenum(VI) ligands bridged binuclear complexes. That both the (acac) group displaced by these ligands was supported by the absence of characteristic peaks of ν(C=O) (1560 cm^{-1}) and ν(C=C) (1510 cm^{-1}) of coordinated acetylacetone, groups[12].

The free Schiff bases exhibit in the IR spectra a strong band at 1625-1600 cm^{-1} which is assigned to the ν(C=N) mode. This band shifts to lower energy side by 15-30 cm^{-1} in the complexes indicating coordination of nitrogen to the metal ion[13].

The ν(C=N) cyclic arising from pyrazolone and sulpha drug skeletons in the ligands appear as 1590-1580 and 1630-1620 cm^{-1}, do not show any change in the IR spectra of complexes. It seems ν(CN_2) cyclic merged with the azomethine group. The observations indicate non-participation of cyclic ν(C=N_2) in chelate formation[14]. The coordination of ring nitrogen (N1) is unlikely due to the steric demand of the bulky phenyl group attached with it. All the ligands show a very strong band of 1655-1625 cm^{-1} due to ν(C=O) in a cyclic environment of the pyrazolone skeleton. These bands remain unaffected in the spectra of the chelate showing non-involvement of carbonyl oxygen towards coordination to MoO_2^{2+} moiety[15,16].

The IR spectra of both the ligands show two strong bands as 1360-1320 and 1150*1100 cm^{-1} which are due to asymmetric and symmetric stretching vibration of SO_2 group. In the spectra of complexes both the bands get splitted into two bands. The bands observed around 1360-1320 cm^{-1} the spectra of respective ligands get splitted into two bands appearing of 1380-1350 and 1230-1250 cm^{-1} while the band at 1150-1100 cm^{-1} is split into two bands at 1160-1115 and 1090-1060 cm^{-1} in the spectra of complexes. Splitting of these bands shows that one of the sulphonyl oxygen is coordinated to the metal centre in the present complexes[17,18].

The slightly higher shifted bands 1380-1350 and 1160-1110 cm^{-1} correspond to the vibrations of uncoordinated (S=O) band and the lower bands 1330-1250 and 1095-1060 cm^{-1} correspond to the vibration of coordinated (S=O). Hence the present ligands are coordinated to the MoO_2^{2+} moiety through one of the oxygen atom of the sulphonyl group[19,20].

The IR spectra of all the complexes display two bands at 3580-3450 and 3460-3130 cm^{-1} which are attributed to stretching modes of coordinated hydroxyl group. The ν(NH) modes in the sulphonamide group of the uncoordinated Schiff bases which are observed at 3425-3390 and 3350-3300 cm^{-1} remain unperturbed and merged with ν(OH) modes in the spectra of their complexes, suggesting non-involvement of sulphonamide nitrogen in coordination[21-25].

The ν(C=N) cycle arising from pyrazolone skeleton in ligand appears at 1590-1585 cm^{-1}, do not change in the IR spectrum of complex. This observation indicates that non-participation of cyclic (C=N_2) of pyrazolone in chelate formation. The stretching wave numbers due to N-N in the coordinated compound was slightly affected from 1034 cm^{-1} which indicate the unsharing of this linkage in the coordination to central metal atom. The band appears at 1610 cm^{-1} show

TABLE-2
INFRARED ABSORPTION SPECTRAL DATA OF MoO_2(VI) COMPLEXES

Compound	ν(C=N) azomethine	ν_{as} (SO_2)	ν_s(SO_2)	ν(OH)	ν(O=Mo=O)	ν_{as}(O=Mo=O)	ν(C=O)
$C_{56}H_{54}N_4O_{16}S_2Mo_2$	1575 s	1380 s 1260 s	1160 s 1095 m	3425 m 3350 s	945 s	890 m	1630 s
$C_{56}H_{54}N_{14}O_{16}S_2Mo_2$	1570 sh	1375 1240 m	1165 s 1090 m	3400 s 3330 s	940 s	900 m	1640 s

the attachment of bulky phenyl group at N_1-nitrogen of pyrazalone moiety and no change of this signal observed in the spectra of complex indicates the non-participation of this -C_6H_5 group during coordination with metal ion (Table-2)[26].

Magnetic and electronic spectral studies: All the dioxomolybdenum complexes are diamagnetic in nature[27]. Electronic spectra of the complexes shows bands at 300-360 nm which may be due to intra ligand transitions $n\rightarrow\pi^*/\pi\rightarrow\pi^*$. The peak appearing in the region around 340 and 390 nm may be due to the ligand to metal charge transfer transition between the lowest empty molybdenum d-orbital and the highest occupied ligand molecular orbital[28] above observations show octahedral geometry of the complexes.

^{1}H NMR studies: The ^{1}H NMR spectra of all compounds were recorded in DMSO-d_6. All the compounds show a singlet due to presence of methyl proton of pyrazolone skeleton as well as another sharp singlet is appeared at the region δ = 2.62-2.69 ppm due to -C-CH_3 of pyrazolone ring. While a sharp singlet is appeared in the region δ = 3.28-3.34 ppm due to -N-CH_3 proton associate to nitrogen atom of pyrazol ring[29]. The signal due to five aromatic proton of antipyrine phenyl ring appear as multiplet between δ = 7.26-7.73 ppm in all the dioxo molybdenum(VI) complexes[30]. The singlet due to -OH group proton appear at δ = 12.50 ppm, on analyzing the spectrum of all dioxomolybdenum(VI) complexes of HL1, HL2, no appreciable change of signal is observed that indicate the non-participation of OH-group during coordination with metal.

Each complex show a singlet at δ = 6.0 ppm indicates the presence of -NH (sulphonamide) group proton. The multiplet is appeared at δ = 6.39-6.54 ppm due to four aromatic protons of attached with azomethine moiety. While multiplet at δ = 6.30-6.50 ppm indicate the presence of four aromatic proton to sulpha drugs (Table-3).

Antimicrobial activity: A comparative study of the ligand and its complexes (MIC values) indicates that the complexes exhibit slightly higher antimicrobial activity than the free ligand (Table-4). Such increased activity of the complexes can be explained on the basis of overtones concept[31] and Tweedys Chelation theory[32]. According to overtones concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only the lipid-soluble materials due to which liposolubility is an important factor, which controls the antimicrobial activity. On chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of π-electrons over the whole chelate ring and enhances the lipophilicity of the complexes. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of the proteins that restricts further growth of the organism. Furthermore, the mode of action of the compound may involve formation of a hydrogen bond through the azomethine group with the active centre of cell constituents, resulting in interference with normal cell process.

Conclusion

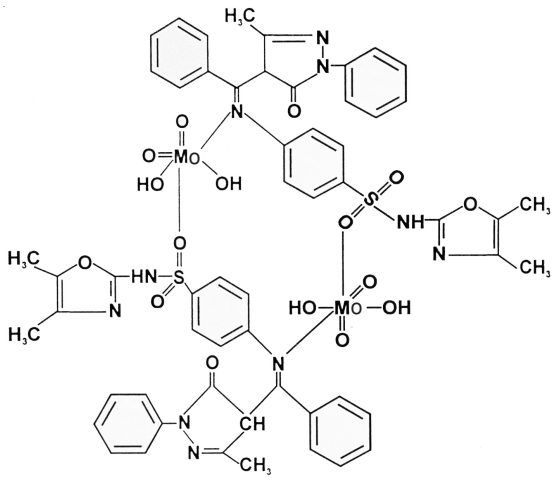
The following structure of metal complexes are proposed.

TABLE-3
^{1}H NMR DATA FOR METAL COMPLEXES OF BINUCLEAR MOLYBDENUM(VI) COMPLEXES

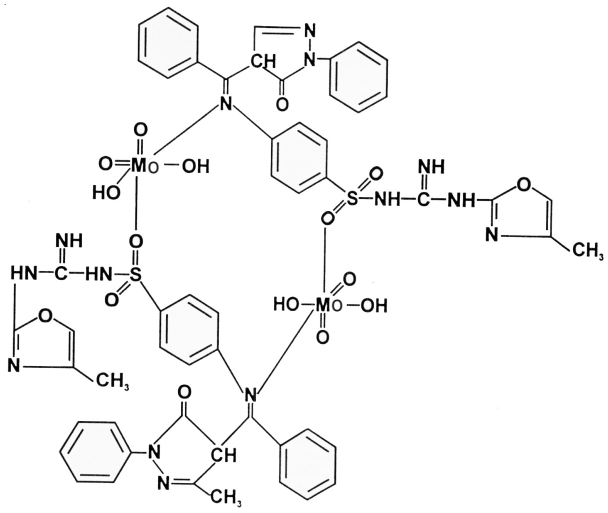
Metal complexes	Chemical Shift in δ ppm					
	HC=N	Aromatic protons	-OH	-N-CH_3 of pyrazolone	NH sulphonamide	δ (-CH_3) in pyrazol
$C_{56}H_{54}N_4O_{16}S_2Mo_2$	6.40	7.90-6.85	12.50	3.30	3.90	2.65
$C_{56}H_{54}N_{14}O_{16}S_2Mo_2$	6.54	7.90-6.80	12.51	3.34	3.92	2.69

TABLE-4
ANTIMICROBIAL STUDY OF THE INVESTIGATED COMPOUNDS (MIC × 10^{-2} M)

Compound	*E. coli*	*S. aureus*	*K. pneumoniae*	*C. albicans*	*R. stolonifer*
$C_{28}H_{25}N_2O_4S$	2.8	2.2	3.6	2.8	2.9
$C_{28}H_{25}N_7O_4S$	3.2	2.5	3.2	2.9	4.4
$C_{56}H_{54}N_4O_{16}S_2Mo_2$	4.1	3.2	4.9	4.1	5.1
$C_{56}H_{54}N_{14}O_{16}S_2Mo_2$	5.8	5.9	5.5	5.8	5.9
Ampicillin	2.1	4.0	4.9	3.0	5.2
Norfloxacin	2.8	3.6	4.5	3.5	6.1



Dioxymolybdenum(VI) complex of
(4-benzyl-3-methyl-1-phenyl-2-pyrazline-5-one) sulphamoxole



Dioxymolybdenum(VI) complex of
(4-benzyl-3-methyl-1-phenyl-2-pyrazline-5-one) sulphaguanol

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