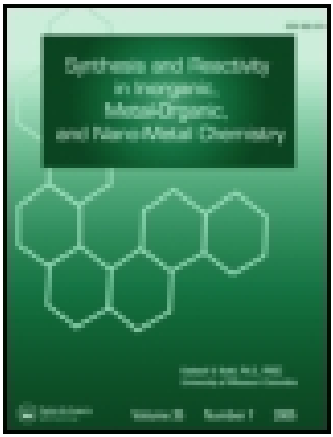

Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry

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Synthesis, Physico-Chemical, and Biological Studies on Oxovanadium(IV) Complexes with Thiosemicarbazones Derived from Thiophene-2-Aldehyde

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SYNTHESIS, PHYSICO-CHEMICAL AND BIOLOGICAL STUDIES ON OXOVANADIUM(IV) COMPLEXES WITH THIOSEMICARBAZONES DERIVED FROM THIOPHENE-2-ALDEHYDE

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ABSTRACT

Oxovanadium(IV) complexes of the types $[VOL_2]$ and $[VO(LH)_2]SO_4$ (where LH = thiosemicarbazones derives from thiophene-2-aldehyde and various substituted thiosemicarbazides) have been synthesized and characterised on the basis of elemental analyses, conductance, magnetic moments and spectral (electronic and IR) data. The antifungal, antiviral and antibacterial activities of the complexes were also investigated.

INTRODUCTION

Thiosemicarbazones and their metal complexes possess a wide range of biological applications: antitumor, antiviral, antibacterial, antimalarial, and antifungal activities have been studied[1-4]. The biological activity of the metal complexes is often found to be greater than that of the uncomplexed ligand. The nature of the group(s) attached to ^4N seems to

affect the biological properties. Since the discovery[5] that 2-formylpyridine thiosemicarbazone possesses antitumor activity, much attention has been directed towards the synthesis of heterocyclic thiosemicarbazones and their metal complexes as potential anticancer agents. Heterocyclic thiosemicarbazones exercise their beneficial therapeutic properties in mammalian cells by inhibiting ribonuclotide reductase, a key enzyme in the synthesis of DNA precursors[6]. Their ability to provide this inhibitory action is thought to be due to coordination of the metal via the N-N-S tridentate chelating system[7,8].

In this paper, we report studies on oxovanadium(IV) complexes with various thiosemicarbazones derived by the condensation of various N-substituted thiosemicarbazides and thiophene-2-aldehyde. The structures of the various ligands used for the present work are shown in Fig. 1.

RESULTS AND DISCUSSION

The reactions of oxovanadium(IV) sulphate with thiosemicarbazones have been studied in methanol in the presence of an alcoholic solution of potassium hydroxide or in the absence of a base. Two type of products viz., $[VOL_2]$ and $[VO(LH)_2]SO_4$ have been isolated. The reactions appear to proceed as shown below:

$$VOSO_4 + 2\ LH \xrightarrow[KOH]{Methanol} [VOL_2]$$

$$VOSO_4 + 2\ LH \xrightarrow{Methanol} [VO(LH)_2]SO_4$$

where

LH = TPTH, TMTH, TMOTH, TCTH or TBTH.

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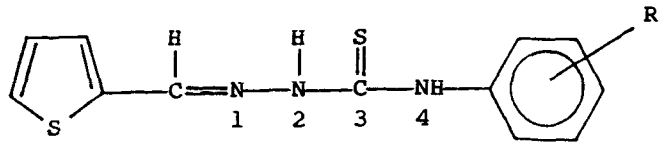
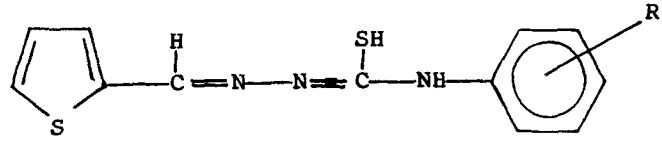


(Thione form)



(Thiol form)

R = H (TPTH), 4-CH_3(TMTH), 4-OCH_3(TMOTH), 4-Cl (TCTH), 4-Br (TBTH)

Fig. 1. Structure of the Ligands

The analytical data of the complexes are given in Table I. The complexes are brown coloured solids, which are soluble in DMF, DMSO, nitrobenzene and THF. Low values of molar conductances (8-10 Λ^{-1} cm^{-2} $mole^{-1}$) in dimethylformamide for $[VOL_2]$ type complexes show these complexes to be non-electrolytes. However, the complexes of the type $[VO(LH)_2]SO_4$ show high values of conductances (90-110 Λ^{-1} cm^{-2} $mole^{-1}$), indicating 1:2 electrolytic nature of the complexes.

Magnetic Moments and Electronic Spectra

The room temperature magnetic moments of the oxovanadium(IV) complexes lie in the range 1.70-1.75 B.M. These values are within the range reported[9,10] for oxovanadium(IV) complexes, where the orbital contribution is completely quenched as it is expected to be by the low symmetry fields. The electronic

Table I. Reactions of Oxovanadium(IV) Sulphate with Thiosemicarbazones Derived from Thiophene-2-aldehyde

Reactants[a] (Molar ratio)	Refluxing time (hrs)	Product Colour, Yield (%) Dec.temp. (°C)	Empirical formulas (Formula weights)	Found (Calcd) %					
				C	H	N	V	S	Cl/Br
$VOSO_4.5H_2O$ + TPTH (1:2 in presence of KOH)	20	$[VO(TPT)_2]$, brown, 68, 10	$C_{24}H_{20}N_6S_4OV$- (587.64)	49.0 (49.0)	3.3 (3.4)	14.0 (14.3)	8.5 (8.7)	21.7 (21.8)	-
$VOSO_4.5H_2O$ + TPTH (1:2)	15	$[VO(TPTH)_2]SO_4$ dark brown, 62, 155	$C_{24}H_{22}N_6S_5O_5V$ (691.42)	41.4 (41.6)	3.2 (3.2)	12.0 (12.1)	7.2 (7.4)	23.8 (24.0)	-
$VOSO_4.5H_2O$ + TMTH (1:2 in presence of KOH)	16	$[VO(TMT)_2]$ light brown, 65, 140	$C_{26}H_{24}N_6S_4OV$ (615.68)	50.5 (50.7)	3.7 (3.9)	13.5 (13.6)	8.2 (8.2)	20.5 (20.8)	-
$VOSO_4.5H_2O$ + TMTH (1:2)	15	$[VO(TMTH)_2]SO_4$, brown, 58, 148	$C_{26}H_{26}N_6S_5O_5V$ (713.72)	43.6 (43.7)	3.5 (3.7)	11.5 (11.8)	7.1 (7.1)	22.3 (22.4)	-
$VOSO_4.5H_2O$ +TMOTH (1:2 in presence of KOH)	15	$[VO(TMOT)_2]$ brown, 62, 180	$C_{26}H_{24}N_6S_4O_3V$ (647.66)	48.2 (48.2)	3.5 (3.7)	12.8 (12.9)	7.8 (7.9)	19.7 (19.8)	-

$VOSO_4.5H_2O$ +TMOTH (1:2)	15	$[VO(TMOTH)_2]SO_4$ dark brown,60, 172	$C_{26}H_{26}N_6S_5O_7V$ (633.74)	49.1 (49.3)	4.0 (4.1)	13.1 (13.3)	7.9 (8.0)	25.1 (25.3)	-
$VOSO_4.5H_2O$ + TCTH (1:2 in presence of KOH)	20	$[VO(TCT)_2]$, brown, 64, 170	$C_{24}H_{18}N_6S_4OCl_2V$ (596.51)	31.4 (31.6)	3.0 (3.0)	14.0 (14.1)	8.3 (8.5)	21.3 (21.5)	11.8 (11.9)
$VOSO_4.5H_2O$ +TCTH (1:2)	15	$[VO(TCTH)_2]SO_4$, brown, 54, 182	$C_{24}H_{20}N_6S_5O_5Cl_2V$ (754.55)	38.0 (38.2)	2.6 (2.7)	11.0 (11.1)	6.7 (6.7)	21.2 (21.2)	9.2 (9.4)
$VOSO_4.5H_2O$ +TBTH (1:2 in presence of KOH)	17	$[VO(TBT)_2]$ light brown, 62, 150	$C_{24}H_{18}N_6S_4OBr_2V$ (745.43)	38.6 (38.7)	2.2 (2.4)	11.2 (11.3)	6.6 (6.8)	17.0 (17.2)	21.1 (21.4)
$VOSO_4.5H_2O$ +TBTH (1:2)	15	$[VO(TBTH)_2]SO_4$, dark brown, 55 128	$C_{24}H_{20}N_6S_5O_5Br_2V$ (843.47)	34.0 (34.2)	2.3 (2.4)	10.0 (10.0)	5.9 (6.0)	18.8 (19.0)	18.8 (18.9)

[a] TPTH = Thiosemicarbazone derived from thiophene-2-aldehyde and thiosemicarbazide
TMTH = Thiosemicarbazone derived from thiophene-2-aldehyde and 4-methylthiosemicarbazide
TMOTH = Thiosemicarbazone derived from thiophene-2-aldehyde and 4-methoxythiosemicarbazide
TCTH = Thiosemicarbazone derived from thiophene-2-aldehyde and 4-chlorothiosemicarbazide
TBTH = Thiosemicarbazone derived from thiophene-2-aldehyde and 4-bromothiosemicarbazide.

spectra of thiosemicarbazone complexes show bands in the regions 12500, 13000, 16500-17200 and 23000-23200 cm^{-1}, which may be assigned[11,12] to $b_2 \longrightarrow e^*$ ($^2B_2 \longrightarrow E$), $b_2 \longrightarrow b_1^*$ ($^2B_2 \rightarrow {}^2B_1$) and $b_2 \longrightarrow a_1$ ($^2B_2 \longrightarrow {}^2A_1$) transitions in increasing order of energy of the basis of energy level schemes developed by Ballhausen and Gray (B. G. Scheme)[13] and Selbin[14].

Infrared Spectra

The infrared spectra of the ligands show bands in the regions 3200-3250, 1620-1630 cm^{-1} which are assigned to ν(NH) and ν(C=N) vibrations. The bands at $\sim$3200-3250 cm^{-1} persist in the complexes which indicates the non-coordination of the hydrazinic group. However, the bands in the region 1620-1630 cm^{-1} (due to νC=N) are lowered by 15-20 cm^{-1} in the complexes indicating[15,16] coordination of the azomethine nitrogen to the metal. The bands observed at 390-415 cm^{-1} may be assigned to ν(V-N).

The four bands occurring in the regions 1460-1500, 1250-1275, 1040-1060 and 760-780 cm^{-1} in the spectra of the ligands, may be assigned[16,17] to thioamide-I, II, III, IV vibrations, respectively. The appearance of these four bands indicates the existence of the ligand in the thione form in the solid state. These bands appear due to the mixed contributions of δ(N-H), ν(C=N), ν(C-S) and δ(C-H) vibrations. In the spectra of oxovanadium(IV) complexes of the type $[VO(LH)_2]SO_4$, the thioamide-IV band (having maximum ν(C=S) contribution) shifts to lower frequency (35-25 cm^{-1}) suggesting[16] the coordination of the sulphur atom to metal. The new band appearing in the complexes at ca. 360-340 cm^{-1} may be assigned

to ν(V-S). However, all the thioamide bands are found to be absent in the spectra of the complexes of the type $[VOL_2]$. The disappearance of thioamide bands in the complexes indicates[16] the possibility of thione-thiol tautomerism. These complexes show bands near 700 cm^{-1} which are assigned to ν(C-S).

In the spectra of the ligands, thiophene ring bands occur at *ca.* 3050 cm^{-1} and at 1580 cm^{-1}. These bands remain at the same position in the complexes indicating[18] the non-participation of the heterocyclic ring sulphur in coordination.

In all oxovanadium(IV) complexes a band occurring at 970 cm^{-1} is assigned to the ν(V=O) vibration. This value is in the range observed for monomeric oxovanadium(IV) complexes. The presence of an ionic sulphate group in the complexes of the type $[VO(LH)_2]SO_4$ has been confirmed by the appearance of three bands at 1130 (ν_3), 950 (ν_1) and 600 cm^{-1} (ν_4). The absence of a ν_2 band and non-spliting of the ν_3 band indicate that Td symmetry is still held[19].

Thus, the infrared spectra reveal that all of these ligands act as bidentate chelating agents. However, their coordination behaviour depends upon the pH of the media. When the reactions are carried out in the presence of base (as for $[VOL_2]$ complexes), the ligands behave as monobasic bidentate chelating agents having the azomethine nitrogen and thiol sulphur as coordination sites. However, when the reactions are carried out in the absence of base (as for $[VO(LH)]SO_4$ complexes), the ligands behave as neutral bidentate chelating agents having coordination sites at the azomethine nitrogen and thiocarbonyl sulphur atoms.

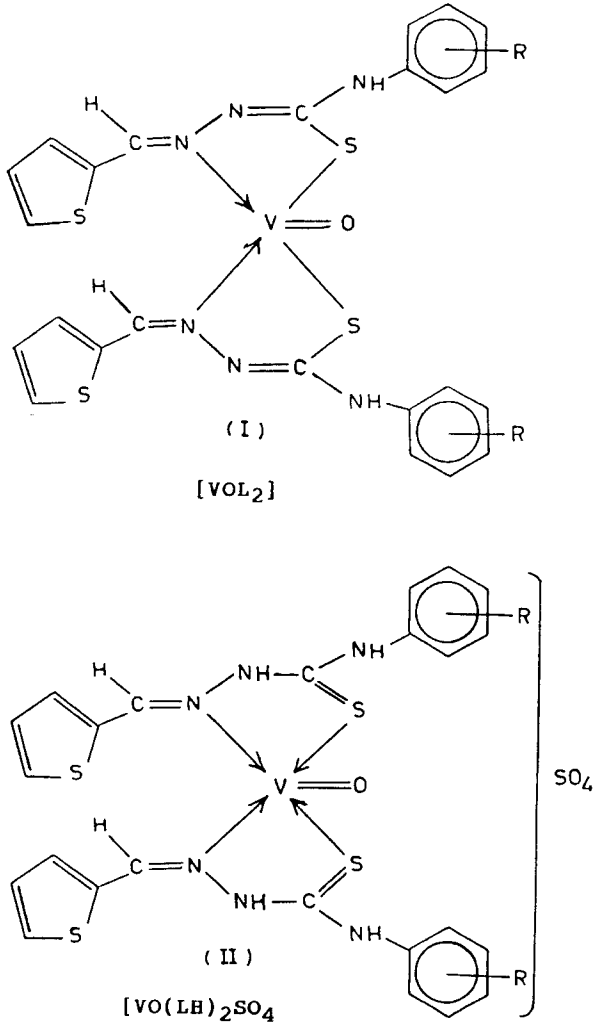


Fig. 2. Suggested Structures of the Complexes

Thus, on the basis of elemental analyses, electrical conductance and spectral data, the following structures may be proposed for $[VOL_2]$ (I) and $[VO(LH)_2]SO_4$ (II) complexes (Fig. 2).

Antifungal Activity

The antifungal activity of the oxovanadium(IV) complexes with thiosemicarbazones was evaluated against Aspergillus niger and Helminthosporium oryzae by the agar plate technique[20] at three concentrations: viz., 1000 ppm, 100 ppm and 10 ppm, with three replications in each case. The average percentage inhibition after 96 hours by various compounds was calculated from the expression below:

$$\text{Inhibition } (\%) = 100\ (C-T)/C$$

C = diameter of fungus colony in control plates after 96 h, and
T = diameter of fungus colony in tested plates after 96 h.

The results are recorded in Table II. The following conclusions can be derived:

(a) All the compounds have significant toxicity at 1000 ppm against both species of fungus and the complexes are more active than their corresponding ligands. In other words, the activity increases on complexation.

(b) The activity decreases on dilution.

(c) The thiosemicarbazones and their oxovanadium(IV) complexes are more active against Aspergillus niger than Helminthosporium oxyzae.

(d) Compounds with the thiosemicarbazone ligand where R = 4-Cl are found to be the most active against both species of fungi.

Table II. Fungicidal and Viricidal Screening Data

Compound	Average inhibition (%) after 96 h						Organism - Cucumber mosaic Host plant: Chenopodium amaranticolor. Concentration used: 1000 ppm
	Organism: A. niger			Organism: H. oryzae			
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm	Inhibition (%)
TPTH	45.6	40.8	36.2	40.8	32.5	26.2	6
$[VO(TPT)_2]$	52.0	46.3	40.8	47.6	42.5	36.7	8
$[VO(TPTH)_2]SO_4$	58.6	50.2	48.7	54.5	46.2	39.8	10
TMTH	50.6	42.8	40.6	46.6	39.2	34.3	10
$[VO(TMT)_2]$	57.2	50.6	43.8	55.6	48.1	41.3	12
$[VO(TMTH)_2]SO_4$	60.5	57.5	50.9	58.2	50.4	45.4	15
TMOTH	53.8	48.2	44.4	49.6	41.7	39.6	8
$[VO(TMOT)_2]$	63.3	56.2	49.8	60.1	53.6	47.2	10
$[VO(TMOTH)_2]SO_4$	66.1	60.8	52.7	62.2	55.5	49.2	18
TCTH.	65.2	58.6	52.7	60.1	54.2	50.3	15
$[VO(TCT)_2]$	78.5	70.6	66.2	74.1	67.6	60.8	20
$[VO(TCTH)_2]SO_4$	84.2	77.1	70.5	78.5	72.0	65.4	25
TBTH	64.8	60.2	55.6	59.2	54.5	48.2	12
$[VO(TBT)_2]$	72.7	68.6	62.9	70.5	64.3	59.6	15
$[VO(TBTH)_2]SO_4$	75.4	70.2	66.4	71.9	67.8	62.7	18

(e) Compounds of the type $[VO(LH)_2]SO_4$ are found to be more active then compounds of the type $[VO(L)_2]$ against both species of fungi.

Activiral Activity

The antiviral activity was evaluated by noting the reduction in the number of local lesions produced by cucumber virus on Chenopodium amaranticolor, when mixed with the chemical. Standard extracts of the virus were mixed in an equal quantity of solution of compound. Inoculations were made by the leaf rubbing method. One half of each leaf was inoculated with inoculum containing the virus and chemical and the remainder was inoculated with the standard virus extract. Infections on different samples were calculated on the basis of local lesions produced by each treatment and the percentage inhibition was calculated from the expression below:

$$\text{Inhibition (5)} = \frac{\text{No. of local lesions by control} - \text{No. of local lesions by treatment}}{\text{No. of lesions by control}} \times 100$$

All compounds display weak antiviral activity (Table II), however, the ligands are less active than their corresponding oxovanadium(IV) compounds.

Antibacterial Activity

The ligands and their oxovanadium(IV) complexes were screened for their antibacterial activity in vitro against the bacteria E. coli, P. pyocyancus and S. citrus at 1000 ppm concentration using the inhibition zone technique[21]. The screening data are given in Table III. All compounds show moderate activity.

Table III. Antibacterial Activity of Thiosemicarbazones and their Oxovanadium Complexes

Compound	Zone of inhibition (mm)		
	E.coli	P.pyocyancus	S.citrus
TPTH	6	15	18
$[VO(TPT)_2]$	10	20	24
$[VO(TPTH)_2]SO_4$	12	22	28
TMTH	10	18	20
$[VO(TMT)_2]$	12	23	26
$[VO(TMTH)_2]SO_4$	15	25	28
TMTH	7	14	16
$[VO(TMOT)_2]$	12	18	20
$[VO(TMOTH)_2]SO_4$	14	20	23
TCTH	12	20	25
$[VO(TCT)_2]$	16	25	28
$[VO(TCTH)_2]SO_4$	20	30	32
TBTH	10	18	21
$[VO(TBT)_2]$	14	23	26
$[VO(TBTH)_2]SO_4$	18	27	29

However, the activity of the oxovanadium(IV) complexes are found to be greater than that of the corresponding ligands. The best activity was shown by TCTH and its oxovanadium(IV) complexes against C. citrus.

EXPERIMENTAL

AnalaR grade chemicals were used throughout. Oxovanadium(IV) sulphate was supplied by Aldrich. The ligands were prepared by the method reported in the literature[16]. Elemental analyses and physical measurements were done as reported earlier[10].

Preparation of Complexes

Oxovanadium(IV) Complexes with Thiosemicarbazones in the Presence of Base. To a solution of vanadyl sulphate (5.0 g, 0.02 mol) in methanol (20 mL) was added a solution of the appropriate thiosemicarbazone (0.04 mole) dissolved in methanol (15 mL). To this, a saturated alcoholic solution (1 mL) of potassium hydroxide was added. The reaction mixture was refluxed 15-20 h. The precipitate, thus obtained, was filtered, washed with water and ethanol and dried under vacuo.

Oxovanadium(IV) Complexes with Thiosemicarbazone in the Absence of Base. Vanadyl sulphate (5.0 g, 0.02 mol) in 15 mL methanol was added to the solution of the appropriate ligand (0.04 mol) dissolved in methanol (20 mL). The mixture was refluxed for about 15 h when the colour of the solution turned brown or greenish-brown. The solution was concentrated and kept in a refrigerator for overnight. Dark crystals separated and were thoroughly washed with cold methanol and dried under vacuo.

The physical properties and analytical data of the complexes are given in Table I.

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