

SYNTHESIS AND ANTIFUNGAL ACTIVITY OF OXOVANADIUM(IV) COMPLEXES WITH SCHIFF BASES

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A series of preparations are reported representing complexes between a range of ligands [KHL = potassium salt of salicylidene- β -alanine, A¹ = 2,2'-bipyridylamine, A² = bis(benzylidene)ethylenediamine, A³ = thiophene-*o*-carboxaldene-aniline, A⁴ = thiophene-*o*-carboxaldene-*p*-toluidine, A⁵ = bis(benzylidene)-1,8-diaminonaphthalene, A⁶ = bis(acetophenone)ethylenediamine] and oxovanadium(IV) ion. Relevant electronic (UV), infrared (IR) spectra, thermogravimetric analyses, elemental analyses, and magnetic measurements are reported and interpreted in terms of the metal ion coordination geometry and, where appropriate, the likely octahedral structures of the compounds. The complexes are paramagnetic in nature. The antifungal activity of the complexes against *A. niger*, *F. oxysporum* and *A. flavus* species is reported. All the tested complexes show higher antifungal activity as compared to free ligands, vanadyl sulfate, and the control (DMSO), but moderate activity as compared to the reference fungicides bavistin and emcarb.

The coordination chemistry and reactivity of vanadium has continued to play a significant role not only because of the physiological relevance of this metal but also for its activity in various industrial processes. Vanadium chelates containing O, N and S have been explored as catalysts for olefin polymerization/copolymerization and as advanced materials [1 – 4]. Biologically, vanadium is known for its exceptional ability to interact with biomolecules in both cationic and anionic forms and its numerous oxidation states. Several therapeutic effects have been described for vanadium including hormonal, cardiovascular, anticarcinogenic, and insulin mimetic activities [5 – 9]. In continuation of earlier work [10], we have prepared oxovanadium(IV) mixed-ligand complexes with Schiff bases.

Microanalytical data along with some physical properties of the complexes are summarized in Table 1. All the synthesized complexes appear as green crystalline solids. The mixed-ligand complexes are stable in air and soluble in dimethylsulfoxide (DMSO). The IR spectra of all oxovanadium(IV) mixed-ligand complexes display a strong band at 1000 cm⁻¹ assignable to V=O modes [11]. The $\nu(\text{O-H})$ [12] band originally found in the spectra of Schiff bases disappeared upon complexation, which was indicative of deprotonation of the phenolic hydroxy group and coordination of the phenolic oxygen to the metal. This is further supported by a shift in the stretching frequency of the phenolic $\nu(\text{C-O})$ [13] from 1530 cm⁻¹ toward higher frequencies by $\sim 10 - 20$ cm⁻¹. The $\nu(\text{C=N})$ band, which is found at ~ 1625 cm⁻¹ in the spectra of A², A³, A⁴, A⁵, and A⁶ ligands, shifts to lower frequency at ~ 1600 cm⁻¹ upon complexation, which indicates that the azomethine nitrogen participates in coordination [14]. The $\nu(\text{C=N})$ band of 2,2'-bipyridylamine [15] appears at 1580 cm⁻¹. This band shifts to higher frequency (~ 1610 cm⁻¹) in the complex, this being indicative of a bidentate N-N coordination of the ligand. The new band observed in the [VO(L)(A³)] and [VO(L)(A⁴)] complexes around $\sim 410 - 425$ cm⁻¹ can be assigned to the $\nu(\text{M-S})$ mode [16]. In the low-frequency region, the bands observed in the range of $\sim 525 -$

535 cm⁻¹ are attributed to $\nu(\text{M-N})$ [17], bands in the region of $\sim 460 - 470$ cm⁻¹ are attributed to $\nu(\text{M-O})$ phenolic, and bands in the region of $\sim 415 - 420$ cm⁻¹ are attributed to $\nu(\text{M-O})$ carboxy [18]. Two absorption bands occurring near 1595 and 1400 cm⁻¹ in the spectra of Schiff bases correspond to the asymmetric and symmetric stretching vibrations of the ionic carboxy group $\nu(\text{COO})$. In the spectra of mixed-ligand complexes, these bands are shifted to lower frequencies: ~ 1585 and 1390 cm⁻¹, respectively [19].

The effective magnetic moments of the VO(IV) complexes at room temperature are 1.70 – 1.82 B. M., which are within the range for a single electron and are due to orbital contributions. These data suggest that the complexes prepared in this investigation are mononuclear [20].

The electronic spectra of the complexes were recorded in the solid state. However, more evidence seems to favor the ordering proposed by Ballhausen and Gray [21], with some modifications by Kuska and Yang [22]. Mixed-ligand complexes exhibit three spin-allowed transitions in the 23,500 – 24,500, 15,500 – 17,000 and 12,500 – 13,500 cm⁻¹ regions, which have been assigned to ${}^2\text{B}_2 \rightarrow {}^2\text{A}_1$, ${}^2\text{B}_2 \rightarrow {}^2\text{B}_1$, and ${}^2\text{B}_2 \rightarrow {}^2\text{E}$ transitions, respectively [20]. These results suggest an octahedral structure of the complexes.

The thermal decomposition behavior of the synthesized VO(IV) complexes was studied by means of thermogravimetric analysis. It has been found that all the VO(IV) complexes do not exhibit weight loss between 50 and 80°C, which indicates that crystal water and coordinated water molecules are not present in the complexes. All the complexes showed the weight losses corresponding to ligand molecules in the interval from 180 to 800°C. The final products for all complexes are metal oxides. These results are in good agreement with the known compositions of complexes. The structures of the VO(IV) complexes are shown in Fig. 1.

Experimental chemical part

Reagent and solvents. All the chemicals used were of analytical grade; 2,2'-bipyridylamine, 1,8-diaminonaphthalene, and thiophene-*o*-carboxaldehyde were purchased from the Eastgate (White Lund, Morecambe, Lancaster, England); salicylaldehyde, β -alanine, benzaldehyde, acetophenone, aniline, *p*-toluidine, ethylenediamine, potassium hydroxide, and vanadyl sulfate were purchased from E. Merck Ltd. (Mumbai, India). The organic solvents were purified by standard methods [23].

Potassium salt of salicylidene- β -alanine (KHL). A solution of potassium hydroxide (10 mmol, 0.56 g) in 30 ml absolute alcohol was added to 10 mmol (0.891 g) of β -alanine. The mixture was stirred until complete dissolution of β -alanine in the ethanol – KOH solution. Then an ethanol solution of salicylaldehyde (10 mmol, 1.22 g) was quickly added. The reaction was allowed to complete by stirring at 60°C for an hour. The product was crystallized out by diffusion of excess absolute diethyl ether into the solution. The product was filtered and dried in a vacuum desiccator. Yield, 66 %; m.p., 174°C.

Bis(benzylidene)ethylenediamine (A²) was synthesized according to a published procedure [24].

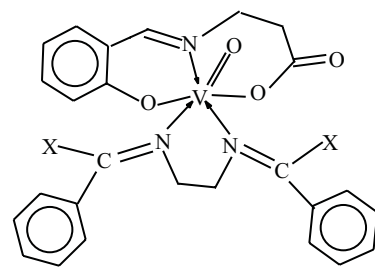
Thiophene-*o*-carboxaldeneaniline (A³). An ethanol solution (100 ml) of thiophene-*o*-carboxaldehyde (10 mmol, 1.12 g) and an ethanol solution (100 ml) of aniline (10 mmol, 0.99 g) in a 1 : 1 molar ratio were mixed on stirring, boiled with reflux for six hours, cooled, and allowed to stand overnight at room temperature. The precipitated yellow crystals were separated by filtration and dried in air. Yield, 60%; m.p., > 360°C.

Thiophene-*o*-carboxaldene-*p*-toluidine (A⁴). An ethanol solution (100 ml) of thiophene-*o*-carboxaldehyde (10 mmol, 1.12 g) and an ethanol solution (100 mL) of *p*-toluidine (10 mmol, 1.07 g) in 1 : 1 molar ratio were mixed on stirring, boiled with reflux for six hours, cooled, and allowed to stand overnight at room temperature. The precipitated yellow crystals were separated by filtration and dried in air. Yield, 60%; m.p., > 360°C.

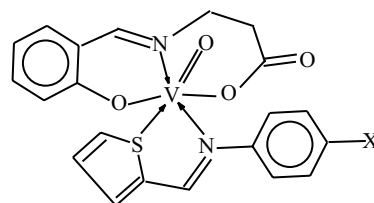
Bis(benzylidene)-1,8-diaminonaphthalene (A⁵). An ethanol solution (100 mL) of 1,8-diaminonaphthalene (10 mmol, 1.58 g) and an ethanol solution (100 mL) of benzaldehyde (20 mmol, 2.12 g) in a 1 : 2 molar ratio were mixed on stirring, boiled with reflux for five hours, and cooled in a refrigerator to 0 – 2°C overnight. The precipitated fine crystalline yellow product was filtered and dried in air. Yield, 68%; m.p., 235°C.

Bis(acetophenone)ethylenediamine (A⁶) was synthesized according to a published procedure [25].

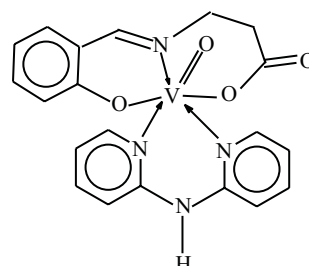
Preparation of mixed-ligand complexes. Mixed-ligand complexes were obtained by mixing an aqueous solution (100 ml) of vanadyl sulfate (10 mmol, 2.53 g) and a hot methanol solution (100 ml) of potassium salt of salicylidene- β -alanine (KHL) (10 mmol, 2.17 g) and A¹ (10 mmol, 1.71 g) or A² (10 mmol, 2.36 g) or A³ (10 mmol, 1.87 g) or A⁴ (10 mmol, 2.01 g) or A⁵ (10 mmol, 3.34 g) or A⁶ (10 mmol, 2.64 g) in 1:1:1 mole ratio. The mixed-ligand complexes were formed by heat-



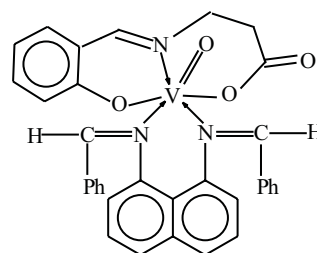
[VO(L)(A²)] X = H or [VO(L)(A⁶)] X = CH₃



[VO(L)(A³)] X = H or [VO(L)(A⁴)] X = CH₃



[VO(L)(A¹)]



[VO(L)(A⁵)]

Fig. 1. Structures of the synthesized VO(IV) complexes.

ing the mixture in a water bath for 1 – 2 h at 50°C. The mixture was kept overnight at room temperature. A fine colored crystalline product was separated by filtration, washed with water and ethanol, and dried in air.

Experimental biological part

Fungal species were isolated using dilution plate method [26]. A series of dilution tubes containing 9 ml of sterile distilled water was prepared. A 1.0 g sample of soil was placed in a dilution tube and the tube was agitated for 15 min. Serial dilutions were performed, 0.1 ml sample of the final three dilutions were inoculated on potato dextrose agar plates and spread with sterile spreader. The plates were incubated at 30°C. Each dilution should result in 40 to 60 colonies. After incubation, the grown species were characterized by colony characterization and microscopic examination techniques. Selected and isolated fungi were

Yields and Physicochemical characteristics of VO(IV) Complexes

Compounds* Empirical Formula	Mol. Wt.	Colour	% Found (Calcd.)					M.p. (°C)	μ_{eff} (B.M.)	% Yield
			C	H	N	S	Metal			
KHL	231.19	Yellow	51.86 (51.94)	4.39 (4.32)	6.18 (6.05)	–	–	174	–	66
C ₁₀ H ₁₀ KNO ₃ A ²	236.16	Yellow	81.32 (81.36)	6.78 (6.77)	11.83 (11.85)	–	–	235	–	72
C ₁₆ H ₁₈ N ₂ A ³	187.19	Yellow	70.54 (70.57)	4.83 (4.80)	7.45 (7.47)	17.16 (17.13)	–	> 360	–	60
C ₁₁ H ₉ NS A ⁴	201.20	Yellow	71.66 (71.63)	5.43 (5.46)	6.91 (6.95)	15.92 (15.94)	–	> 360	–	58
C ₁₂ H ₁₁ NS A ⁵	334.24	Yellowish Brown	86.21 (86.23)	5.35 (5.38)	8.36 (8.37)	–	–	235	–	68
C ₂₄ H ₁₈ N ₂ A ⁶	264.18	Yellow	81.80 (81.83)	7.56 (7.57)	10.57 (10.59)	–	–	260	–	75
C ₁₈ H ₂₀ N ₂ [VO(L)(A ¹)]	429.14	Green	55.97 (55.97)	4.17 (4.19)	13.01 (13.04)	–	11.81 (11.87)	> 360	1.79 (1.73)	63
C ₂₀ H ₁₈ VN ₂ O ₄ [VO(L)(A ²)]	494.20	Green	63.20 (63.18)	5.03 (5.05)	8.44 (8.49)	–	10.36 (10.30)	> 360	1.72 (1.73)	58
C ₂₆ H ₂₅ VN ₃ O ₄ [VO(L)(A ³)]	445.15	Green	56.58 (56.65)	4.11 (4.04)	6.24 (6.29)	(7.18)	11.37 (11.44)	> 360	1.76 (1.73)	62
C ₂₁ H ₁₈ VN ₃ O ₄ S [VO(L)(A ⁴)]	459.16	Green	57.59 (57.54)	4.32 (4.35)	6.12 (6.09)	(6.96)	11.04 (11.09)	> 360	1.80 (1.73)	64
C ₂₂ H ₂₀ VN ₂ O ₄ S [VO(L)(A ⁵)]	592.28	Green	69.01 (68.94)	4.49 (4.55)	6.98 (7.09)	–	8.54 (8.60)	> 360	1.82 (1.73)	66
C ₃₄ H ₂₇ VN ₃ O ₄ [VO(L)(A ⁶)]	522.22	Green	64.27 (64.39)	5.51 (5.55)	8.05 (8.04)	–	9.76 (9.75)	> 360	1.70 (1.73)	56

* KHL = Potassium salt of salicylidene- β -alanine;

A¹ = 2,2'-bipyridylamine;

A² = Bis(benzylidene)ethylenediamine;

A³ = Thiophene-*o*-carboxaldeneaniline;

A⁴ = Thiophene-*o*-carboxaldene-*p*-toluidine;

A⁵ = Bis(benzylidene)-1,8-diaminonaphthalene;

A⁶ = Bis(acetophenone)ethylenediamine.

maintained on potato dextrose agar plates at 4°C for subsequent experimental work.

Antifungal activity. A number of organic compounds have been used as antifungal agents whose fungal activity

depends on the size, shape and structure of the molecule, while it has been found that a majority of the complexes possess antifungal activity. The antifungal activity of the control (dimethylsulfoxide, DMSO), the reference fungicides (bavistin and emcarb), the ligands, vanadyl sulfate and its complexes were evaluated by the plate poison technique [27]. For evaluating the antifungal activity of the complexes, a solution of desired concentration (500 µg/ml) was obtained by dissolving 50 mg of each compound in DMSO and added to potato dextrose agar (PDA) medium in 90-mm sterile Petri dishes replicated thrice for each treatment. Pure PDA with DMSO served as the control. Each plate was inoculated with a 5-mm-diameter mycelial disc taken from 7-day-old culture raised on PDA. The inoculated plates were incubated at 27°C for 72 h. After incubation, the growth diameter relative to the control and the percentage inhibition were calculated. The test fungi included (a) *A. niger*, (b) *F. oxysporum*, and (c) *A. flavus*. The test results are presented in Table 2.

Results and discussion

The results show that the mixed-ligand complexes are more toxic than their parent ligands and vanadyl sulfate against the same microorganisms under identical experimental conditions. The increase in antifungal activity of the mixed-ligand complexes may be due to the effect of

Table 2
Antifungal Activity of VO(IV) Complexes

Compounds	Growth diameter in mm (% Inhibition)		
	<i>A. niger</i>	<i>F. oxysporum</i>	<i>A. flavus</i>
DMSO (control)	29	46	39
Bavistin	00(100)	00(100)	00(100)
Emcarb	00(100)	00(100)	00(100)
KHL	21(26)	34(27)	26(32)
A ¹	20(31)	31(32)	30(23)
A ²	22(23)	34(27)	26(32)
A ³	18(38)	33(28)	29(25)
A ⁴	20(31)	31(32)	29(25)
A ⁵	18(38)	38(17)	27(30)
A ⁶	19(34)	31(32)	29(25)
VOSO ₄ ·5H ₂ O	22(23)	34(27)	29(25)
[VO(L)(A ¹)]	16(45)	19(59)	19(51)
[VO(L)(A ²)]	15(48)	19(59)	20(49)
[VO(L)(A ³)]	12(58)	18(61)	21(46)
[VO(L)(A ⁴)]	13(55)	19(59)	20(49)
[VO(L)(A ⁵)]	13(55)	29(37)	20(49)
[VO(L)(A ⁶)]	14(52)	19(59)	23(41)

the metal ion on the normal cell process. A possible mode for toxicity increase may be considered in terms of the Tweedy chelation theory [28], according to which chelation considerably reduced the polarity of the metal ion because of partial sharing of its positive charge with the donor groups and π -electron delocalization over the whole chelate ring. Such chelation could enhance the lipophilic character of the central metal atom, which subsequently favors its permeation through the lipid layer of cell membrane. Although there is a sufficient increase in the fungicidal activity of the mixed-ligand complexes as compared to free ligands, vanadyl sulfate and the control (DMSO), the effect does not attain the level exhibited by the reference fungicides bavistin and emcarb.

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СИНТЕЗ И ФУНГИЦИДНАЯ АКТИВНОСТЬ КОМПЛЕКСОВ ОКСОВАНАДИЯ(IV) С ОСНОВАНИЯМИ ШИФФА

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Синтезирован ряд комплексов оксованадия(IV) с основаниями Шиффа, включая калиевую соль салицилиден- β -аланина (KHL), 2,2'-бипиридил-амин (A^1), бис(бензилиден)этилендиамин (A^2), тиофен-*o*-карбоксальденанилин (A^3), тиофен-*o*-карбоксальден-*n*-толуидин (A^4), бис(бензилиден)-1,8-диаминонафталин (A^5), и бис(ацетофенон)этилендиамин (A^6). Приведены химические и физические характеристики полученных веществ и рассмотрена координация иона металла в комплексах. Исследованы свойства комплексов в отношении штаммов *A. niger*, *F. Oxysporum* и *A. Flavis*. Фунгицидный эффект комплексов выше, чем активность свободных лигандов, сульфата ванадия и ДМСО, но ниже чем активность препаратов сравнения (бавистин, эмкарб).