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# Oxovanadium(IV) Complexes with Cephradine: Synthesis, Semi-Empirical Study, Spectroscopy, Potentiometric Study and Antimicrobial Activity

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The reactions between cephradine and VOSO<sub>4</sub>.3H<sub>2</sub>O in 1:1, 1:2 and 1:3 molar ratios in methanol were investigated at room temperature, 0 °C and -10 °C. In various pH conditions, the different complexes formulated as  $VO(H_2O)_3L^{2^-}$ ,  $VO(H_2O)L_2^{2^-}$  and  $VL_3^-$  were formed by titration of VOSO<sub>4</sub>.3H<sub>2</sub>O and cephradine with NaOH. These complexes were characterized by elemental analysis and IR spectroscopy. IR spectra of all the complexes show the disappearance of v(O-H) band of cephradine, which confirms complexation. Estimation of vanadium in the complexes was carried out by ICP-AES. The stability constants of each complexes. In complex (1) the cephradine ligand bind in bidentate [O,O] fashion together with a terminal oxo ligand and water molecules complete the metal coordination sphere. In complex (2) the cephradine ligands bind in bis-bidentate [O,O] fashion and the axial positions are occupied by the oxo ligand and a trans-water molecule. Biological screening tests show significant antibacterial and anti-fungal activities against various bacterial and fungal strains.

Keywords: Oxovanadium(IV) complexes, IR, Potentiometric study, PM6 calculations, Biological activities

# INTRODUCTION

Vanadium is a ubiquitous element dispersed throughout the earth's crust, rivers, lakes and oceans [1]. Vanadium is a powerful alloying agent; a small amount adds strength, toughness and heat resistance. Vanadium-aluminum-titanium alloys are used in high-speed airframes and jet engines. The halides of vanadium generally react with different ligands to form complexes of the type  $[ML_6]^{3+}X_3$ ,  $[ML_4X_2]^+X^-$ ,  $[ML_3X_3]$ and  $[ML_2X_3]$  as well as several anionic types formed with unidentate ligands.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are pain-relievingmedications which also have the effect of reducing inflammation when used over a period of time. The major clinical application of NSAIDs is their action as antiagents in muscle skeletal diseases [2]. inflammatory Mefenamic acid (2-[(2,3-dimethylphenyl)amino-]benzoic acid). ketoprofen (2-(3-benzoylphenyl)propionoic acid), flurbiprofen (2-(2-fluro-4-biphenyl)propanoic acid, Ibuprofen (2-(4-isobutylphenyl)propanoic acid), are only a few examples of non-steroidal anti-inflammatory drugs. Several transition metal complexes with NSAIDs have extensively been studied. Vanadium forms complexes with NSAIDs that are mainly

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Fig. 1. Chemical structure of cephradine (HL).

effective in their biological activity as compared to their parent ligand [3]. Vanadium complexes potentially active as anti-tumors. They are also used as anti-diabetic and anticarcinogenic agents. From among the complexes of vanadium in +4 oxidation state, mostly oxovanadium complexes with NSAIDs have been reported as being effective anti-diabetic agents. Moreover, these complexes are reported to possess certain other biological activities [4].

We are reporting here the oxovanadium(IV) complexes of cephradine, (6R-(6alpha,7))-((amino-,1,4-cyclohexadien-1-ylacetyl)amino)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid (Fig. 1), a first generation cephalosporin antibiotics and their characterization by elemental analysis, IR spectroscopy, potentiometric and semi-empirical study. These complexes were duly screened against different bacterial and fungal strains to check their biological activity.

# **EXPERIMENTAL**

### **Materials and Methods**

All the reagents and solvents were commercially available in the highest grade and used without further purification.  $VOSO_4.3H_2O$  was purchased from Aldrich. Melting points were determined in a capillary tube on an electrothermal melting point apparatus model Sanyo Gallen Kamp MPD-350 BM3.5 and were uncorrected.

Infrared spectra were recorded in the range of 4000-400 cm<sup>-1</sup> as KBr pellets on a Bio-Red Elmer 16 FPC FTIR Spectrophotometer. Distilled water was used for the preparation of 0.2 M NaOH solution. Methanol was used as a solvent for the preparation of 0.01 M solution of vanadyl sulphate trihydrate and 0.01 M solution of cephradine. pH

meter was calibrated by using the buffer tablet of pH 4.

#### **Quantum Chemical Methods**

The structure of complexes (1) and (2) were modeled by MOPAC 2007 [5] program using PM6 method [6] parts of the molecule not containing the metal ion were preoptimized using molecular mechanics method before subjecting the whole molecule to geometry optimization. Molecular Mechanics correction was applied to the -CO-NH- barrier. Stability constants were calculated using the computer program BEST [7].

#### **General Procedure**

For potentiometric titrations, 1:1, 1:2 and 1:3 molar ratios were prepared by mixing 25 ml of 0.01 M VOSO<sub>4</sub>.3H<sub>2</sub>O solutions with 25 ml, 50 ml and 75 ml of 0.01 M solution of cephradine in volumetric flask. The titrations were carried out at 20 °C, 0 °C and -10 °C with standard 0.2 M NaOH. The 20 °C was the room temperature, while 0 °C and -10 °C were maintained by keeping the titration flask in ice and ice-salt bath, respectively.

The reaction mixtures were stirred on a magnetic stirrer while the titrations were being carried out and pHs were measured after every 0.2 ml addition of NaOH solution. For all the three molar ratios, the first addition of NaOH solution caused color change of the solutions with turbidity, which meant that complexation had started. At the end of the reactions all solutions became clear and white precipitates of Na<sub>2</sub>SO<sub>4</sub> were formed. These precipitates were filtered and solvents evaporated at room temperature. Green-colored solid products obtained were recrystallized in choroform:petroleum ether (1:1).

## **RESULTS AND DISCUSSION**

The complexes (1)-(3) were obtained in good yield, stable at room temperature and showed good solubility in common organic solvents. Some physical parameters of the complexes are reported in Table 1.

#### Infrared Spectroscopy

The most important features of the infrared spectra of the complexes and corresponding free ligand are shown in Table 2.

Compound	General formula	Mol. Wt.	Yield (%)	m.p. (°C)	Molar ratios	Elemental analysis calcd. (found)		vsis )
						%C	%H	%N
(1)	$[VO(H O) I]^{2}$	454	62	147	1:1	42.29	5.06	6.16
	$[VO(\Pi_2O)_3L]$					(42.32)	(5.02)	(6.20)
(2)	$[VO(H_2O)L_2]^{2-}$	751	69	123	1:2	51.13	4.79	7.45
						(51.09)	(4.75)	(7.49)
(3)	$[VL_3]^-$	1002	80	112	1:3	57.48	5.08	8.38
						(57.44)	(5.12)	(8.42)
						. /	, ,	. /

Table 1. Physical Parameters of Oxovanadium(IV) Complexes of Cephradine

Table 2. Infrared Spectral Data (cm<sup>-1</sup>) for Oxovanadium(IV) Complexes of Cephradine

		ν(0	COO)		/		
Compound	$\nu(H_2O)$	Asym.	Sym.	$\triangle v$	v(V-O)	v(V=O)	v(C=O)
NaL	-	1692	1382	308	-	-	1762
(1)	3432	1570	1410	160	560	911	1751
(2)	3445	1597	1452	145	572	908	1750
(3)	-	1553	1419	134	591	904	1752

The significant absorption frequencies were v(O-H), v(C=O),  $v_{asym}(COO)$ ,  $v_{sym}(COO)$ , v(V-O) and v(H<sub>2</sub>O). The values assigned to these bands were in accordance with the values reported in literature [8,9]. The complexation of vanadium(IV) with the ligand is confirmed by the disappearance of v(O-H) band in complexes occurring at 2874 cm<sup>-1</sup> which is a characteristic of carboxylic acid. The complexation of vanadium with oxygen donor ligand is also confirmed by the appearance of v(V-O) band in the range 591-560 cm<sup>-1</sup> and v(V=O) band in the range of 911-904 cm<sup>-1</sup>. The v(COO) stretching vibrations are significant in predicting the bonding mode of ligand. The fall of  $v_{asym}(COO)$  vs. the rise of  $v_{sym}(COO)$  for carboxylate group show the bidentate nature of ligand in the complexes.

The different  $\Delta v$  of  $v_{asym}(COO)$  and  $v_{sym}(COO)$  stretching values for complexes (1)-(3) which fall in the range 160-134 cm<sup>-1</sup> show that ligand acts as bidentate. The strong bands observed at 1750-1752 cm<sup>-1</sup> can be assigned to v(C=O) of other carboxylate groups in the ligand which remain practically unchanged after complexation. The overall infrared spectral evidence suggests that ligand acts as bidentate and

 Table 3. Vanadium Content for Oxovanadium(IV)

 Complexes of Cephradine

Compound	% V				
	calcd. (found)				
(1)	11.23 (11.29)				
(2)	6.79 (6.85)				
(3)	5.08 (5.02)				

coordinates through carboxylic oxygen atoms forming octahedral structure.

#### **ICP-AES**

The oxovanadium samples were digested with the help of nitric acid and perchloric acid and diluted with double-distilled water. Linear calibration method was used to quantify the results. An inductively coupled argon plasma atomic emission spectrometer (ICP-AES) was used for the determination of vanadium. The data for the compounds (1)-(3) are given in Table 3.

#### **Potentiometric Study**

The potentiometric titration curves for M/L ratios of 1:1, 1:2 and 1:3, at different temperatures, are given in Fig. 2. These figures shows that titration curves of VO(IV) complexes at different temperatures have less depression but more twist indicating low stability constants values with more species present at a time. The log $\beta$  values (Table 4) show that the order of the stability would be 1:1 > 1:3 > 1:2 M/L molar ratio.

In case of 1:1 and 1:3, the degree of hydrolysis is the same which implies that entropy should be the same. This is because in both reactions only one  $H^+$  is produced. According to equation (ii) and (iii), both types of mechanism are possible for 1:2 M/L ratio. Equation (ii) shows that entropy of 1:1 and 1:2 complexes should be the same but in case of second mechanism as given in equation (iii) entropy should be in negative value.

We can show the stability order as: 1:1 > 1:3 > 1:2

Stability of 1:3 is greater than that of 1:2 due to the removal of vanadyl oxygen during the formation of 6-coordinated complex with bidentate ligand. The pK value of the cephradine in the methanol/water solution is 8.79. The proposed structures of oxovanadium(IV) complexes in 1:1, 1:2 and 1:3 M/L ratios are given in Fig. 3.

#### Semi-Empirical Study

In complex (1) the cephradine ligands bind in bidentate [O,O] fashion. The terminal oxo ligand and additional water molecules complete the metal coordination sphere. In complex (2) the cephradine ligands bind in bis-bidentate [O,O] fashion and the axial positions are occupied by the oxo ligand and a trans-water molecule. Both the modeled structures (Figs. 4 and 5) show distorted octahedral geometry around vanadium. The apical vanadium oxygen distance of 1.548 Å in (1) and 1.551 Å in (2) are typical of V(IV)=O bond length. The V(IV)-Obond lengths for the coordinated water molecules in the equatorial plane in (1) are 2.149 Å and 2.240 Å, respectively. These values are close to the similar ranges of values in the literature [10]. The long V(IV)-O bond length in the axial position 2.56 Å in (1) and 2.65 Å in (2) may be due to the trans influence of the oxo group. The vanadium ion is 0.623 Å and 0.698 Å above the mean equatorial plane formed by the four oxygen atoms in (1) and (2), respectively. The bond lengths and bond angles for all non-hydrogen atoms are



**Fig. 2.** Potentiometric titration curves for 1:1 (1), 1:2 (2) and 1:3 (3) at 20 °C (A), 0 °C (B) and -10 °C (C).

Temperature (°C)	M/L Ratio	logβ	pqr <sup>a</sup>
	1:1	3.32	1,6,1
20	1:2	5.48	1,2,2
	1:3	7.67	1,0,3
	1:1	3.21	1,6,1
0	1:2	5.39	1,2,2
	1:3	7.50	1,0,3
	1:1	3.12	1,6,1
-10	1:2	5.29	1,2,2
	1:3	7.32	1,0,3

 Table 4. Stability
 Constants
 for
 VO(IV)-Cephradine

 Complexes at Different Temperatures

 ${}^{b}p$  = number of metal, q = number of hydrogen, r = number of ligand in the complex.



**Fig. 3.** Proposed structures of oxovanadium(IV) complexes in (a) 1:1, (b) 1:2 and (c) 1:3.



Fig. 4. Geometry Optimised Structure of V(IV)=O(H<sub>2</sub>O)<sub>3</sub> (Cephradine) (1).

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Fig. 5. Geometry Optimised Structure of V(IV)=O(H<sub>2</sub>O) (Cephradine)<sub>2</sub> (2).

tabulated in Tables 5-8, respectively.

### **Anti-Bacterial Screening Tests**

Anti-bacterial activity of compounds (1)-(3) was evaluated against six bacterial strains by agar well diffusion method [11]. All the tested complexes show significant anti-bacterial activity against the listed bacteria and the results are given in Table 9. Based on the results, all the tested compounds show significant activity especially against *Escherchia coli* and *Bacillus subtilis* and moderate activity against *Staphylococcus aureus* species.

## Anti-Fungal Screening Test

The antifungal tests were carried out by using agar tube dilution protocol method [11]. The antifungal results of the synthesized complexes are given in Table 10. All complexes showed significant antifungal activity against *Trichophyton longifusus, Candida albicans, Fusarium solani* and *Candida glaberata.* The complexes show moderate activity against *Microsporum canis.* 

# CONCLUSIONS

The elemental analyses showed a good agreement between

the calculated and observed values for C, H and N. Pka values were determined for 1:1, 1:2 and 1:3 M/L ratio at different temperatures, which showed that end points of the titration were sharp. The order of the stability was 1:1 > 1:3 > 1:2which is justified on the grounds of the proposed mechanism. IR data show that ciprofloxacine acts as bidentate ligand and 6-coordinated complexes are obtained for 1:1, 1:2 and 1:3 M/L ratios. In complex (1) the cephradine ligands bind in bidentate [O,O] fashion which, together with a terminal oxo ligand and water molecules, complete the metal coordination sphere, while in complex (2) the cephradine ligands bind in bisbidentate [O,O] fashion and the axial positions are occupied by the oxo ligand and a trans-water molecule. Biological activity data show that all the complexes are biologically active as compared to free ligand and can be used as drugs.

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			-	A tom 1	A tom?	Atom?	Bond angle
Atom1	Atom2	Bond length (°A)		Atom	Atom2	Atoms	(deg)
V1	02	2 195	-	C14	C15	C16	113.49
V 1	02	2.175		C15	C16	C17	123.23
02	C3	1.287		C17	C18	C20	113.77
C4	C3	1.483		C16	C17	C18	122.85
C4	N5	1.425		C18 C20	C20	C14 C15	123.17
N5	C6	1 /19/		C14	C14 C10	N11	112.68
07	60	1.474		C9	C10	N11	107.53
C/	Co	1.571		C9	C10	C14	112.76
C7	N8	1.441		N8	C9	O28	115.49
N8	C9	1.425		N8	C9	C10	118.37
C10	C9	1 537		CIU N8	• C9	C28	126.04
C10	27	1.405			C7 N8	C30	112.93
C10	NII	1.495	X	N8	C7	C6	118 51
C14	C10	1.517		C30	C7	C6	86.00
C14	C15	1 507		O31	C30	C7	138.39
015	010	1.501		<b>O</b> 31	C30	N5	130.79
C15	C16	1.501		C30	N5	C6	94.46
C16	C17	1.335		N5	C6	C7	88.40
C17	C18	1.499		C7	C30	N5	90.69
C20	C14	1340		S33	C6	C7	113.96
C20	014	1.340		N5	C6	S33	109.73
C18	C20	1.498		C6	S33	C34	98.02
C9	O28	1.212		333 C34	C34	C35	113.03
N5	C30	1 427		C35	C4	N5	122.87
C20	630	1.127		C4	N5	C6	123.32
C30	C/	1.574		C36	C35	C4	122.63
C30	O31	1.203		C36	C35	C34	114.46
C6	<b>S</b> 33	1.807		C35	C4	C3	123.49
622	C24	1 912		C4	N5	C30	129.77
333	C34	1.015		N5	C4	C3	113.18
C34	C35	1.492		C4	C3	043	121.83
C35	C36	1.486		C4	C3 C2	02	123.03
V1	043	2 145		043	U3 V1	02	60.20
V 1	045	2.145		043	V1 V1	044	108.03
C3	043	1.292		044	V1	051	106.03
V1	O44	1.548		051	V1	O48	67.99
V1	O45	2.561		O48	V1	O45	60.05
$\mathbf{V}^{1}$	049	2 240		O45	V1	O2	63.17
V I	048	2.240		V1	O43	C3	93.22
V1	O51	2.149		V1	O2	C3	91.07

 Table 5. Bond Lengths of V(IV)=O(H<sub>2</sub>O)<sub>3</sub> (Cephradine) (1)

 Table 6. Bond Angles of V(IV)=O(H<sub>2</sub>O)<sub>3</sub> (Cephradine) (1)

Atom1	Atom2	Bond length (°A)	Atom1	Atom2	Atom3	Bond angle
<u>C1</u>	N2	1 489	C26	C27	C22	123.15
N2	$C_3$	1 423	C27	C22	C23	122.56
C4	C3	1.496	C27	C22	C18	122.91
C4	05	1.275	C22	C18	N19	112.84
C4	06	1.284	C18	C22	C23	114.51
05	V7	2.278	N19	C18	C17	107.17
O6	V7	2.194	C18	C17	O36	124.89
V7	O8	1.551	O36	C17	N16	116.90
V7	O9	2.163	C18	C17	N16	118 12
O9	C10	1.285	C10 C17	N16	C15	124.78
V7	011	2.266	N16	C15	C13	118.07
C10	O11	1.277	C14	C15	C38	86.64
C12	C10	1.500	$C_{15}$	C38	N13	89 59
C12	N13	1.417	C19	N12	C14	01.10
N13	C14	1.490	C38	N15 C29	020	94.49
C15	C14	1.564		C38	039	137.04
C15	N16	1.446	039	C38	N13	132.63
N16	C17	1.410	N13	C14	S41	110.95
C18	C17	1.540	C14	541	C42	99.70
C18 C22	N19	1.494	N13	C12	C10	114.66
C22	C18 C22	1.517	C10	011	V7	88.25
C27	C22 C27	1.50/	09	C10	011	117.56
C20	C27	1.301	011	V7	08	110.15
C23	C20	1.557	08	V7	05	106.82
C24	C23	1 3 3 0	05	V7	06	58.54
C17	036	1.335	06	W7	087	85 45
N13	C38	1 447	087	V7 V7	00/	84 60
C15	C38	1.579	09	V7 V7	011	59.22
C38	039	1.186	05	C4	06	117.49
C14	S41	1.813	C4	C4 C3	C51	123 56
S41	C42	1.818	NO NO	C5	0%5	123.50
C43	C12	1.356	INZ NO	C60	085 C61	80.00
C42	C43	1.491	N2 C61	C00 N62	C01	09.99
C1	\$53	1.810	01	1102	005	125.25
C52	S53	1.815	N62	C63	082	116.51
C51	C56	1.490	C3	N2	C60	130.80
N2	C60	1.431	N2	C3	C4	113.19
C1	C61	1.566	C63	C64	C68	112.71
C61	N62	1.445	C68	C69	C70	113.48
N62	C63	1.412	C69	C70	C71	123.18
C63	C64	1.540	S53	C1	N2	109.93
C64	N65	1.494	S53	C1	C61	114.51
C63	O82	1.216	C3	C4	06	120.56
C60	085	1.195	V7	09	C10	92.65
V7	O87	2.651	011	C10	C12	122.19

 Table 7. Bond Length of V(IV)=O(H<sub>2</sub>O) (Cephradine)<sub>2</sub> (2)

Table 8. Bond Angles of  $V(IV)=O(H_2O)$  (Cephradine)<sub>2</sub>(2)

<b>Table 9.</b> Anti-Bacterial Activity <sup>a,t</sup>	<sup>°</sup> Data for	Vanadium(IV)	) Comple	exes of Cep	ohradine
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Name of bacteria	Zone of inhibition (mm)						
	HL	(1)	(2)	(3)	Standard drug		
Escherichia coli	0	25	25	25	30		
Bacillus subtilis	0	24	24	30	33		
Shigella flexenari	0	24	24	25	27		
Staphylococcus aureus	0	25	25	25	33		
Pseudomonas aeruginosa	0	20	20	25	24		
Salmonella typhi	0	20	20	25	25		

<sup>a</sup>Standard drug; Imipenum = 10  $\mu$ g disc<sup>-1</sup>. <sup>b</sup>Concentration of sample = 3 mg ml<sup>-1</sup> of DMSO.

Table 10. Anti-Fungal Activity<sup>a-d</sup> Data for Vanadium(IV) Complexes of Cephradine

Name of fungus %Inhibition				Standard drug	Percent inhibition	MIC	
	HL	(1)	(2)	(3)			$(\mu g m l^{-1})$
Trichophyton longifusus	0	40	40	45	Miconazole	100	70
Candida albicans	0	60	40	60	Miconazole	100	110.8
Aspergillus flavus	0	40	40	30	Amphotericum B	100	20
Microsporum canis	0	60	50	40	Miconazole	100	98.4
Fusarium solani	0	55	60	30	Miconazole	100	73.25
Candida glaberata	0	65	60	65	Miconazole	100	110.8

<sup>a</sup>concentration of sample 200  $\mu$ g ml<sup>-1</sup> of DMSO. <sup>b</sup>Incubation period 7 days. <sup>c</sup>Incubation temp. 27 °C. <sup>d</sup>MIC = Minimum inhibitory concentration.

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