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Difluorovanadium(IV) Dicarboxylates: Coordination Behavior and Biological Activity[1]

R. Ashraf[a], S. Shahzadi[a], S. Ali[a], M. H. Bhatti[b], S. Yaqub[a], and F. Ahmad[c]

[a] *Department of Chemistry, Quaid-i-Azam University, 45320-Islamabad, Pakistan*
[b] *Department of Chemistry, Allama Iqbal Open University, H / 8 Islamabad, Pakistan*
[c] *NESCOM, Islamabad, Pakistan*
E-mail: drsa54@yahoo.com

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Abstract—Different vanadium(IV) complexes of general formula VF_2L_2 have been synthesized, where L are various nonsteroidal antiinflammatory drugs. The complexes are characterized by elemental analysis, UV-visible, and infrared spectroscopy. The metal contents estimated by the ICP-AES method in the synthesized complexes are in good agreement with their calculated values and spectroscopic data proposed the octahedral geometry for the reported complexes. Conductance measurements show the nonelectrolytic nature of complexes. Biological screening tests against different bacteria and fungi show significant antibacterial and antifungal activity for all the complexes.

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Recently, vanadium and its compounds came to focus in many areas including the medical and biological sciences due to their discovered biochemical activity [1, 2]. Vanadium in its oxidation state +4 is able to interact with metal ion binders of biological system containing negatively charged oxygen donors, such as phenolates, phosphates, and carboxylates [3, 4].

Nonsteroidal anti-inflammatory drugs (**NSAIDS**) are medications having pain relieving, as well as, the effect of reducing inflammation when used over a period of time. The major clinical application is their action as anti-inflammatory agents in muscle skeletal diseases [5]. It is well known that most of anti-inflammatory drugs are carboxylic acids in which the carboxylate group is available for metal ligand interaction [6]. Mefenamic acid (2-[(2,3-dimethylphenyl)amino]benzoic acid), ketoprofen (2-(3-benzoylphenyl)propionoic acid), flurbiprofen (2-(2-fluro-4-biphenyl)propanoic acid), pefloxacin (l-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinoline), ibuprofen (2-(4-isobutylphenyl)propanoic acid), cetrizine dihydrogenchloride (2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy acetic acid), diclofenac acid (2-[(2,6-dichlorophenylamino)phenyl]ethanoic acid), and warfarin acid (4-oxo-3-(oxo-1-phenylbutyl)2H-1-benzopyran-2-one) are different nonsteroidal antiinflammatory drugs. Several transition metal complexes with NSAIDS have extensively been studied. Vanadium forms complexes with NSAIDS that are more effective in their biological activity as compared to its parent ligand [7]. The vanadium complexes have potential antitumor activity. The vanadium complexes are also used as anti diabetic and anticarcinogenic agents. Among the complexes of vanadium in the oxidation state +4, and mostly the oxovanadium complexes with NSAIDS were reported and found to be successful antidiabetic agents, and show other biological activities [8]. In the present investigation, we describe the synthesis and characterization of some new complexes of vanadium(IV) with NSAIDs taking vanadium(IV) fluoride as a precursor. Moreover, the antibacterial and antifungal activity of these complexes were also checked.

EXPERIMENTAL

Materials and instrumentation. All the reagents and solvents were commercially available (highest grade) and used without further purification. Vanadium tetrafluoride was purchased from Aldrich. Mefenamic acid was kindly supplied by the Ferozsons Laboratories Ltd. (Nowshera, Pakistan), while diclofenac sodium was given by Wilson Pharmaceuticals (Islamabad). Pefloxacin, cetrizine dihydrogenchloride and warfarin sodium were kindly supplied by Shaigan Pharmaceuticals (Pvt.) (Rawalpindi). Flurbiprofen was donated by Upjohn Pakistan (Pvt.) Ltd. (Islamabad). Ketoprofen and ibuprofen were supplied by Werrick Pharmaceuticals (Islamabad).

Melting points were determined in a capillary tube on an electrothermal melting point apparatus (model

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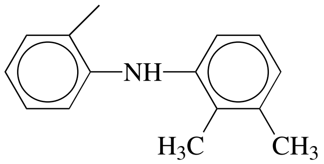
[1] The article was submitted by the authors in English.

Sanyo Gallen Kamp MPD-350 BM 3.5) and were uncorrected. UV-visible spectra were recorded on a UV-visible spectrophotometer (Shimadzu, model TCC-240A). Infrared spectra were recorded in a range of 4000–400 cm^{-1} as KBr pellets and as thin film on a Bio-Red Elmer 16 FPC FTIR spectrophotometer. Conductance measurements were made using an EC meter (model Cyber Scan 500).

General procedure for the synthesis of the vanadium(IV) complexes. Method 1. A solution of a drug (2 mmol) in 50 ml of methanol was prepared and placed in a 250-ml two-necked round-bottom flask equipped with a water condenser, a magnetic stirrer, and a hot plate. Then, vanadium tetrafluoride (1 mmol) dissolved in 25 ml of methanol was added into the reaction flask dropwise with constant stirring. The reaction mixture had pH 3. The resulting mixture was refluxed for 2 h and kept overnight with stirring at room temperature. The solvent was removed on a rotary apparatus under reduced pressure. The solid product was recrystallized in a methanol-*n*-hexane (1 : 1) mixture. The general chemical reaction is given below:

$$VF_4 + 2RCOOH \xrightarrow[\substack{\text{(ii) Reflux for 2 h;} \\ \text{(iii) Overnight stirring}}]{\text{(i) Dry methanol;}} V(RCOO)_2F_2,$$

where R = R^1–R^6.



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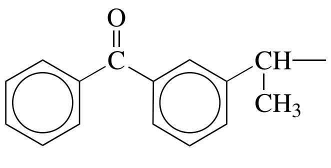

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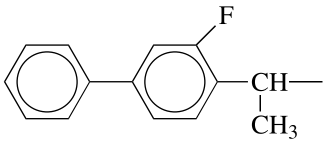

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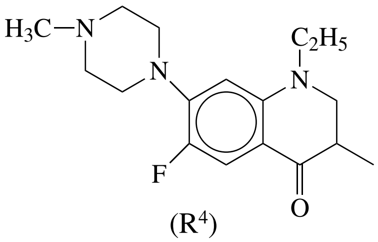

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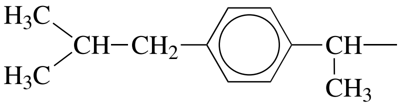
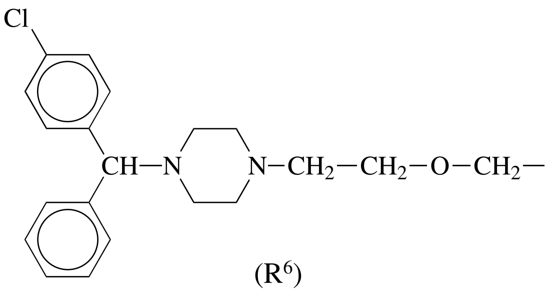


(R^5)



(R^6)

Method 2. Ligands in the form of sodium salt were converted to the corresponding acid by dissolving them in distilled water, and concentrated HCl was added dropwise. White precipitates obtained were washed with distilled water, in dried air, and checked for the melting point. The complexes were synthesized by the method mentioned above. The general chemical reactions are given below:

$$RCOONa + H_2O \xrightarrow{HCl_{conc}} RCOOH + NaCl,$$

$$RNa + H_2O \xrightarrow{HCl_{conc}} ROH + NaCl,$$

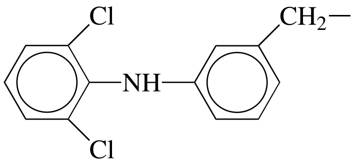
where R = R^7, R^8.

Table 1. The elemental analysis data and some physical properties of the vanadium(IV) complexes

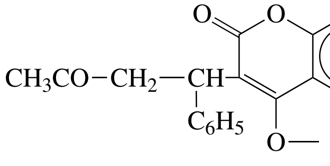
Compound	Empirical formula	Mol. weight	Yield, %	M.p., °C	Ω_M, Ohm^{-1} cm^2 mol^{-1}	Contents (calcd/found), %			
						C	H	N	V**
I	$VF_2C_{30}H_{28}O_4N_2$	569	70	226–8	0.049	63.2/63.4	4.9/4.7	4.9/5.0	8.95/8.63
II	$VF_2C_{32}H_{26}O_6$	595	72	*	0.045	64.5/64.1	4.3/4.8		
III	$VF_4C_{30}H_{24}O_4$	575	75	94–6	0.015	62.6/62.1	4.1/4.6		8.60/8.37
IV	$VF_4C_{34}H_{38}O_6N_6$	753	76	224–6	0.262	54.1/53.9	5.0/5.8	11.1/11.7	6.78/6.39
V	$VF_2C_{26}H_{34}O_4$	499	80	86–8	0.052	62.5/62.9	6.8/6.1		10.20/10.41
VI	$VF_2C_{42}H_{52}O_6N_4Cl_6$	1010	82	142–6	0.082	49.9/50.4	5.1/4.8	5.5/5.9	
VII	$VF_2C_{28}H_{20}O_4N_2Cl_4$	679	75	162–6	0.199	49.4/49.8	2.9/3.1	4.1/4.5	8.38/8.53
VIII	$VF_2C_{38}H_{30}O_8$	703	77	170	0.043	64.8/64.1	4.2/4.9		7.25/7.99

Notes: * Gel-like state.

** The estimation of vanadium was done by using atomic emission spectroscopy (ICP–AES).



(R^7)



(R^8)

RESULTS AND DISCUSSION

Physical properties. The reaction of vanadium(IV) fluoride with nonsteroidal antiinflammatory drugs in dry methanol at pH 3 resulted in the formation of complexes of general formula VF_2L_2 (where L are L^1–L^8 in complexes **I–VIII**, respectively). The synthesized complexes were in the crystalline solid/gel-like state, green-colored, and fairly stable at room temperature. They show good solubility in common organic solvents. The molar conductance values of all the synthesized complexes determined in methanol at room temperature suggest the nonelectrolytic nature of the complexes. The elemental analysis data and some physical properties of vanadium(IV) complexes are given in Table 1.

The UV-visible spectra for all the synthesized complexes were recorded in methanol and are shown in Table 2. The vanadium(IV) complexes generally exhibit three bands due to *d–d* transitions. These bands are not well developed. It seems more probable that the first two transitions lie under the envelope of the band I [9]. Band III is not observed but is thought to be buried beneath the low-energy tail of the strongly intense charge-transfer band [10], and when it is observed that it is generally a shoulder, so that its maximum position is known with least accuracy [11]. All other bands above 30000 cm^{-1} are charge-transfer in origin.

The assignments of electronic absorption spectral bands of the vanadium(IV) complexes were a matter of controversy [12, 13]. According to ordering of the energy levels (Ballhausen and Gray scheme), band I in a range of 11737–13003 cm^{-1} results from the $B_2 \longrightarrow E$ transition. Band II in a range of 16556–17730 cm^{-1} is assigned to the $B_2 \longrightarrow B_1$ transition, and band III in a range of 25062–28490 cm^{-1} is attributed to the $B_2 \longrightarrow A_1$ transition. The shift of the $B_2 \longrightarrow E$ and $B_2 \longrightarrow B_1$ bands to the red and blue regions, respectively, compared with that of VF_4, agrees with carboxylate coordination to the metal center [14, 15]. Other bands above 30000 cm^{-1} are charge-transfer in origin.

Infrared spectroscopy. The most important features of the infrared spectra of the complexes and corresponding free ligands are shown in Table 3. The presence of various ring vibrations and C–H absorption makes the spectra fairly complicated for complete assignments of individual bands. The important absorption frequencies are ν(O–H), ν(N–H), ν(C=O), ν_{as}(COO), ν_s(COO), ν(V–O), and ν(V–F). The values assigned to these bands are in accordance with the values reported in literature [16, 17]. The complexation of vanadium(IV) fluoride with the ligands is confirmed by the disappearance of the ν(O–H) band in the spectra of the complexes occurring at 3440–3405 cm^{-1}, which is characteristic of carboxylic acids. The complexation of vanadium with an oxygen donor ligand is also confirmed by the appearance of the ν(V–O) band in the range 595–504 cm^{-1}. The ν(V–F) band appeared in the range 484–400 cm^{-1}. The ν(COO) stretching vibrations are important to predict the bonding mode of the ligand. The peak for ν(COO) in the region 1741–1630 cm^{-1} for carboxylic acids was shifted to lower-frequency side showing complexation. The lowering of ν_{as}(COO) and rise of ν_s(COO) for the carboxylate group show the

Table 2. UV-visible spectral data for the vanadium(IV) complexes

Compound	Absorption bands (ν, cm^{-1})			
	band I $^2E \leftarrow {}^2B_2$	band II $^2B_1 \leftarrow {}^2B_2$	band III $^2A_1 \leftarrow {}^2B_2$	charge-transfer bands
I	12484	16752	28490	35842 44943
II	12658	17530	27777	41841 47619
III	12468			33557 39215
IV	11737	16778	27777	35842 45454
V	12391	16750	27777	36764 45454
VI	13003		25510	36630 42553
VII	12269	17730	27777	35842 45454
VIII	12556	16556	25062	35211 43859

bidentate nature of the ligand in the complexes [18]. The difference $\Delta\nu$ of ν_{as}(COO) and ν_s(COO) stretching values for complexes **I–VII** fall in the range 204–130 cm^{-1} and shows that the ligands is bidentate. The strong bands observed at 1707–1730 cm^{-1} can be assigned to ν(C=O) of other than carboxylate group ligands L^2, L^4, and L^8, which remains practically unchanged after complexation. The overall IR spectral evidence suggests that all the ligands act as bidentate and are coordinated through the carboxylic oxygen atoms, forming an octahedral structure.

Thermal analyses data confirms the bidentate nature of ligand in vanadium(IV) complexes in solid state too. The thermocomposition data can be directly received at author Saqip Ali–e-mail: drsa54@yahoo.com

Biological activity. All the synthesized complexes were estimated for their microbial toxicity against a set of bacterial and fungal strains. The antibacterial activity of the complexes was tested using the agar well-diffusion method [19], and the results are given in Table 4. The results show that all the complexes have significant antibacterial activity.

The antifungal tests were carried out by using the agar tube dilution protocol method [20]. The antifungal results of the synthesized complexes are given in Table 5. All the complexes showed significant antifungal activity against *Trichophyton longifusus*, *Candida albicans*, *Fusarium solani* and *Candida glaberata*. The complexes show moderate activity against *Microsporum canis*. All the complexes are inactive against *Aspergillus flavus*.

Table 3. Infrared spectral data (cm^{-1}) for ligands and their vanadium(IV) complexes

Compound	ν(O–H)	ν(N–H)	ν(COO)		$\Delta\nu$	ν(V–O)	ν(V–F)	ν(C=O)
			asym.	*sym.*				
L^1	3415	3313	1652	1329	323			
I		3310	1577	1385	192	569	475	
L^2	3439		1697	1379	318			1730
II			1653	1449	204	595	484	1723
L^3	3405		1702	1383	319			
III			1692	1478	130	575	471	
L^4	3440		1630	1269	361			1717
IV			1577	1385	192	528	463	1715
L^5	3426		1719	1420	299			
V			1710	1510	200	586	421	
L^6	3415		1741	1434	307			
VI			1624	1425	199	510	476	
L^7	3415	3324	1724	1420	304			
VII		3324	1693	1504	189	580	400	
L^8	3415							1707
VIII						504	441	1707

Table 4. Antibacterial activity data for vanadium(IV) complexes

Name of bacteria*	Zone of inhibition, mm								
	I	II	III	IV	V	VI	VII	VIII	standard drug**
Escherichia coli	30	25	25	25	25	25	18	20	30
Bacillus subtilis	28	24	24	30	25	25	15	20	33
Shigella flexenari	25	24	24	25	20	25	20	20	27
Staphylococcus aureus	25	25	25	25	20	22	20	18	33
Pseudomonas aeruginosa	10	20	20	25	20	20	20	22	24
Salmonella typhi	20	20	20	25	20	15	20	20	25

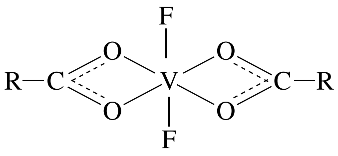
Notes: * Concentration of sample is 3 mg/ml of DMSO.
** Imipenum is 10 μg/disc.

Table 5. Antifungal activity*,** data for the vanadium(IV) complexes

Name of fungus	Inhibition, %									
	I	II	III	IV	V	VI	VII	VIII	standard drug	MIC***, μg/ml
Trichophyton longifusus	40	40	45	35	35	65	40	70	Miconazole	70
Candida albicans	60	40	60	75	75	75	75	75	Miconazole	110.8
Aspergillus flavus	0	0	0	0	0	0	0	0	Amphotericum B	20
Microsporum canis	60	0	40	0	0	0	0	30	Miconazole	98.4
Fusarium solani	55	0	30	40	40	50	40	50	Miconazole	73.25
Candida glaberata	65	60	65	60	75	70	75	75	Miconazole	110.8

Notes: * Incubation period 7 days.
** Incubation temp. 27°C.
*** Concentration of sample 200 μg/ml of DMSO.

So by interpreting the spectroscopic results, we proposed the octahedral geometry for synthesized complexes **I–VIII**:



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