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Synthesis and characterization of some vanadyl complexes with flavonoid derivatives as potential insulin-mimetic agents

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Abstract Two new complexes with formula $VOL_2 \cdot nH_2O$ ((**1**) L: 4′,5,7-trihydroxyflavone-7-rhamnoglucoside (naringin), $n = 8$; (**2**) L: 3′,4′,7-tris[*O*-(2-hydroxyethyl)]rutin (troxerutin), $n = 0$) were synthesised and characterised. The IR and UV–Vis spectral data indicate that these flavones act as bidentate chelating ligands and generate VO(II) complexes with a square-pyramidal stereochemistry. The thermal analysis (TG, DTA) elucidated the composition and also the number and nature of the water molecules. The thermal behavior indicates also a strong interaction between oxovanadium (IV) and these oxygen donor ligands.

Keywords Naringin · Vanadyl(IV) complex · Troxerutin · Thermal stability

Introduction

Nowadays many studies concerning vanadium complexes are directed through discovery of new species able either activates the insulin or even supply the insulin in human metabolism [1]. The problems that should be solved in this field are the balance the hydrophilicity with lipophilicity as well as the toxicity reducing. The lipophilicity can be enhanced both for V(V) and VO(II) by using anionic chelating ligands that can generate neutral complexes. As result of chelate ring formation the complex stability is raised and the rate of metabolisation is slower leading thus to a lower toxicity. Having in view these requirements many vanadium compounds with a broad variety of organic derivatives have been studied and demonstrated antidiabetic properties, some of them being in the same time orally active [2–11].

On the other hand, the complexes toxicity can be controlled by using naturally occurring ligands such as flavonoid derivatives. Besides having chelate ability the bioflavonoids demonstrated so far a large spectrum of biological activities such as anti-inflammatory [12, 13] antitumor [14–19], and anti-infectious, respectively, [20–23]. For troxerutin, a derivative used clinically for treating venous disorder, it was evidenced also the ability to protect biomembranes and DNA of normal tissue against the deleterious effect of γ-radiation [24]. On the other hand, naringin showed hypoglycemic effect by reducing the activity of some enzymes involved in glucose metabolism [25]. More over some complexes with such ligands were evaluated for their insulin-mimetic activities [26, 27]. Our group have been succeeded also in synthesis and characterisation of some VO(II) complexes with flavonoid derivatives such as fisetin, quercetin, and morin. It was shown also that these derivatives display an interesting thermal behaviour [28].

Having in view these aspects, new complexes of the type $VOL_2 \cdot nH_2O$ with other flavonoid derivatives (naringin and troxerutin) were synthesised and characterised by elemental analysis as well as UV–IR and UV–Vis data.

In addition to flavonoid nucleus (Fig. 1a), the 4′,5,7-trihydroxyflavone-7-rhamnoglucoside (naringin) contains a hydroxyl group at C_5 and a rhamnoglucoside group at C_7 (Fig. 1b). The other ligand 3′,4′,7-tris[*O*-(2-hydroxyethyl)]rutin (troxerutin) is a rutin derivative (Fig. 1c).

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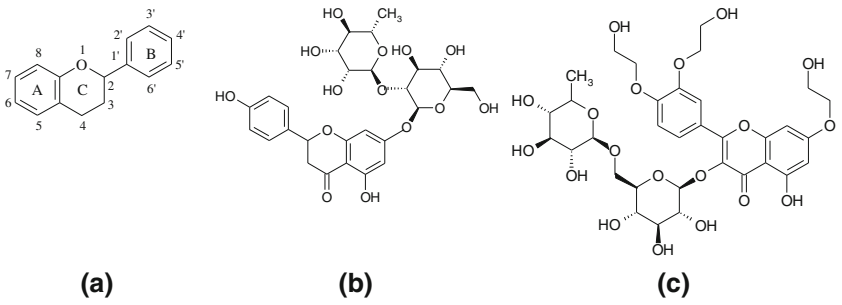


Fig. 1 **a** Base structure of flavonoids; **b** Structure of naringin; **c** Structure of troxerutin

Both molecules possess chelating properties due the 5-hydroxy and the 4-carbonyl groups in the C ring. This chelating ability of naringin was otherwise evidenced in solution toward Fe(III) [29]. Furthermore some Cu(II) complexes with naringin showed higher antioxidant, anti-inflammatory and antitumor activities [30] as well as antioxidative properties [31].

Considering the low solubility in water of complexes, developing proper drug delivery systems requires the thermal analysis among others [32]. As result, the thermal analysis (TG and DTA) of the complexes was performed in order to establish the thermal stability of these compounds that showed also insulin-mimetic properties. The thermal curves elucidated also the composition and the number and nature of the water molecules.

Experimental

Materials and methods

All chemicals were purchased from Sigma-Aldrich or Acros Organics, reagent grade and were used without further purification.

The chemical analyses were performed on a Perkin Elmer PE 2400 analyzer (for C, H, N) and a Shimadzu AA 6300 spectrometer (for V).

IR spectra were recorded in KBr pellets with a FT-IR VERTEX 70 (Bruker) spectrometer in the range 400–4000 cm^{-1}.

Electronic spectra by diffuse reflectance technique, with Spectralon as standard, were recorded in the range 200–1000 nm, on a Jasco V 670 spectrophotometer.

The heating curves (TG and DTA) were recorded using a Labsys 1200 SETARAM instrument, with a sample mass of 14–15 mg over the temperature range of 30–900 °C, using a heating rate of 10 K/min. The measurements were carried out in synthetic air atmosphere (flow rate 16.66 mL^3/min) by using alumina crucibles.

The X-ray powder diffraction patterns were collected on a DRON-3 diffractometer with a nickel filtered Cu K_α radiation ($\lambda = 1.5418$ Å) in a 2(range of 5–70°, a step width of 0.05° and an acquisition time of 2 s on each step.

Synthesis of the complexes and spectral data

*Synthesis of VO(naringin)$_2$(H_2O)$_8$ (**1**)*

A saturated solution of $VOSO_4 \cdot 5H_2O$ (2 mmoles) was drop wise added to a solution of naringin·$2H_2O$ (4 mmoles) in 50 cm^3 of water containing few NaOH pellets (pH = 8). The pH was adjusted to ~6 with H_2SO_4 1 M and the reaction mixture was stirred at room temperature for 0.5 h until a green-yellowish sparingly soluble microcrystalline compound was formed. This product was filtered off through a fritted glass funnel, washed several times with water, methanol, ethanol, and air dried. Analysis, found: V, 3.48; C, 47.26; H, 5.78%; calculated for $VC_{54}H_{78}O_{37}$: V, 3.72; C, 47.34; H, 5.74%.

*Synthesis of VO(troxerutin)$_2$ (**2**)*

To a solution obtained by dissolving $VOSO_4 \cdot 5H_2O$ (1 mmole) in 50 mL methanol was added in small portion 2 mmoles of troxerutin. Green microcrystals were obtained by slow evaporation of this solution at room temperature after few days. This product was filtered off through a fritted glass funnel, washed several times with water and dried in desiccator over $CaCl_2$. Analysis, found: V, 3.13; C, 51.04; H, 5.35%; calculated for $VC_{66}H_{82}O_{39}$: V, 3.29; C, 51.13; H, 5.33%.

Results and discussion

Physico-chemical characterization of complexes

In this paper, we report the preparation and physico-chemical characterisation of some complexes with flavonoid derivatives as 4',5,7-trihydroxyflavone-7-rhamnoglucoside (naringin) and 3′,4′,7-tris[O-(2-hydroxyethyl)]rutin (troxerutin) (Fig. 1).

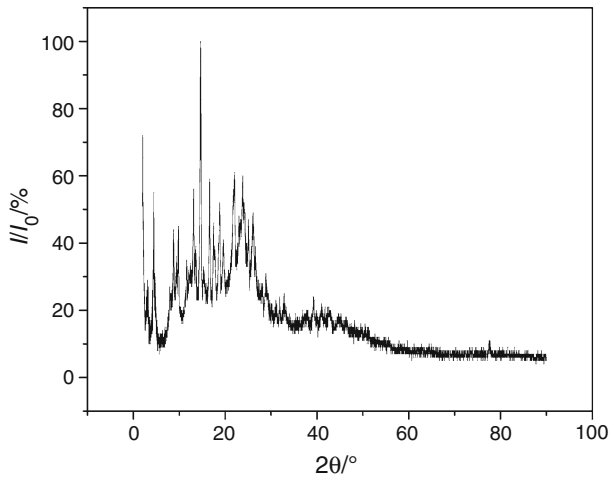


Fig. 2 Diffractogram pattern of $VO(C_{27}H_{31}O_{14})_2(H_2O)_8$ (**1**)

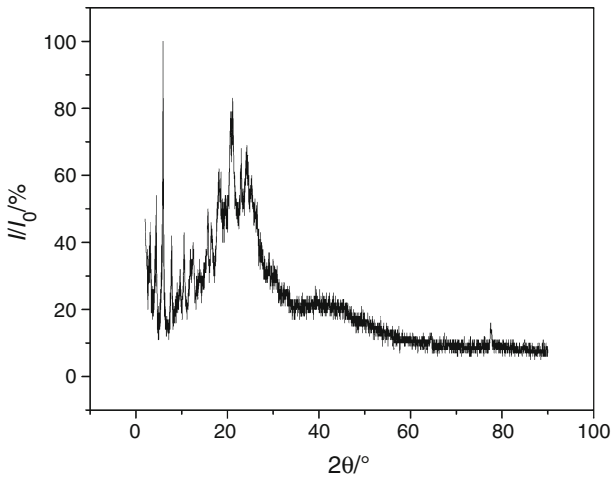


Fig. 3 Diffractogram pattern of $VO(C_{33}H_{41}O_{19})_2$ (**2**)

The major goal of this article was to evidence the thermal behaviour of complexes isolated from the reactions of these flavonoids with $VO(SO_4)\cdot 5H_2O$. The complexes have been formulated on the basis of chemical analysis, IR, and electronic spectra as follows:

$$VO(C_{27}H_{31}O_{14})_2(H_2O)_8 \quad (1)$$

$$VO(C_{33}H_{41}O_{19})_2 \quad (2)$$

The X-ray powder diffraction patterns for the new microcrystalline complexes are shown in Figs. 2 and 3. The *d* values and the relative intensity of peaks are summarized in Table 1.

The IR spectra of the complexes (Figs. 4, 5) exhibit the characteristic patterns of flavonoids (Table 2).

In the complexes spectra the bands assigned to the carbonyl group are shifted to lower wavenumbers in

Table 1 X-ray diffraction data for complexes

Compound	*d*/Å	I/I_0/%
$VO(C_{27}H_{31}O_{14})_2(H_2O)_8$	20.298	55
	10.051	44
	8.990	45
	6.701	57
	6.021	100
	5.336	59
	4.691	52
	4.059	61
	3.743	60
	3.388	49
	2.299	24
$VO(C_{33}H_{41}O_{19})_2$	28.660	46
	20.296	54
	15.120	100
	11.441	42
	8.450	44
	7.025	40
	5.625	50
	4.799	61
	4.185	83
	3.878	68
	3.677	69

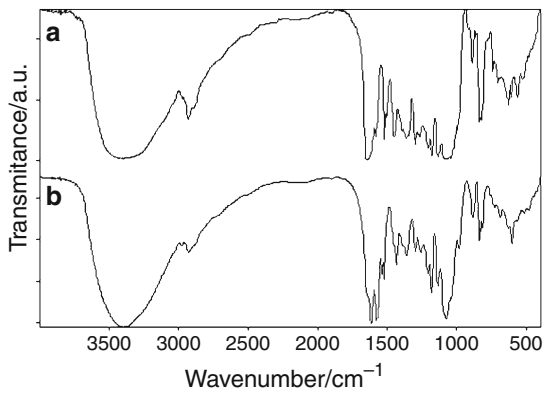


Fig. 4 IR spectra of naringin (*a*) and $VO(naringin)_2(H_2O)_8$ (*b*)

comparison with that of the free ligand as result of its coordination. Furthermore the additional bands around 980 cm^{-1} for both complexes can be assigned to the ν(V=O) stretching mode [33].

The electronic spectra of complexes (Fig. 6) display the absorptions in range 660–870 and about 570 nm that can be assigned to the spin allowed $^2B_2 \rightarrow {}^2E$, and $^2B_2 \rightarrow {}^2B_1$ transitions for VO(II) in a square pyramidal stereochemistry [34]. Furthermore, the shoulder about 420 nm can be

Table 2 Selected absorption maxima (cm^{-1}) for naringin, troxerutin and complexes

Naringin	(**1**)	Troxerutin	(**2**)	Assignments
3400vs, br	3400vs, br	3400vs, br	3390vs, br	$\nu(H_2O) + \nu(OH)_{phenol}$
1645vs	1614vs	1655s	1627s	ν(C=O)
1581s	1576s	1598s	1590s	ν(C=C)
1363m	1362m	1348m	1350m	ν(C–OH)
1264m	1256m	1273m	1267m	ν(C–O–C)
–	986m	–	980m	ν(V=O)

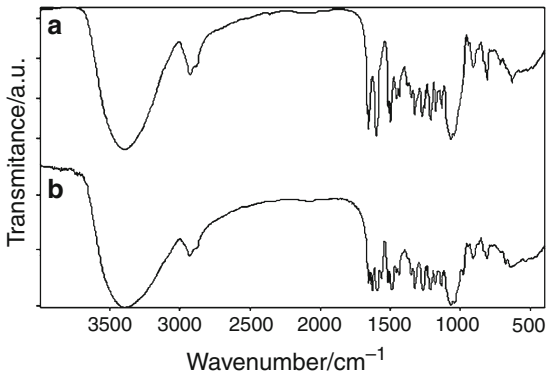


Fig. 5 IR spectra troxerutin (*a*) and VO(troxerutin)$_2$ (*b*)

assigned to the ligand-to-metal charge transfer (LMCT) transition (Table 3).

On the basis of above data, the proposed coordination for the complexes is as it follows (Fig. 7):

Thermal behavior of complexes

The results concerning the thermal behaviour of the new complexes are presented as it follows.

Thermal decomposition of $VO(C_{27}H_{31}O_{14})_2(H_2O)_8$

The TG and DTA curves corresponding to the complex (**1**) heated in the 30–900 °C temperature range are presented in Fig. 8.

The thermal decomposition of $VO(C_{27}H_{31}O_{14})_2(H_2O)_8$ (**1**) occurs in three, well-defined steps (Table 4). The first step, endothermic one, corresponds to the loss of all water molecules. The reaction proceeds with a maximum rate at 106 °C. The low temperature range corresponding to this transformation indicates the presence of crystallisation water [35–38]. The anhydrous compound suffers then a phase transition accompanied by a weak endothermic effect at 176 °C. that can be assigned to the conformational change from chair to boat of glycosidic moiety. Furthermore this species is stable over a large temperature range (155–208 °C), which demonstrates a great stability of compound. This stability can be correlated with the chelate ring as well as the strong interaction between the VO(II) (hard acid) and ligands with oxygen donor atoms (hard bases). This anhydrous species decomposes after 208 °C, the mass loss corresponds to the glycoside moiety oxidative degradation. This step is a complex one being an overlapping of at least two oxidative processes as both TG and DTA indicate.

The third step, an exothermic one, corresponds to the oxidative degradation of the remaining organic component.

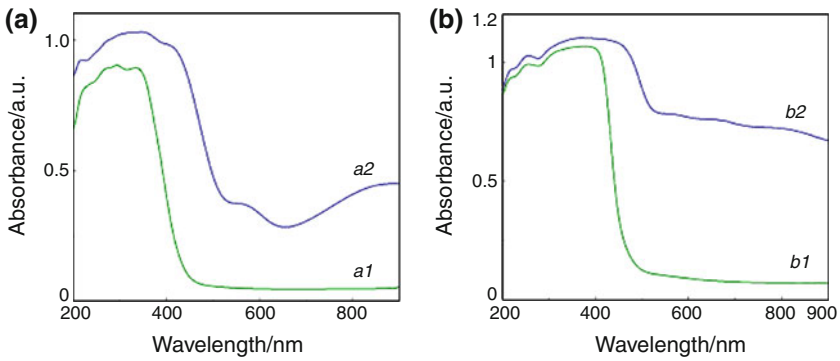
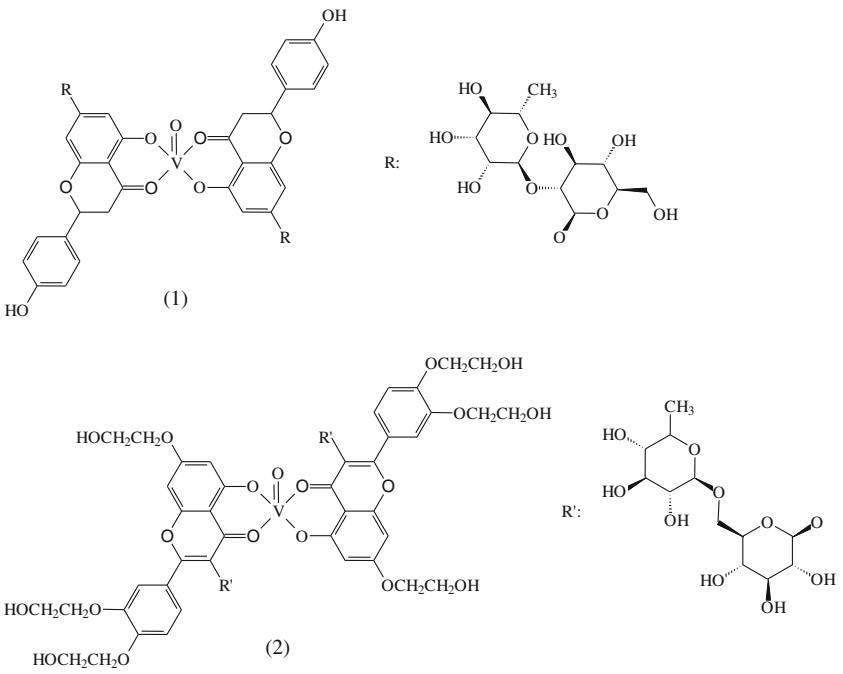


Fig. 6 *a* UV–Vis spectra of naringin (*a1*) and VO(naringin)$_2$(H$_2$O)$_8$ (*a2*) and *b* troxerutin (b1) and VO(troxerutin)$_2$ (*b2*)

Table 3 Electronic data for complexes (nm)

Complex	Band I $^2B_2$ (d_{xy}) → ^2E (d_{xz}, d_{yz})	Band II $^2B_2$ (d_{xy}) → $^2B_1$ (dx^2-y^2)	Band III $^2B_2$ (d_{xy}) → $^2A_1$(dz^2)
(**1**)	869	564	410
(**2**)	765, 659	569	422

Fig. 7 The proposed coordination for complexes



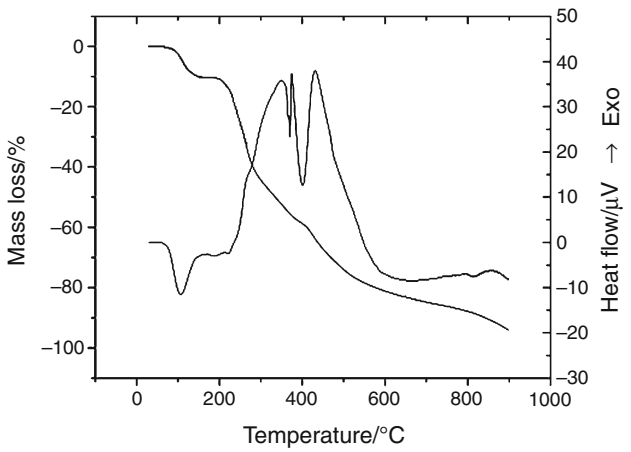


Fig. 8 TG and DTA curves of $VO(C_{27}H_{31}O_{14})_2(H_2O)_8$

The final product is shcherbinaite modifications of V_2O_5 as powder XRD reveals (ASTM 41-1426) (found/calcd. overall mass loss: 93.9/93.9).

Thermal decomposition of $VO(C_{33}H_{41}O_{19})_2$

The first step for complex $VO(C_{33}H_{41}O_{19})_2$ (**2**) corresponds most probably to the six acetaldehyde molecules elimination in an endothermic process (Fig. 9; Table 4).

The second step, which is exothermic, corresponds to oxidative degradation of glycoside moiety oxidative degradation. This step consists in at least three processes according to DTA curve profile. The third step corresponds to the oxidative degradation of the remaining intermediate that leads also to the shcherbinaite modifications of V_2O_5 as final product (found/calcd. overall mass loss: 94.5/94.5).

Table 4 Thermal behaviour data (in air atmosphere) for the complexes

Complex	Step	Thermal effect	Temperature interval/°C	Δm_{exp}/%	Δm_{calc}/%
$VO(C_{27}H_{31}O_{14})_2(H_2O)_8$ (**1**)	1	Endothermic	65–155	10.4	10.5
	2	Endothermic	176	0	0
	3	Exothermic	208–398	47.4	47.3
	4	Exothermic	398–900	36.1	36.1
	Residue (V_2O_5)			6.1	6.1
$VO(C_{33}H_{41}O_{19})_2$ (**2**)	1	Endothermic	60–180	16.9	17.0
	2	Exothermic	180–380	39.8	39.7
	3	Exothermic	380–900	37.8	37.8
	Residue (V_2O_5)			5.5	5.5

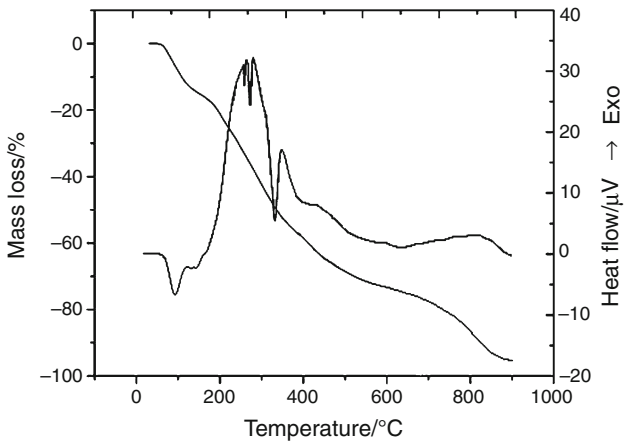


Fig. 9 TG and DTA curves of $VO(C_{33}H_{41}O_{19})_2$

Conclusions

The new complexes of oxovanadium (IV) with flavonoids that belong to a class of coordination compounds of current interest for their biologic activity have been synthesised and characterised. Spectral data indicate a square pyramidal stereochemistry for complexes and a chelate coordination mode for flavonoid molecules.

Thermal analysis (TG, DTA) of these complexes confirms the complexes composition and allows the number and nature of the water molecules determination. It was also evidenced intermediate steps corresponding to the glycoside moiety oxidative degradation. The residue was in all cases shcherbinaite modifications of V_2O_5 as powder X-ray diffraction indicated.

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