J Therm Anal Calorim (2010) 99:823–827
DOI 10.1007/s10973-009-0387-7

Thermal stability of new vanadyl complexes with flavonoid derivatives as potential insulin-mimetic agents

Mihaela Badea · Rodica Olar · Dana Marinescu ·
Valentina Uivarosi · Victoria Aldea ·
Teodor Octavian Nicolescu

MEDICTA2009 Conference

A series of new complexes of the type $VO(OH)L{\cdot}nH_2O$ ((**1**) L: fisetin, $n = 3$; (**2**) L: quercetin, $n = 2$; (**3**) L: morin, $n = 4$) were synthesised and characterised by analytical as well as IR and electronic data. The modification evidenced in IR spectra was correlated with the presence of flavonoid as bidentate in all complexes. The electronic reflectance spectra showed the *d–d* transition characteristic for the square-pyramidal stereochemistry of vanadium (IV) ion. The thermal analysis (TG, DTA) in synthetic air flow elucidated the composition and also the number and nature of the water molecules. The TG curves show three well-separated thermal events. The first corresponds to the water loss at lower temperatures, which is followed by flavonoid derivative decomposition and pyrolysis at higher temperatures. The final product is vanadium (V) oxide.

Keywords Flavonoid derivative · Vanadyl(IV) complex · Thermal stability

Introduction

A broad variety of vanadium compounds with organic ligands have been evaluated for their insulin-mimetic [1–5] and antitumoral activity [6–11]. Vanadium absorption in the gastro-intestinal tract can be improved and their toxicity reduced by incorporating the oxovanadium (IV) ion into chelating systems. Such systems could be generated by natural flavonoids, polyphenolic compounds that have many biological activities: antioxidant anti-cancer, anti-inflammation, antiviral, anti-allergic and anti-osteoporosis activities [12–16]. Metal complexes of naturally occurring flavonoids were investigated also for their antioxidant [17, 18], antitumor [17, 19, 20], antimicrobial, antiinflammatory [21] and insulin-mimetic [22, 23] activities. A polymeric species of composition $[VO(Quer)_2EtOH]$ has been recently investigated for the antitumoral and osteogenic activities [20]. The VO^{2+} complex of flavanone hesperidin with composition $Na_4[VO(Hesp)(OH)_3]{\cdot}3H_2O$ has been obtained recently and studied for the antioxidant effects and its role in cancer chemoprevention [17]. Based on these issues, new complexes of the type $VO(OH)L{\cdot}nH_2O$ with some flavonoid derivatives (fisetin, quercetin and morin) were synthesized and characterized by elemental analysis and some spectral properties (UV–VIS and IR). The most probable structures of the compounds have been proposed. Because flavonoid compounds and most of their metal complexes are poor water-soluble compounds, the complex study, including thermal analysis, of the drug delivery systems is necessarily [24]. As result, the thermal analysis (TG and DTA) of the complexes was performed also in order to establish the thermal stability of these compounds during the pharmaceutical development studies. The thermal curves elucidated the composition and the number and nature of the solvent molecules also.

Experimental

Materials and methods

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

M. Badea (✉) · R. Olar · D. Marinescu
Department of Inorganic Chemistry, Faculty of Chemistry,
University of Bucharest, 90-92 Panduri Street, Sector 5,
050663 Bucharest, Romania
e-mail: e_m_badea@yahoo.com

V. Uivarosi · V. Aldea · T. O. Nicolescu
Department of Inorganic Chemistry, Carol Davila University of
Medicine and Pharmacy, 6 Traian Vuia Street, Bucharest,
Romania

The chemical analyses were performed on a Perkin Elmer PE 2400 analyser (for C, H, N, S) and an AAS Carl Zeiss Jena AAS1 spectrometer (for V).

IR spectra were recorded in KBr pellets with a FT-IR VERTEX 70 (Bruker) spectrometer in the range 400–4,000 cm^{-1}.

Electronic spectra by diffuse reflectance technique, with MgO as standard, were recorded in the range 300–1,500 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 16–31 mg over the temperature range of 20–900 °C, using a heating rate of 10 K/min. The measurements were carried out in synthetic air atmosphere (flow rate 16.66 cm^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 2θ 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

All the complexes were obtained following the general procedure: 2.00 g (6.2 mmol fisetin, 5.9 mmol quercetin and 5.9 mmol morin) of ligand dihydrate were dissolved in 50 cm^3 of distilled water containing a few NaOH platelets. To the resulting solution, a saturated solution of $VOSO_4 \cdot 5H_2O$ (in the molar ratio VO:ligand 1:2) were dropwise added, under continuous stirring. After the pH was adjusted to ~6 with H_2SO_4 1 M, a green-brown solid precipitated immediately. The sparingly soluble product was filtered off through a fritted glass funnel, washed several times with water and dried in desiccator over $CaCl_2$.

Complex VO(OH)(fisetin)$(H_2O)_3$ (**1**): Analysis, found: V, 12.48; C, 42.65; H, 4.41%; calculated for $VC_{15}H_{17}O_{11}$: V, 12.01; C, 42.43; H, 4.05%; IR (KBr pellet), cm^{-1}: $\nu(H_2O)$, 3405 m, $\nu(OH)_{phenole}$, 3227 m; ν(C=O), 1613 vs; ν(C=C), 1503 m; ν(C–O–C), 1274 vs; ν(V=O), 960 m; ν(V–OH–V), 824 w; ν(V–O), 528 w.

Complex VO(OH)(quercetin)$(H_2O)_2$ (**2**): Analysis, found: V, 12.49; C, 43.05; H, 3.72%; calculated for $VC_{15}H_{15}O_{11}$: V, 12.09; C, 42.77; H, 3.36%; IR (KBr pellet), cm^{-1}: $\nu(H_2O)$, 3404 s, $\nu(OH)_{phenole}$, 3221 m; ν(C=O), 1626 vs; ν(C=C), 1506 m; ν(C–O–C), 1274vs; ν(V=O), 964 m; ν(V–OH–V), 825w; ν(V–O), 519 w.

Complex VO(OH)(morin)$(H_2O)_4$ (**3**): Analysis, found: V, 11.45; C, 39.04; H, 4.22%; calculated for $VC_{15}H_{19}O_{13}$: V, 11.14; C, 39.40; H, 3.98%; IR (KBr pellet), cm^{-1}: $\nu(H_2O)$, 3411 m, sh., $\nu(OH)_{phenole}$, 3198 s; ν(C=O), 1604 vs; ν(C=C), 1504 m; ν(C–O–C), 1276 m; ν(V=O), 973 s; ν(V–OH–V), 836 w; ν(V–O), 535 w.

Results and discussion

Physico-chemical characterization of complexes

In this paper, we report the preparation and physico-chemical characterisation of some complexes with flavonoids as quercetin, fisetin and morin (Fig. 1).

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

$$VO(OH)(C_{15}H_{10}O_6)(H_2O)_3 \tag{1}$$

$$VO(OH)(C_{15}H_{10}O_7)(H_2O)_2 \tag{2}$$

$$VO(OH)(C_{15}H_{10}O_7)(H_2O)_4 \tag{3}$$

The IR spectra of complexes exhibits the characteristic patterns of flavonoids (experimental part) that generate bands about 3200 ($\nu(OH)_{phenole}$), 1610 (ν(C=O)) and 1270 cm^{-1} (ν(C–O–C). The band assigned to the carbonyl group is shifted to lower wavelength comparing with that of free ligand as a proof of its coordination. Supplementary bands about 970 cm^{-1} are assigned to the ν(V=O) stretching mode. The presence of a band at 830 cm^{-1} indicates, according to literature data, a bridging coordination mode of the hydroxyl ligand [25]. The presence of water molecule in complexes could be responsible for the appearance of a large band about 3400 cm^{-1} assigned to ν(OH) stretching vibrations [25]. Moreover, the new band that appear around 530 cm^{-1} can be assigned to the ν(V–O) stretching mode.

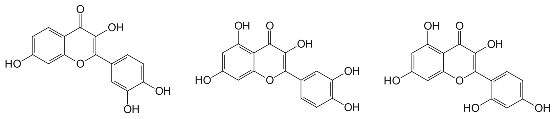
The solid-state *d–d* spectra of complexes show the characteristic bands of VO^{2+} in a square-pyramidal environment (Table 1).

The assignment of the absorptions at about 920 nm and the shoulders at about 650 and 440 nm to the spin allowed ${}^2B_2 \rightarrow {}^2E$, ${}^2B_2 \rightarrow {}^2B_1$ and ${}^2B_2 \rightarrow {}^2A_1$ transitions are based on literature data [26, 27].

On the basis of the above data, the proposed coordination for the complexes is as it follows (Fig. 2).

Thermal behaviour of complexes

The results concerning the thermal decomposition/degradation of the new complexes are presented as it follows.



Fisetin Quercetin Morin

Fig. 1 The ligand formulas

Table 1 Electronic data for complexes

Complex	Band I (nm) $^2B_2$ (d_{xy}) → ^2E (d_{xz}, d_{yz})	Band II (nm) $^2B_2$ (d_{xy}) → $^2B_1$ (d_{x2-y2})	Band III (nm) $^2B_2$ (d_{xy}) → $^2A_1$($d_z{}^2$)
(1)	923	690 (sh)	454 (sh)
(2)	922	636 (sh)	401 (sh)
(3)	926	680 (sh)	464 (sh)

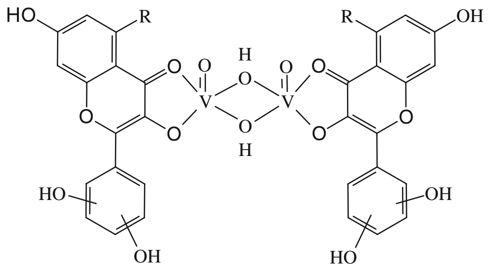


Fig. 2 The proposed coordination for complexes

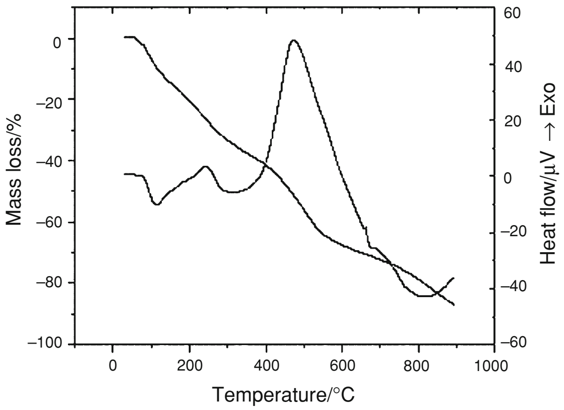


Fig. 3 TG and DTA curves of $VO(OH)(C_{15}H_{10}O_6)(H_2O)_3$

Thermal decomposition of $VO(OH)(C_{15}H_{10}O_6)(H_2O)_3$

The TG and DTA curves corresponding to the complex (**1**) heated in the 20–900 °C temperature range are presented in Fig. 3.

The thermal decomposition of $VO(OH)(C_{15}H_{10}O_6)(H_2O)_3$ (**1**) occurs in three, well-defined steps (Table 2). The first step, which is endothermic, corresponds to the loss of water molecules. Considering the low temperature corresponding to this transformation, we can appreciate the nature of water as for crystallisation [28–31]. The resulted anhydrous compound decomposed in the second step with pyrocatechine elimination. This step is complex being an overlap of at least two oxidative processes as DTA curve indicates. The IR spectrum of the residue isolated at 380 °C displays the same pattern as the initial complex (Fig. 4).

The third step, an exothermic one, corresponds to the oxidative degradation of the remaining organic component being composed also by two processes well-defined (as both TG and DTA indicate). The final product is a mixture of α (ASTM 72-0433) and β (ASTM 45-1074) modifications of V_2O_5 (Fig. 5) (found/calculated overall mass loss: 78.4/78.5).

Table 2 Thermal behaviour data (in static air atmosphere) for the complexes

Complex	Step	Thermal effect	Temperature interval (°C)	Δm_{exp} (%)	Δm_{calc} (%)
$VO(OH)(C_{15}H_{10}O_6)(H_2O)_3$ (**1**)	1	Endothermic	55–140	12.7	12.8
	2	Exothermic	140–380	26.0	26.0
	3	Exothermic	380–900	39.7	39.7
	Residue (V_2O_5)			21.6	21.5
$VO(OH)(C_{15}H_{10}O_7)(H_2O)_2$ (**2**)	1	Endothermic	51–100	8.6	8.6
	2	Exothermic	100–307	26.0	26.1
	3	Exothermic	307–900	43.7	43.7
	Residue (V_2O_5)			21.7	21.6
$VO(OH)(C_{15}H_{10}O_7)(H_2O)_4$ (**3**)	1	Endothermic	50–120	15.8	15.8
	2	Exothermic	120–313	24.0	24.1
	3	Exothermic	313–900	40.2	40.3
	Residue (V_2O_5)			20.0	19.8

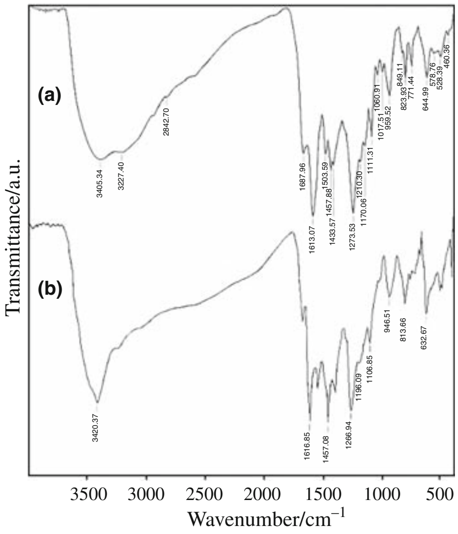


Fig. 4 IR spectra of complex (**1**) (**a**) and the intermediate obtained at 380 °C (**b**)

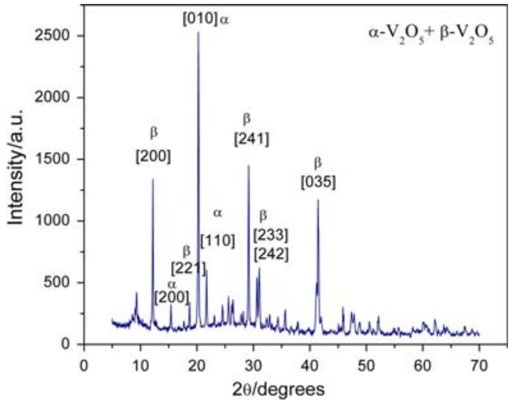


Fig. 5 Powder X-ray diffraction pattern for residue

Thermal decomposition of VO(OH)($C_{15}H_{10}O_7$)(H_2O)$_2$

Thermal analysis for (**2**) has confirmed the first step of compound transformation as an endothermic elimination of water molecules (Fig. 6). The reaction proceeds with a maximum rate at 80 °C. Based on the low temperature corresponding to the dehydration process, it could be assumed that the water molecule is also for crystallisation [28–31].

The second step, which is exothermic, corresponds to oxidative degradation of the organic ligand with pyrocatechine elimination. The third step corresponds to the oxidative degradation of the remaining intermediate that leads to the V_2O_5 formation as the final product (found/calculated overall mass loss: 78.34/78.4). According to both TG and DTA curves profiles this step comprises at least two processes.

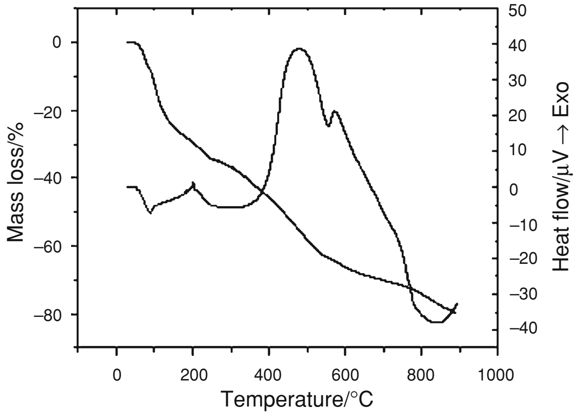


Fig. 6 TG and DTA curves of VO(OH)($C_{15}H_{10}O_7$)(H_2O)$_2$

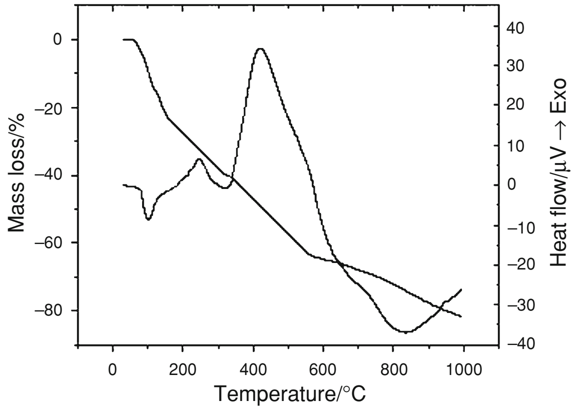


Fig. 7 TG and DTA curves of VO(OH)($C_{15}H_{10}O_7$)(H_2O)$_4$

Thermal decomposition of VO(OH)($C_{15}H_{10}O_7$)(H_2O)$_4$

The same three steps could be observed for complex (**3**) (Fig. 7). The water elimination up to 120 °C indicates the crystallisation nature of these molecules. The resorcin elimination as result of the oxidative degradation of the organic ligand occurs in at least two processes as both TG and DTA curves indicate. The third step, accompanied by a strong exothermic effect, corresponds to remaining part elimination also in at least two processes according to the TG and DTG curves profile. The final product is V_2O_5 (found/calculated overall mass loss: 80.0/80.2).

Conclusions

The new complexes of V(IV) with ligands belong to a class of coordination compounds of current interest for their insulin-mimetic and antitumoral activity have been synthesised and characterised by analytical and spectral investigations. A square-pyramidal stereochemistry for metallic ion was proposed based on the electronic spectra while the IR spectra features indicated a chelate coordination mode of flavonoids.

Thermal analysis (TG and DTA) of these complexes elucidated the composition and also the number and nature of the water molecules. It was also evidenced the existence of an intermediate step corresponding to the flavonoids decomposition with a diphenol derivative release. The final product of thermal decomposition was in all cases V_2O_5 as powder X-ray diffraction indicated.

Acknowledgements This work was supported by the PNII Grant no. 61-042/2007 of the Romanian Ministry of Education and Research.

References

1. McNeill JH, Yuen VG, Hoveyda HR, Orvig C. Bis(maltolato)-oxovanadium(IV) is a potent insulin mimic. J Med Chem. 1992;35:1489–91.
2. Yuen VG, Caravan P, Gelmini L, Glover N, McNeill JH, Setyawati IA, et al. Glucose-lowering properties of vanadium compounds: comparison of coordination complexes with maltol or kojic acid as ligands. J Inorg Biochem. 1997;68:109–16.
3. Sakurai H, Fujii K, Watanabe H, Tamura H. Orally active and long-term acting insulin-mimetic vanadyl complex: bis(picolinato)oxovanadium(IV). Biochem Biophys Res Commun. 1995; 214:1095–101.
4. Sakurai H, Sano H, Takino T, Yasui H. An orally active antidiabetic vanadyl complex, bis(1-oxy-2-pyridinethiolato)oxovanadium(IV), with $VO(S_2O_2)$ coordination mode; in vitro and in vivo evaluations in rats. J Inorg Biochem. 2000;80:99–105.
5. Sakurai H, Katoh A, Yoshikawa Y. Chemistry and biochemistry of insulin-mimetic vanadium and zinc complexes. Trial for treatment of diabetes mellitus. Bull Chem Soc Jpn. 2006;79: 1645–64.
6. El-Naggar MM, El-Waseef AM, El-Halafawy KM, El-Sayed IH. Antitumor activities of vanadium(IV), manganese(IV), iron(III), cobalt(II) and copper(II) complexes of 2-methylaminopyridine. Cancer Lett. 1998;133:71–6.
7. Etcheverry SB, Williams PAM, Barrio DA, Salice VC, Ferrer EG, Cortizo AM. Synthesis, characterization and bioactivity of a new VO^{2+}/Aspirin complex. J Inorg Biochem. 2000;80:169–71.
8. Etcheverry SB, Barrio DA, Williams PAM. Three new vanadyl(IV) complexes with non-steroidal anti-inflammatory drugs (Ibuprofen, Naproxen and Tolmetin). Bioactivity on osteoblast-like cells in culture. J Inorg Biochem. 2002;88:94–100.
9. Thompson KH, Böhmerle K, Polishchuk E, Martins C, Toleikis P, Tse J, et al. Complementary inhibition of synoviocyte, smooth muscle cell or mouse lymphoma cell proliferation by a vanadyl curcumin complex compared to curcumin alone. J Inorg Biochem. 2004;98:2063–70.
10. Mohammadi K, Thompson KH, Patrick BO, Storr T, Martins C, Polishchuk E, et al. Synthesis and characterization of dual function vanadyl, gallium and indium curcumin complexes for medicinal applications. J Inorg Biochem. 2005;99:2217–25.
11. Lampronti I, Bianchi N, Borgatti M, Fabri E, Vizziello L, Khan MT, et al. Effects of vanadium complexes on cell growth of human leukemia cells and protein-DNA interactions. Oncol Rep. 2005;14:9–15.
12. Elangovan V, Sekar N, Govindasamy S. Chemopreventive potential of dietary bioflavonoids against 20-methylcholanthrene-induced tumorigenesis. Cancer Lett. 1994;87:107–13.
13. Middleton E Jr. Effect of plant flavonoids on immune and inflammatory cell function. Adv Exp Med Biol. 1998;439:175–82.
14. Gabor M. Anti-inflammatory and anti-allergic properties of flavonoids. Prog Clin Biol Res. 1986;213:471–80.
15. Zhu BT, Ezell ET, Liehr JG. Catechol-O-methyltransferase-catalyzed rapid O-methylation of mutagenic flavonoids: metabolic inactivation as a possible reason for their lack of carcinogenicity in vivo. J Biol Chem. 1994;269:292–9.
16. Nijveldt R, van Nood E, van Hoorn D, Boelens P, van Norren K, van Leeuwen P. Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr. 2001;74:418–25.
17. Etcheverry SB, Ferrer EG, Naso L, Rivandeneira J, Salinas V, Williams PA. Antioxidant effects of the VO(IV) hesperidin complex and its role in cancer chemoprevention. J Biol Inorg Chem. 2008;13:435–47.
18. Kostyuk VA, Potapovich AI, Kostyuk TV, Cherian MG. Metal complexes of dietary flavonoids: evaluation of radical scavenger properties and protective activity against oxidative stress in vivo. Cell Mol Biol. 2007;53:62–9.
19. Ferrer EG, Salinas MV, Correa MJ, Naso L, Barrio DA, Etcheverry SB, et al. Synthesis, characterization, antitumoral and osteogenic activities of quercetin vanadyl(IV) complexes. J Biol Inorg Chem. 2006;11:791–801.
20. Zhou J, Wang LF, Wang JY, Tang N. Synthesis, characterization, antioxidative and antitumor activities of solid quercetin rare earth(III) complexes. J Inorg Biochem. 2001;83:41–8.
21. Pereira RM, Andrades NE, Paulino N, Sawaya AC, Eberlin MN, Marcucci MC, et al. Synthesis and characterization of a metal complex containing naringin and Cu, and its antioxidant, antimicrobial, antiinflammatory and tumor cell cytotoxicity. Molecules. 2007;12(7):1352–66.
22. Shukla R, Barve V, Padhye S, Bhonde R. Synthesis, structural properties and insulin-enhancing potential of bis(quercetinato) oxovanadium(IV) conjugate. Bioorg Med Chem Lett. 2004;14: 4961–5.
23. Shukla R, Barve V, Padhye S, Bhonde R. Reduction of oxidative stress induced vanadium toxicity by complexing with a flavonoid, quercetin: a pragmatic therapeutic approach for diabetes. BioMetals. 2006;19:685–93.
24. Kanaze FI, Kokkalou E, Niopas I, Georgarakis M, Stergiou A, Bikiaris D. Thermal analysis study of flavonoid solid dispersions having enhanced solubility. J Therm Anal Calorim. 2006;83: 283–90.
25. Nakamoto K. Infrared and Raman spectra of inorganic and coordination compounds. New York: Wiley; 1986. p. 226.
26. Lever ABP. Inorganic electronic spectroscopy. Amsterdam: Elsevier; 1986. p. 385.
27. Modi CK, Thaker BT. Some novel tetradentate Schiff base complexes VO(IV) and Cu(II) involving fluorinated heterocyclic β-diketones and polymethylene diamines of varying chain length. Synthesis, spectral, coordination and thermal aspects. J Therm Anal Calorim. 2008;94:567–77.
28. Modi CK, Patel MN. Synthetic, spectroscopic and thermal aspects of some heterochelates. J Therm Anal Calorim. 2008;94: 247–55.
29. Abou El-Enein SA. Polymeric and sandwich Schiff's bases complexes derived from 4,4′-methylenedianiline: characterization and thermal investigation. J Therm Anal Calorim. 2008;91: 929–36.
30. Gaber M, Rehab AF, Badr-Eldeen DF. Spectral and thermal studies of new Co(II) and Ni(II) hexaaza and octaaza macrocyclic complexes. J Therm Anal Calorim. 2008;91:957–62.
31. Vikram L, Sivasankar BN. Hydrazinium metal(II) and metal(III) ethylenediamine tetraacetate hydrates: spectral, thermal and XRD studies. J Therm Anal Calorim. 2008;91:963–70.